Modified HARmonized Protocol Template to Enhance Reproducibility – HARPER+

CMS has drafted this standardized real-world evidence (RWE) protocol template, called HARPER+, to be used by manufacturers or other sponsors when creating a study protocol using real-world data (RWD). The HARPER+ protocol template is based on the HARmonized Protocol Template to Enhance Reproducibility (HARPER), but adapted for medical devices and Medicare coverage criteria. We urge interested parties who intend to submit a Coverage with Evidence Development (CED) study protocol using RWD for CMS approval to adhere to the template and provide all requested information to the best of their ability. Use of the standardized format will facilitate efficient review of the protocol.

Helper text to assist with using the harmonized protocol template is provided in green. This helper text may be deleted after filling out the template. Information to fill in is typically noted as "<Text>". If a section is not applicable, enter "n/a." For studies utilizing data from a commercial vendor, some portions of the template, including the measurement validations, may require input from the data vendor and are highlighted below in green. CMS expects measurement validations for critical study variables; if validation information is unavailable, indicate a reason. CMS intends that information in this protocol will not be publicly shared; however, information contained in this protocol may be discoverable via the Freedom of Information Act.

1. Title Page

Title	<Text>
Research question and objectives	<Text>
Protocol version	<Text>
Last update date	<Text>
Contributors	Primary Investigator contact information: <Text> Contributor names: <Text>
Study registration in clinicaltrials.gov	Site: <Text> Identifier: <Text>
Sponsor	Organization: <Text> Contact: <Text>
Conflict of interest: any real or perceived financial conflicts of interest (e.g., salary, consulting fees, ownership interests that may influence the research outcomes)	<Text>

Table of Contents

2. Abstract

Include a brief description of the background, research question(s) and objective(s), study design, data source(s), and analytic approach.

<Text>

3. Amendments and Updates

Indicate amendments and updates to the study protocol in Table 1, as indicated below. In the "reason" column, note whether the amendment occurred after protocol registration/finalization/approval. Minor changes to the protocol do not require a formal resubmission and review by CMS. If a change is more than minor, or the sponsor has a question about what changes require resubmission, please ask your CMS point-of-contact. When appropriate, please update the registered study at clinicaltrials.gov to reflect protocol updates.

Version date: Date of the protocol version change.

Version number: Number or other identifier for the protocol version.

Section of protocol: Sections/subsections of the protocol that were amended.

Amendment or update: Brief text description of what changes were involved with the protocol amendment.

Reason: Brief text description of the rationale for the protocol amendment.

Table 1. Documentation of the Amendments and Updates to the Study Protocol

Version date	Version number	Section of protocol	Amendment or update	Reason
<Text>	<Text>	<Text>	<Text>	<Text>
<Text>	<Text>	<Text>	<Text>	<Text>
<Text>	<Text>	<Text>	<Text>	<Text>
<Text>	<Text>	<Text>	<Text>	<Text>

4. Milestones

Enter planned (best estimates of) dates for study milestones, including interim and final results reporting. CMS recognizes that RWE study milestones are subject to change. Completion and results of milestones should be reported to CMS.

Milestone: Brief text description of the milestone or deliverable. The milestones listed below in Table 2 are required, but additional milestones can be added, as appropriate.

Date: Anticipated date of completion.

Table 2. Milestones

Milestone	Date
IRB approval or exemption	<Text>
Obtain data use agreements	<Text>
Present interim results, including data quality checks, generalizability analysis, and enrollment/sample size update	<Text>
Date when coverage under a Continued Access Study begins	<Text>
Review date with CMS	<Text>
Submit results for publication	<Text>

5. Rationale and Background

What is known about the condition (e.g., current standard of care including limitations, side effects): <Text>

What is known about the exposure of interest (e.g., expected benefits, indications/contraindications, subpopulations who benefit, mechanism of action, pertinent anatomy and physiology; in case of devices, performance metrics including battery life, failure rates): <Text>

CMS-identified evidence deficiency and knowledge gaps: <Text>

What is the expected contribution of this study? <Text>

6. Research Question and Objectives

Table 3. Primary and Secondary Research Questions and Objective

The primary objective(s) defines the main aim of the study whereas the hypothesis refers to the main question being tested. This is usually what the study will be powered to detect. Secondary objectives are ancillary questions that may provide more information about the effects of treatment. Exposure refers to the therapeutic of interest whereas the comparator refers to an alternative option. The outcome refers to the clinical or other condition for which you are interested in understanding the effect of exposure. Time refers to when follow up begins and ends. Setting refers to the care settings that are relevant for the study (e.g., inpatient, ambulatory, emergency department). The main measure of effect refers to how you will estimate the effect of the exposure compared to the comparator on the outcome (e.g., hazard ratio, risk ratio, risk difference).

Duplicate table sections A and B as necessary for co-primary objectives or multiple secondary objectives.

Objective success criteria: In consultation with CMS and the Agency for Healthcare Research and Quality (AHRQ), state the evidentiary threshold for the primary health outcome(s) to demonstrate clinically meaningful differences with sufficient precision. Please provide references or justification for the objective success criteria for powered endpoints (i.e., endpoints where a power analysis was conducted to understand sample size requirements).

A. Primary research question and objective

Objective:	<Text>
Hypothesis:	<Text>
Population ***(mention key inclusion-exclusion criteria):***	<Text>
Exposure(s):	<Text>
Comparator(s):	<Text>
Outcome:	<Text>
Time ***(when follow up begins and ends):***	<Text>
Setting of exposure/intervention:	<Text>
Main measure of effect:	<Text>
Objective success criteria of powered endpoints:	<Text>

B. Secondary research question and objective

Objective:	<Text>
Hypothesis:	<Text>
Population *(mention key inclusion-exclusion criteria):*	<Text>
Exposure(s):	<Text>
Comparator(s):	<Text>
Outcome:	<Text>
Time *(when follow up begins and ends):*	<Text>
Setting of exposure/intervention:	<Text>
Main measure of effect:	<Text>
Objective success criteria of powered endpoints:	<Text>

7. Research Methods

7.1. Study Design

Research design (e.g., cohort, case-control): <Text>

Rationale for study design choice: <Text>

7.2. Study Design Diagram

Provide a design diagram to describe time 0 and relevant study windows used in the study design. A recommended framework is outlined in Wang and Schneeweiss 2022's paper, *A Framework for Visualizing Study Designs and Data Observability in Electronic Health Record Data*. The diagram following this framework can be created using PowerPoint templates or other software program of choice (www.repeatinitiative.org/projects). It is intended to be read from top to bottom, reflecting the order of operations to create an analytic cohort from a source longitudinal healthcare database. Temporality of assessment windows are clearly shown relative to the study entry ("index") date, which is considered time 0. Bracketed number ranges denote the inclusive time windows for washout, inclusion/exclusion, and covariate assessment windows as well as follow up. Whether or not time 0 is included in an assessment window can also be visually distinguished by whether it overlaps the vertical arrow representing the primary anchor.

The diagram may include footnotes specifying the inclusion/exclusion criteria, covariates, and censoring criteria relevant to each assessment window. Alternative design visualization approaches can be used as appropriate.

<Diagram>

7.3. Setting

7.3.1. Context and Rationale for Definition of Time 0 (and Other Primary Time Anchors) for Entry to the Study Population

The criteria that define the primary temporal anchor(s) that define how patients enter the study population are specified in this section. Other assessment windows used in the study design are defined relative to the primary temporal anchor(s). For example, assessment windows for inclusion-exclusion criteria or the follow up window. The primary temporal anchor is sometimes referred to as "time 0," an "index date," or "cohort entry date."

<Text>

Table 4. Operational Definition of Time 0 (Index Date) and Other Primary Time Anchors

There should be (at least) one row for each study population. A key primary anchor is time 0, for when patients enter the study population and/or begin treatment, depending on the study. A primary time anchor is used as an anchor for defining assessment windows for inclusion-exclusion criteria, baseline characteristics, or follow up. If the study is descriptive, there may only be one primary temporal anchor for the study population. An active comparator study may have two rows, one for the exposure of interest and one for the comparator. Other, more complex study designs may have multiple primary temporal anchors. For example, a nested case-control study may have a primary anchor defined for the base cohort, and another for the case-defining event. A pregnancy study may have anchors defined by last menstrual period, trimester boundaries, and delivery date. The table below requests the following operational details:

Study population name(s): A brief text descriptor naming the study population that is identified for a primary or secondary analysis (e.g., exposed, comparator, pregnant women, patients with diabetes).

Time anchor description: A brief text description of the criterion used to define the time anchor, including at least one entry to define time 0, the point at which the patient enters the cohort (e.g., date of incident dispensation of Drug X, date of heart failure diagnosis, last menstrual period).

Number of entries: Indicate whether patients are allowed to enter the study population only once or multiple times (e.g., single entry, multiple entry).

Type of entry: Indicate whether the criterion for entry to the study population reflects an incident, prevalent, or other condition.

Washout window: If entry to the study population is defined as incident, use bracketed numbers representing time intervals anchored on a primary anchor (usually time 0) to specify the washout window. For example, [-180, -1] would reflect a washout window of 180 days prior to time 0, where the brackets indicate that the window is inclusive of the endpoints. In the context of medical devices, a washout window refers to a period of time during which a patient should refrain from using or administering the device, or from being exposed to its effects, in order to minimize the potential for interference or contamination from previous use.

Care setting: Specify the care setting(s) that are used in the algorithm to define the time 0 (or another primary anchor) criterion. For example, IP = inpatient, ED = emergency department, etc.

Code type: Specify the type(s) of clinical codes that are used to define the time 0 (or another primary anchor) criterion. For example, ICD10 = International Classification of Diseases 10th edition, CPT = current procedural terminology, etc.

Code position: If the algorithm to define the time 0 (or other primary anchor) criterion used diagnosis or procedure codes, specify whether the algorithm restricts to primary codes (indicating that the code is the primary reason for the encounter) or allows codes in secondary or any position (e.g., primary, secondary, any, n/a).

Incident with respect to: If the type of entry is defined as incident, provide a brief text description of what the patient is required to be incident to. For example, when identifying incident implantation of Device X, the investigator may wish to require that patients be incident with respect to Device X, as well as Device Y. This would be operationalized as having no record of exposure to any of these devices during the specified washout period.

Measurement characteristics/validation: If there are measurement characteristics for the definition of time 0 (e.g., PPV, sensitivity, specificity) from publications, or from validation within the study population (e.g., medical record review), provide this information.

Source of algorithm: Specify the source of algorithms to define the time 0 or primary anchor criteria. If a novel algorithm is used to derive a data element, write "investigators" in this field. If a previously developed algorithm is used, specify an appropriate reference.

Study population name(s)	Time anchor description (e.g., time 0)	Number of entries	Type of entry	Washout window	Care setting[1]	Code type[2]	Code position[3]	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>
<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>
<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] Use the appendix to list the clinical codes for each study parameter.
[3] Specify whether a code is required to be in the primary position (main reason for encounter).

7.3.2. Context and Rationale for Study Inclusion Criteria

In this section, the protocol describes context and rationale for applying each inclusion criterion listed in Table 5. Note that defining "observable" patient time in the healthcare data source will almost always be relevant as an inclusion criterion. When using administrative claims data, this can be measured with dates of enrolment in insurance coverage, with or without bridging of short gaps in enrolment. When using electronic health record (EHR) data, defining observable patient time may require making some strong assumptions. For example, assuming that patient encounters are always observable, that patients are observable between the first and last recorded encounter in the record, that patients are observable for X days before and after any recorded encounter, etc. Alternatively, one could specify inclusion based on algorithms to measure "loyalty" to a healthcare provider or EHR system. If applicable, discuss participant recruitment strategy.

<Text>

Table 5. Operational Definitions of Inclusion Criteria

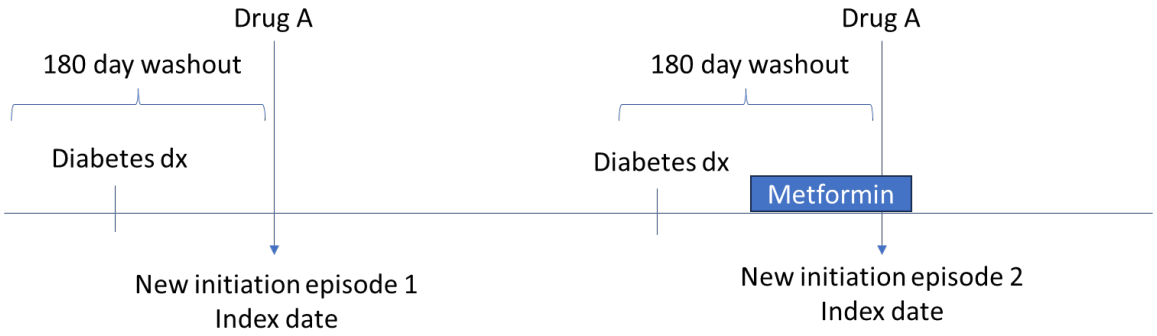
The table below requests the following operational details:

Criterion: A brief text entry naming the inclusion criterion (e.g., baseline observable time, age, sex, atrial fibrillation).

Details: A brief text entry to provide more information about the inclusion criterion (e.g., age in years defined by (time 0 – year of birth)/365, baseline enrolment measured by Part A, B, D, and no HMO insurance coverage with 30-day gaps allowed).

Order of application: Specify whether the inclusion criterion is applied before or after selection of the study entry date. For example, enter "before" if you will identify all possible study entry dates and apply the inclusion criterion to each possible entry date before choosing one or more study entry dates that have met the inclusion criterion. Enter "after" if you select the first possible study entry date and then apply the inclusion criterion. If the patient does not meet the inclusion criterion, then the patient will not be included. These decisions can impact which samples of person-time are included in the study. Example: A study of new initiators of Drug A vs Drug B requires patients to have diagnosed diabetes in the 180 days prior to initiation and be on metformin on the day of initiation. The analyst could identify all index dates for which patients meet the washout criteria for Drug A or B (there could be multiple episodes of new initiation per person), apply the eligibility criteria for diabetes diagnosis and metformin, and then keep the first index date (or all index dates) that meet these criteria. Alternatively, they could identify the first new initiation episode that a patient has, then apply the eligibility criteria relative to that index date and include the patient only if they meet all eligibility criteria.

In the figure below, if "before" is selected, then new initiation episode 2 will be included because the patient has a diabetes dx within 180 days of that new initiation index date and metformin on the index date. If "after" is selected, then this patient will not contribute to the analysis because the eligibility criteria are applied after selecting the first potential index date (new initiation episode 1) and this episode does not have concurrent metformin on the index date.



Assessment window: Use bracketed numbers representing time intervals anchored on a primary anchor (usually time 0) to specify the window over which to evaluate patient data relevant for the inclusion criterion. For example, [-180, 0] would reflect an assessment window of 180 days prior to and including time 0, where the brackets indicate that the window is inclusive of the endpoints.

Care setting: Specify the care setting(s) that are used in the algorithm to define the inclusion criterion. For example, IP = inpatient, ED = emergency department, etc.

Code type: Specify the type(s) of clinical codes that are used to define the inclusion criterion. For example, ICD10 = International Classification of Diseases 10th edition, CPT = Common Procedural Terminology, etc.

Code position: If the algorithm to define the time 0 (or other primary anchor) criterion used diagnosis or procedure codes, specify whether the algorithm restricts to primary codes (indicating that the code is the primary reason for the encounter) or allows codes in secondary or any position (e.g., primary, secondary, any, n/a).

Applied to study populations: Indicate which study populations the inclusion criterion should be applied to (study population names are specified in Table 4).

Measurement characteristics/validation: If there are measurement characteristics for the inclusion criteria (e.g., PPV, sensitivity, specificity) from publications, or from validation within the study population (e.g., medical record review), provide this information.

Source of algorithm: Specify the source of algorithms to define the inclusion criteria. If a novel algorithm is used to derive a data element, write "investigators" in this field. If a previously developed algorithm is used, specify an appropriate reference.

Criterion	Details	Order of application	Assessment window	Care settings[1]	Code type[2]	Code position[3]	Applied to study populations	Measurement characteristics/ validation	Source for algorithm
<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>
<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>
<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>
<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>
<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] Use the appendix to list the clinical codes for each study parameter.
[3] Specify whether a code is required to be in the primary position (main reason for encounter).

7.3.3. Context and Rationale for Study Exclusion Criteria

In this section, the context and rationale for applying each exclusion criterion listed in Table 6 are described.

<Text>

Table 6. Operational Definitions of Exclusion Criteria

The table below requests the following operational details:

Criterion: A brief text entry naming the exclusion criterion (e.g., age, sex, atrial fibrillation).

Details: A brief text description to provide more information about the exclusion criterion (e.g., age in years defined by (time 0 – year of birth)/365, baseline enrollment measured by Part A, B, D, and no HMO insurance coverage with 30-day gaps allowed).

Order of application: Specify whether the exclusion criterion is applied before or after selection of the study entry date. For example, enter "before" if you plan to apply the criterion, identify all possible study entry dates, and then choose one or more. Enter "after" if you select the first possible study entry date and then apply the exclusion criterion. If the patient does not meet the criterion, then the patient drops out. These decisions can impact which samples of person-time are included in the study. See the above Inclusion Criteria section for an example.

Assessment window: Use bracketed numbers representing time intervals anchored on a primary anchor (usually time 0) to specify the window over which to evaluate patient data relevant for the exclusion criterion. For example, [-180, 0] would reflect an assessment window of 180 days prior to and including time 0, where the brackets indicate that the window is inclusive of the endpoints.

Care setting: Specify the care setting(s) that are used in the algorithm to define the exclusion criterion. For example, IP = inpatient, ED = emergency department, etc.

Code type: Specify the type(s) of clinical codes that are used to define the exclusion criterion. For example, ICD10 = International Classification of Diseases 10th edition, CPT = Common Procedural Terminology, etc.

Code position: If the algorithm to define the time 0 (or other primary anchor) criterion used diagnosis or procedure codes, specify whether the algorithm restricts to primary codes (indicating that the code is the primary reason for the encounter) or allows codes in secondary or any position (e.g., primary, secondary, any, n/a).

Applied to study populations: Indicate which study populations the exclusion criterion should be applied to (study population names are specified in Table 4).

Measurement characteristics/validation: If there are measurement characteristics for the exclusion criteria (e.g., PPV, sensitivity, specificity) from publications, or from validation within the study population (e.g., medical record review), provide this information.

Source of algorithm: Specify the source of algorithms to define the exclusion criteria. If a novel algorithm is used to derive a data element, write "investigators" in this field. If a previously developed algorithm is used, specify an appropriate reference.

Criterion	Details	Order of application	Assessment window	Care settings[1]	Code type[2]	Code position[3]	Applied to study populations	Measurement characteristics/ validation	Source for algorithm
<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>
<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>
<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>
<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>
<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] Use the appendix to list the clinical codes for each study parameter.
[3] Specify whether a code is required to be in the primary position (main reason for encounter).

7.3.4. Generalizability of Study Population

Explain how the above inclusion and exclusion criteria enable generalizability of the study population to the Medicare beneficiaries who are the intended population of the intervention. For example, if the Evidence Preview identified a lack of evidence in patients over 65 years old, provide a quantitative analysis of the number of patients over 65 years old in the source data identified for this study. At a minimum, a discussion is warranted on how well the proposed study population is expected to reflect the intended CMS population of the intervention. Variables to consider in the discussion include racial and ethnic backgrounds, gender, age, disabilities, important comorbidities, and social determinants of health.

<Text>

7.4. Variables

Specify in this section the context, rationale, and operational definition of exposures, outcomes, and other variables including measured risk factors, co-morbidities, co-medications, potential confounding variables and effect modifiers, etc.

7.4.1. Context and Rationale for Exposure(s) of Interest

Conceptually describe the study exposure (and comparator) and provide the context or rationale for choosing the exposure(s) of interest. For devices, provide the brand and model numbers. For products consisting of multiple components, state whether all components of the product are being assessed or if specific components are being assessed.

<Text>

Algorithm to define duration of exposure effect:

If relevant, describe how duration of exposure effect will be defined operationally. For pharmaceuticals, consider stockpiling algorithms, allowable gaps, and hypothesized duration of biological effect beyond the last available dose. For devices, consider time from implant to removal/failure, compliance with appointments, or device-related procedures, etc.

<Text>

Table 7. Operational Definitions of Exposure

Populate table if exposure is not already defined in Table 4 as a primary anchor criterion for defining time 0.

The table below requests the following operational details:

Exposure group names: A brief text entry naming the exposure groups (e.g., Device X, Device Y).

Details: An optional brief text description to provide more information about the exposure (e.g., dual chamber leadless pacemaker).

Washout window: If entry to the study population is defined as incident, use bracketed numbers representing time intervals anchored on a primary anchor (usually time 0) to specify the washout window. For example, [-180, -1] would reflect a washout window of 180 days prior to time 0, where the brackets indicate that the window is inclusive of the endpoints. In the context of medical devices, a washout window refers to a period of time during which a patient should refrain from using or administering the device, or from being exposed to its effects, in order to minimize the potential for interference or contamination from previous use.

Assessment window: Use bracketed numbers representing time intervals anchored on a primary anchor (usually time 0) to specify the window over which to evaluate patient data relevant for defining exposure status. For example, [-180, 0] would reflect an assessment window of 180 days prior to and including time 0, where the brackets indicate that the window is inclusive of the endpoints.

Care setting: Specify the care setting(s) that are used in the algorithm to define exposure. For example, IP = inpatient, ED = emergency department, etc.

Code type: Specify the type(s) of clinical codes that are used to define exposure. For example, ICD10 = International Classification of Diseases 10th edition, CPT = Common Procedural Terminology, UDI = unique device identifier, etc.

Code position: If the algorithm to define the time 0 (or other primary anchor) criterion used diagnosis or procedure codes, specify whether the algorithm restricts to primary codes (indicating that the code is the primary reason for the encounter) or allows codes in secondary or any position (e.g., primary, secondary, any, n/a).

Applied to study populations: Indicate which study populations the exposure definition should be applied to (study population names are specified in Table 4).

Incident with respect to: If exposure is defined as incident, provide a brief text description of what the patient is required to be incident to. For example, when identifying incident implantation of Device X, the investigator may wish to require that patients be incident with respect to Device X, as well as Device Y. This would be operationalized as having no record of exposure to any of these devices during the specified washout period.

Measurement characteristics/validation: If there are measurement characteristics for the outcome algorithm (e.g., PPV, sensitivity, specificity) from publications, or from outcome validation within the study population (e.g., medical record review), provide this information.

Source of algorithm: Specify the source of algorithms to define the exposure. If a novel algorithm is used to derive a data element, write "investigators" in this field. If a previously developed algorithm is used, specify an appropriate reference.

Exposure group name(s)	Details	Washout window	Assessment window	Care setting[1]	Code type[2]	Code position[3]	Applied to study populations	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>
<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>
<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] Use the appendix to list the clinical codes for each study parameter.
[3] Specify whether a code is required to be in the primary position (main reason for encounter).

7.4.2. Context and Rationale for Outcome(s) of Interest

Describe the study outcome(s) and provide the context or rationale for the choices in this section. For all outcomes (primary, secondary, composite, etc.), provide the rationale and justification for the following, as needed: 1) the minimal clinically important differences based on existing literature; 2) composite or surrogate outcomes.

<Text>

Table 8. Operational Definitions of Outcome

The table below requests the following operational details:

Outcome name: A brief text entry naming the outcome (e.g., myocardial infarction, death).

Details: A brief text description to provide more information about the outcome (e.g., 2nd of two codes within seven days).

Primary outcome: Indicate whether the outcome is a primary or secondary outcome (e.g., Yes, if primary; No, if secondary).

Type of outcome: Specify the variable type for the outcome (e.g., time-to-event, binary, count, continuous).

Washout window: If the outcome is required to be incident, use bracketed numbers representing time intervals anchored on a primary anchor (usually time 0) to specify the washout window. For example, if the outcome is incident hospitalization, and re-hospitalizations within 30 days are not considered new events, then the washout period should be [-30, 0] days, where the brackets indicate that the window is inclusive of the endpoints.

Care setting: Specify the care setting(s) that are used in the algorithm to define the outcome. For example, IP = inpatient, ED = emergency department, etc.

Code type: Specify the type(s) of clinical codes that are used to define the outcome. For example, ICD10 = International Classification of Diseases 10th edition, CPT = Common Procedural Terminology, etc.

Code position: If the algorithm to define the time 0 (or other primary anchor) criterion used diagnosis or procedure codes, specify whether the algorithm restricts to primary codes (indicating that the code is the primary reason for the encounter) or allows codes in secondary or any position (e.g., primary, secondary, any, n/a).

Applied to study populations: Indicate which study populations the outcome should be evaluated in (study population names are specified in Table 4).

Measurement characteristics/validation: If there are measurement characteristics for the outcome algorithm (e.g., PPV, sensitivity, specificity) from publications, or from validation within the study population (e.g., medical record review), provide this information.

Source of algorithm: Specify the source of algorithms to define the exclusion criteria. If a novel algorithm is used to derive a data element, write “investigators” in this field. If a previously developed algorithm is used, specify an appropriate reference.

Outcome name	Details	Primary outcome	Type of outcome	Washout window	Care settings[1]	Code type[2]	Code position[3]	Applied to study populations:	Measurement characteristics/ validation	Source of algorithm
<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>
<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] Use the appendix to list the clinical codes for each study parameter.
[3] Specify whether a code is required to be in the primary position (main reason for encounter).

7.4.3. Context and Rationale for Follow Up

Describe the study follow up and provide the context or rationale for the choices in this section.

<Text>

Table 9. Operational Definitions of Follow Up

The table below requests the following operational details:

Follow up start: Specify when follow up begins relative to time 0 (e.g., day 1). Consider whether an induction or latency window is relevant for the hypothesized onset of the effect of exposure on the outcome (operationally, this would mean delaying the start of follow up (e.g., follow up start on day 30).

Date of outcome, Date of death, End of observation in data, Day X following index date, End of study period, End of exposure, Date of add to/switch from exposure, and Other date: Indicate "Yes" or "No" for each of the options.

Follow up start	<Text>	
	Below, indicate "Yes" or "No" to specify if event ends follow up[1]	**Specify additional details as relevant including code sets used to operationalize follow up that have not been previously referenced.**
Date of outcome	<Text>	<Text>
Date of death	<Text>	<Text>
End of observation in data	<Text>	<Text>
Day X following index date *(specify day)*	<Text>	<Text>
End of study period (specify date)	<Text>	<Text>
End of exposure *(specify operational details, e.g., stockpiling algorithm, grace period)*	<Text>	<Text>
Date of add to/switch from exposure *(specify algorithm)*	<Text>	<Text>
Other date *(specify)*	<Text>	<Text>

[1] Follow up ends at the first occurrence of any of the selected criteria that end follow up.

7.4.4. Context and Rationale for Covariates (Confounding Variables and Effect Modifiers, e.g., Risk Factors, Comorbidities, Comedications)

Describe the study covariates and give the context, rationale, and methods for the choices in this section. If applicable, describe the data driven methods to select covariates through machine learning algorithms, with detail on operational choices including parameter settings for the macro/function that are used.

<Text>

Table 10. Operational Definitions of Covariates

The table below requests the following operational details:

Characteristic: A brief text entry naming the characteristic (e.g., age, sex, atrial fibrillation).

Details: A brief text description to provide more information about the covariate (e.g., age in years defined by (time 0 – year of birth)/365) including variable transformations (e.g., normalization, categorization).

Type of variable: Specify the variable type for the covariate (e.g., binary, count, continuous).

Assessment window: Use bracketed numbers representing time intervals anchored on a primary anchor (usually time 0) to specify the window over which to evaluate patient data relevant for the covariate. For example, [-180, 0] would reflect an assessment window of 180 days prior to and including time 0, where the brackets indicate that the window is inclusive of the endpoints.

Care setting: Specify the care setting(s) that are used in the algorithm to define the covariate. For example, IP = inpatient, ED = emergency department, etc.

Code type: Specify the type(s) of clinical codes that are used to define the covariate. For example, ICD10 = International Classification of Diseases 10th edition, CPT = Common Procedural Terminology, etc.

Code position: If the algorithm to define the time 0 (or other primary anchor) criterion used diagnosis or procedure codes, specify whether the algorithm restricts to primary codes (indicating that the code is the primary reason for the encounter) or allows codes in secondary or any position (e.g., primary, secondary, any, n/a).

Applied to study populations: Indicate which study populations the covariate should be measured in (study population names are specified in Table 4).

Measurement characteristics/validation: If there are measurement characteristics for the outcome algorithm (e.g., PPV, sensitivity, specificity) from publications, or from validation within the study population (e.g., medical record review), provide this information.

Source of algorithm: Specify the source of algorithms to define the covariates. If a novel algorithm is used to derive a data element, write "investigators" in this field. If a previously developed algorithm is used, specify an appropriate reference.

Characteristic	Details	Type of variable	Assessment window	Care settings[1]	Code type[2]	Code position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>
<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] Use the appendix to list the clinical codes for each study parameter.
[3] Specify whether a code is required to be in the primary position (main reason for encounter).

7.5. Data Analysis

7.5.1. Statistical Analysis Plan.

A statistical analysis plan (SAP) outlines the statistical methods and procedures for analyzing data in the study. It includes details on the statistical aspects of the trial design, the criteria for selecting data for analysis, and the procedures for analyzing various data items. It also defines included populations and describes how the results will be presented.

7.5.2. Context and Rationale for Analysis Plan

Describe the inferential data analysis plan and the context or rationale for the choices in this section.

<Text>

Table 11. Primary, Secondary, and Subgroup Analysis Specification

The table below requests the following operational details for each sub-table that reflect the primary and secondary analyses:

Hypothesis: State the hypothesis being tested.

Exposure contrast: State the exposure contrast being evaluated.

Outcome: State the outcome being evaluated.

Analytic software: Name the software being used (include packages, version numbers, etc.).

Model(s): Provide details about the models involved in inferential analyses (e.g., Cox proportional hazards outcome model: followuptime*status(0) = exposure; Logistic regression propensity score model: exposure = COV1 + COV2).

Confounding adjustment method: Check the relevant methods and provide relevant details as prompted in the table.

Missing data methods: Check the relevant methods and provide relevant details as prompted in the table.

Subgroup analysis: Describe plans for analyzing demographic subpopulations as well as clinically relevant subgroups as identified in existing evidence. Include the description of plans for exploratory analyses, as relevant subgroups emerge.

A. Primary Analysis

Hypothesis:	<Text>
Exposure contrast:	<Text>
Outcome:	<Text>
Analytic software:	<Text>
Model(s): *(provide details or code)*	<Text>
Confounding adjustment method	*Name method and provide relevant details, e.g., bivariate, multivariable, propensity score matching (specify matching algorithm ratio and caliper), propensity score weighting (specify weight formula, trimming, truncation), propensity score stratification (specify strata definition), other. Describe the plans to quantitatively assess the performance of the confounding adjustment method (e.g., standardized mean differences in confounders between groups after adjustment).*
	<Text>
Missing data methods	Identify assumed mechanisms of missingness (e.g., missing not at random, missing completely at random) and describe the method by *providing relevant details, e.g., missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other. If possible, quantify the extent of missing data explicitly for key exposure, covariate, and outcome variables.*
	<Text>
Subgroup analyses	*List all subgroups*
	<Text>

B. Secondary Analysis

Hypothesis:	<Text>
Exposure contrast:	<Text>
Outcome:	<Text>
Analytic software:	<Text>
Model(s): *(provide details or code)*	<Text>
Confounding adjustment method	*Name method and provide relevant details, e.g., bivariate, multivariable, propensity score matching (specify matching algorithm ratio and caliper), propensity score weighting (specify weight formula, trimming, truncation), propensity score stratification (specify strata definition), other. Describe the plans to quantitatively assess the performance of the confounding adjustment method (e.g., standardized mean differences in confounders between groups after adjustment).*
	<Text>
Missing data methods	Identify assumed mechanisms of missingness (e.g., missing not at random, missing completely at random) and describe the method by *providing relevant details, e.g., missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other. If possible, quantify the extent of missing data explicitly for key exposure, covariate, and outcome variables.*
	<Text>
Subgroup analyses	*List all subgroups*
	<Text>

Table 12. Sensitivity Analyses – Rationale, Strengths, and Limitations

The table below is used to detail the sensitivity analyses, the rationale for conducting them (in other words, stating what the investigator intends to learn from doing the sensitivity analysis), and any strengths or limitations of the sensitivity analysis relative to the primary analysis. If appropriate, include in this table a sensitivity analysis addressing potential unmeasured confounders (e.g., E-values, quantitative bias analysis).

	What is being varied? How?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary
<Text>	<Text>	<Text>	<Text>	<Text>
<Text>	<Text>	<Text>	<Text>	<Text>

7.6. Data Sources

This section includes structured prompts to state the reasons for selecting the data and the strengths and limitations of the data source(s) with respect to the study objective and capturing inclusion-exclusion criteria, exposure, outcome, covariates, and follow up time. Include context about the potential impact of missing data, information about the data source provenance (e.g., where it came from, how it was collected) and curation (e.g., how it was pre-processed/cleaned), and latency of data (i.e., the longest potential time from an event occurring to that event being represented in the data). This may include a detailed evaluation of the fitness-for-purpose of data source options. Particular attention should be paid to how the proposed data sources reflect expected sites of care for Medicare beneficiaries. Where appropriate, provide references to peer-reviewed literature that used the same RWD source for a similar target study population.

7.6.1. Context and Rationale for Data Sources

Describe the data source(s): <Text>

Reason for selection: <Text>

Strengths of data source(s): <Text>

Limitations of data source(s): <Text>

Data source provenance/curation: <Text>

Table 13. Metadata about Data Sources and Software

The table below requests the following meta-data details:

Data source(s): Provide the name of the data source.

Study period: Provide the calendar time boundaries for data used to create the analysed study dataset, including exposures, inclusion and exclusion criteria, covariates, outcome, and follow-up.

Eligible cohort entry period: Provide the calendar time boundaries during which patients could enter the study population.

Data version (or date of last update): Provide information on the version of the source data. This may be a version number, date of last extract-transform-load (ETL) or other meta-data to identify which version of the data were (or will be) used for the research.

Data sampling/extraction criteria: Provide any data sampling or extraction criteria used to select the cut of data in the database (prior to applying the inclusion or exclusion criteria specific to the study). For example, all patients with a diagnosis of diabetes in any care setting between 2013-2020.

Type(s) of data: Provide the type of data. For example, Medicare data may include Master Beneficiary Summary Files (MBSF), inpatient claims, outpatient claims, carrier claims, and other claims files (e.g., home health agency, hospice, skilled nursing facility, and durable medical equipment), and Part D (prescription drug coverage) files. EHR data may include patient demographics, medical problems, medications, vital signs, smoking status, BMI, immunizations, laboratory data, radiology reports, cardiology and other specialty reports, ambulatory clinic notes, progress reports, admission notes, and discharge summaries (e.g., claims, EHR, registry, labs, pharmacy, patient reported outcomes).

Data linkage: Indicate whether the data will be linked to another data source (and if so, how and provide linkage performance characteristics if available). Details can be provided in an appendix that is referenced in the table.

Conversion to common data model: Indicate whether the data is converted to a common data model and which version (e.g., Sentinel CDM v 8.0.0, OMOP CDM v 6.0).

Software for data management: Name software that is used to manage or maintain the data.

	Data 1	Data 2	Data 3
Data source(s):	<Text>	<Text>	<Text>
Study period:	<Text>	<Text>	<Text>
Eligible cohort entry period:	<Text>	<Text>	<Text>
Data version (or date of last update):	<Text>	<Text>	<Text>
Data sampling/extraction criteria:	<Text>	<Text>	<Text>
Type(s) of data:	<Text>	<Text>	<Text>
Data linkage:	<Text>	<Text>	<Text>
Conversion to common data model (CDM)*:	<Text>	<Text>	<Text>
Software for data management:	<Text>	<Text>	<Text>

7.7. Data Management

Describe the data management procedures used in the study, including procedures, policies, and infrastructure for data storage, transfer, data updates, back up, and information security.

<Text>

7.8. Quality Control

Describe steps to ensure data quality including quality assurance and quality check procedures, double programming, source data verification, validation of endpoints, data transformation and linkages, and assessment of the reliability of the data (e.g., missing or miscoded data, lags in data capture, values out of range, correcting for redundant data, data quality audit programs, data capture consistency through time). Indicate whether the analysts will be blind to the outcome status until after balancing covariates between treatment groups (e.g., propensity score matching).

<Text>

7.9. Study Size and Feasibility

Provide projected study size, precision sought for study estimates or calculation of the sample size that can minimally detect a pre-specified effect size with a pre-specified statistical precision. All assumptions used to calculate the study size or precision of the study should be presented with references and justified (including whether feasibility counts were generated). If applicable, indicate and justify adjustments to sample size due to multiplicity (e.g., hierarchical testing or simultaneous confidence intervals), clustering, and loss of follow-up.

<Text>

Table 14. Power and Sample Size

< Provide table with relevant information >

8. Limitation of the Methods

Discuss potential limitations of the study design, variable identification and measurement, and analytic methods, including issues relating to (unmeasured) confounding, selection bias, misclassification bias, generalizability, and random error. Discuss the steps that will be taken to reduce the potential impact of these limitations, e.g., in terms of design or sensitivity analyses.

<Text>

9. Top Threats to Successful Completion of the Study Objectives

In this section, state the top three threats to the successful completion of the study objectives. Consider all limitations discussed above including, but not limited to, study timeline, enrollment numbers, data sources, and methods. Please list the threats in Table 15, ranked by order of importance, and describe mitigation strategies to address the threats.

Table 15. Threats to Successful Completion of Study Objectives

Rank	Threat	Mitigation strategy
1	<Text>	<Text>
2	<Text>	<Text>
3	<Text>	<Text>

10. Protection of Human Subjects/Governance

Describe the information governance , privacy, and data security provisions that have been established to satisfy Federal privacy and security regulations issued pursuant to the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and codified at *45 CFR Parts 160 and 164 (Subparts A C, & E)*, United States Department of Health and Human Services (HHS) regulations at *42 CFR, Part 2: Confidentiality of Substance Use Disorder Patient and HHS regulations at 45 CFR Part 46*, regarding informed consent for clinical study involving human subjects. If the study is an FDA-regulated clinical investigation, this section should also address compliance with applicable FDA regulations, including 21 CFR Parts 50 and 56.

<Text>

11. Reporting of Adverse Events

If relevant, describe procedures for the collection, management, and reporting of adverse events/adverse reactions (see GVP Module VI) and any new information that might influence the evaluation of the benefit-risk balance of the product in the published report. Arrangements made between marketing authorization holders for the management and reporting of adverse events/reactions in joint post-authorization safety studies should be specified. For studies where reporting is not required, this should be stated. See 21 CFR Part 803 and the FDA website on Exemptions, Variances, and Alternative Forms of Adverse Event Reporting for Medical Devices for more information.

<Text>

12. Applicable Federal Regulations

The major tenets of compliance with the applicable federal regulations on privacy and patient protections are summarized below. Please confirm the statements below or if you prefer you can write your own language for this section.

	Confirm/Agree
Sponsor/investigator attests that the study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals.	☐
Sponsor/Investigator commits to registering this study with ClinicalTrials.gov and to providing a complete final protocol to CMS prior to study initiation.	☐
Sponsor/Investigator commits to sharing data, methods, annotated analytic code, and analytical outputs with CMS or with a CMS-approved third party if asked to do so.	☐
Sponsor/Investigator certifies that this study will comply with all applicable laws regarding subject privacy, including section 165.514 of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and 42 CFR, Part 2: Confidentiality of Substance Use Disorder Patient Records.	☐
Sponsor/Investigator commits to providing final results to CMS and to submit them for publication or to report them in a publicly accessible manner within 12 months of the study's primary completion date.	☐
Sponsor/Investigator commits to reporting the study using a reporting guideline appropriate for the study design and structured to enable replication.	☐
Sponsor/Investigator attests that any facts and statements made in this study or research protocol, or project plan submitted to CMS are complete and accurate. Additionally, all components will have been approved by CMS or other appropriate entities as CMS may determine.	☐
Sponsor/Investigator commits to maintaining data on a HIPAA-compliant server.	☐
Sponsor/Investigator commits to ensuring the integrity, security, and confidentiality of the data by complying with the terms of the agreement and applicable law, including the Privacy Act and HIPAA.	☐
Sponsor/investigator affirms that the data requested in this study is the minimum necessary to achieve the objectives of this study.	☐
Sponsor/Investigator affirms that data files will only be accessible and limited to the minimum necessary approved research personnel. Additionally, all personnel that will have access to the data will undergo HIPAA and or security training for access to sensitive data on the HIPAA-compliant server.	☐

	Confirm/Agree
Sponsor/Investigator certifies that remote login will require login from a personal computer or laptop, VPN authentication, and separate authentication to access the data on the server. Approved personnel may not download data onto their personal computers or laptops. Personal computers or laptops used to access the data will be encrypted, and will have their USB ports disabled, to prevent inadvertent disclosure of data. The server will be backed up regularly, and the backup will be encrypted and stored in a secure location.	☐
Sponsor/Investigator commits to ensuring the security programs, practices, and procedures comply with the HIPAA Security Rule and therefore, in the judgment of CMS and its independent third-party HIPAA auditor, provide a level and scope of security that is not less than the level and scope of security requirements set forth in (a) the Office of Management and Budget Circular No. A-130, Appendix III – Security of Federal Automated Information Resources; (b) Federal Information Processing Standard 200, "Minimum Security Requirements for Federal Information and Information Systems"; and (c) NIST Special Publication 800-53, "Recommended Security Controls for Federal Information Systems and Organizations."	☐
Sponsor/Investigator commits to complying with the CMS cell size suppression policy of not publishing or presenting documents with cells containing values between 1 and 10.	☐
Sponsor/Investigator commits that at the end of this study and any follow-up period permitted under the Data Use Agreements or authorized by CMS in connection with a subsequent study, [Sponsor/investigator] copies of the data files (including both primary and archived files) will be destroyed consistent with National Institute of Standards and Technology (NIST) standards. Per NIH policy, all Medicare data will be retained at sponsor/investigator's research institution for two years following the termination of the study. Once this holding period has expired, sponsor/investigator will destroy all remaining data consistent with NIST standards and will certify the data's destruction to CMS. These procedures are governed by the Sponsor/investigator Data Use and Sharing Agreement.	☐
The sponsor/investigator hereby acknowledges that criminal penalties under §1106(a) of the Social Security Act (42 U.S.C. § 1306(a)), including a fine not exceeding $10,000 or imprisonment not exceeding five years, or both, may apply to disclosures of information that are covered by § 1106 and that are not authorized by regulation or by Federal law. The User further acknowledges that criminal penalties under the Privacy Act (5 U.S.C. § 552a(i)(3)) may apply if it is determined that the Requestor or Custodian, or any individual employed or affiliated therewith, knowingly and willfully obtained the file(s) under false pretenses. Any person found to have violated sec. (i)(3) of the Privacy Act shall be guilty of a misdemeanor and fined not more than $5,000. Finally, the sponsor/investigator acknowledges that criminal penalties may be imposed under 18 U.S.C. § 641 if it is determined that the sponsor/investigator, or any individual employed or affiliated therewith, has taken or converted to his own use data file(s), or received the file(s) knowing that they were stolen or converted. Under such circumstances, they shall be fined under Title 18 or imprisoned not more than 10 years, or both; but if the value of such property does not exceed the sum of $1,000, they shall be fined under Title 18 or imprisoned not more than one year, or both.	☐

13. Protocol Signatures

We, the undersigned, have reviewed and approved the clinical investigation plan specified above and agree on its content.

Sponsor Representative's Signature

_____ _____

Sponsor Representative Name Date (DD, MMM, YYYY)

_____

Sponsor Representative Signature

CMS Representative's Signature

_____ _____

CMS Representative Name Date (DD, MMM, YYYY)

_____

CMS Representative Signature

14. References

Provide a numbered list of references for any works cited in the protocol. Sufficient information must be provided to retrieve the cited work.

<Numbered list >

15. Appendix A. Additional Statistical Considerations

15.1. Directed Acyclical Graph

Develop a directed acyclical graph (DAG) to describe the hypothesized relationship between exposure, covariates, and outcome.

<Figure>

15.2. Interim Analyses and Data Monitoring (As Applicable)

Subsections that are not applicable may be deleted entirely.

15.2.1. Purpose of Interim Analyses

Give a description of the interim analyses, timeline for completion of the interim analyses, and why the interim analyses are to be performed. These interim analyses and planned date of completion should also be listed in the Milestones section. Interim analyses may be due to understanding data completeness, data validation, enrollment assumptions, sample sizes, generalizability, confounding adjustment success, data linkage feasibility/success, etc. The data to be analysed in the interim analyses should be explicitly specified (e.g., baseline data, treatment received, safety).

<Text>

15.2.2. Scope of Adaptations

Give an explicit list of which aspects of the study may be revised at an interim analysis. Document any formal rules governing these adaptations. If an interim Statistical Analysis Plan (SAP) will not be produced, or it is appropriate to document the interim analysis in the main SAP, then specify what analyses, summaries or figures will be used to inform the choice of adaptations.

<Text>

15.2.3. Stopping Rules

Document any formal stopping rules for futility, efficacy, or lack of power. Document the probability of each possible eventuality under the null and alternative hypothesis e.g., the probability of stopping for futility or efficacy, or continuing to the next stage.

<Text>

15.2.4. Analysis Methods to Minimize Bias from Naïve Interim Analysis

It is generally advised to perform a naïve analysis that pools all data at the final analysis as if it were collected in a fixed design. However, this may induce biases in estimation. For example, in group sequential designs the estimate of treatment effects will be biased away from the stopping region; for sample sizes that are revised to reflect the estimated treatment effect at the first interim, the naïve pooled estimate will be biased away from the null. Any known biases must be discussed, and any methods proposed to correct the biases must be documented. It must be stated in advance which analysis will be the primary analysis used in the case of conflicting interpretations and for "headline" reporting of the study.

<Text>

15.2.5. Adjustment of Confidence Intervals and P-Values for Interim Analyses

In a design where formal hypothesis testing is used and the interim analyses provide multiple opportunities to stop for efficacy, the overall study significance level will be greater than nominal significance levels used at each stage. Any stopping rules should adjust for this, and correspondingly any confidence intervals or p-values presented must be calculated to adjust for the possibility of stopping earlier and for having reached the observed stage in the study.

Conversely, a study that only has the option to stop early for futility will conservatively preserve the overall significance level. Here the nominal confidence interval and p-value at the end of the study can be used. Investigations should be made into the effect on the power of the study, and only if the power is substantially reduced should adjustments be used.

Describe how you will adjust confidence intervals and p-values for the possibility of stopping early.

<Text>

15.2.6. Interim Analysis for Sample Size Adjustment

If the sample size is to be adjusted at an interim, specify any rules: for example, conditional power calculations.

The weighting of data from different stages of the study needs to either be set in advance independently of (random) sample sizes or have rules given for how the weighting will be determined. The final analyses must specify how these weightings will be used.

<Text>

15.2.7. Practical Measures to Minimize Bias from Unblinding During Interim Analyses

It is important to establish and control who will have access to what information at each stage of the study. Uncontrolled reporting of interim analyses to study centers could lead to investigators responsible for recruiting subjects to change their desire to recruit to a study, which would induce uncontrollable biases into the subject population. The final analyses could be biased by knowledge of interim results by the analyst. Any level of unblinding, either of individual subjects or of treatment estimates, could induce biases.

Explicitly document:

- Who will perform any interim analysis?
- Who will see any data or analyses at the interim and make decisions?
- What information will be publicly available following an interim analysis?
- What information will be provided to the sponsor and investigators?
- Who will be unblinded at any point in the study?
- Who will perform any final analyses and remain blinded?
- If any safety monitoring decision making will remain isolated from efficacy information?

<Text>

15.2.8. Documentation of Interim Analyses

Snapshots of the data available at each interim analysis should be preserved, as should all documentation of analysis plans, programming code and reporting provided at each interim. It should be possible to recreate the decision process from the study archive in the fullness of time when any limitations of access to information by blinded statisticians become redundant.

Record what documents will be created and stored. Describe how you will take snapshots of data and document analysis plans, etc., at each interim analysis.

<Text>

15.3. Multiple Testing

In a confirmatory study, the choice of sample size will be justified in terms of the power, which focuses on a single analysis, which in turn focuses only on one primary endpoint. This typically means there should only be one primary endpoint.

However, exceptions to this maxim do occur. In such circumstances the most acceptable statistical methodology is to either combine the co-primary endpoints through a deterministic function into a single endpoint or adopt a formal closed-testing procedure that examines a variety of hypotheses in such a way that preserves the overall significance level of the analyses; for example, Bonferroni adjustments of the nominal significance level, or gate-keeping approaches to a pre-specified order of hypothesis tests.

Issues arise if there are:

- more than two treatment groups,
- subset analyses,
- multiple time points,
- multiple methods of analysis,

- sensitivity analyses for missing data.

<Text>

15.4. Statistical Plan Deviations

Define the specific protocol deviations that could impact the analysis (e.g., major deviations and a definition of a major deviation) and specify the methods used to describe and analyze them.

<Text>

15.5. Randomization and Blinding (If Applicable)

If applicable, describe essential components of the randomization and blinding methodology and process in enough detail to enable its reproduction. Include any minimization, stratification, or blocking procedures used to avoid or minimize bias. This section may be copied from the protocol, but it may be necessary to include additional information details, particularly regarding block size. However, in a double-blind study it is not appropriate to include such information in the Statistical Analysis Plan (SAP) but document it within the final study report, in which case document that these details will be provided in the final study report. Document any software packages used to perform the randomization and the method used for retrieving the treatment assignments.

<Text>

16. Appendix B. Data Validation Output

To the extent possible, report the validation of the data used in the study. The Kahn Framework (see Table 1) provides a framework of data quality checks useful for secondary health data use. Two example tables of reporting key study variable distributions by exposure groups are provided below. At a minimum, data validation and quality checks will be expected as part of the interim analysis.

<Text>

Table 16. Example of Continuous Variable Data Validation Output, Adjust as Needed.

Exposure group name(s)	Continuous variable	% of study population missing variable	Minimum	Median	Mean	Standard deviation	Maximum
Device A	Age	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>
Comparator	Age	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>
Device A	Income	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>
Comparator	Income	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>
Device A	…	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>
Comparator	…	<Text>	<Text>	<Text>	<Text>	<Text>	<Text>

Table 17. Example of Categorical Variable Data Validation Output. These are Example Categorical Variables and Groups, Adjust as Needed.

Categorical variable	Group	Count in exposure group	% in exposure group	Count in comparator group	% in comparator group
Sex	Female	<Text>	<Text>	<Text>	<Text>
Sex	Male	<Text>	<Text>	<Text>	<Text>
Sex	Missing	<Text>	<Text>	<Text>	<Text>
Race	American Indian or Alaska Native	<Text>	<Text>	<Text>	<Text>
Race	Asian	<Text>	<Text>	<Text>	<Text>

Categorical variable	Group	Count in exposure group	% in exposure group	Count in comparator group	% in comparator group
Race	Black or African American	<Text>	<Text>	<Text>	<Text>
Race	Native Hawaiian or Pacific Islander	<Text>	<Text>	<Text>	<Text>
Race	White	<Text>	<Text>	<Text>	<Text>
Race	Identify with more than one race	<Text>	<Text>	<Text>	<Text>
Race	Missing	<Text>	<Text>	<Text>	<Text>
…	<Text>	<Text>	<Text>	<Text>	<Text>

17. Appendix C. Data Use Agreement

If applicable and permissible, provide the appropriate data use agreements. This is the agreement between the study sponsor and data vendor. In many cases, this may be "boiler plate" language created by the data vendor.

<Text>

18. Appendix D. Data Dictionary

If applicable, provide a data dictionary for the fields used in the analysis. As an example, please see: https://www.ahrq.gov/research/findings/final-reports/ssi/ssiapc.html

<Text>

19. Appendix E. Value Sets

If applicable, provide the value sets used in the analysis and reference source.

<Text>