Retrospective RWE Study Protocol

Cover Page

Study Identifier: *(Should match identifier from RPD)*	Protocol Version: 1 Initial	Protocol Date: July 26, 2019
Research Project Title:	**Incidence and risk of heart failure in patients following metal-on-metal (MoM) hip arthroplasty**	
Short Title:		
Study Champion *(one person's Name)*:		
Study Champion Function *(select from drop-down list):*	Others	
If Other was selected, *please specify:*	**Medical Safety**	
Functional Head *(one person's Name)*:		
Segment *(select from drop-down list):*	Click here for list	
Championing Sector *(select from drop-down list):*	Franchise	
If Regional is checked (*select from drop-down list*):	Click here for list	
Platform or Specialty (*select from drop-down list*):	Joint Reconstruction	
Products: *(enter NA if not applicable)*	NA	

Project Team Information

Internal Research Team *(select from drop-down list):*	MD-EPI
External Service Provider (ESP) *(select from drop-down list):*	No
If Yes, Name of ESP*:*	
Provide names of the following contributors:	
Research Collaborator (Provide Name & Function)**:**	
Primary Programmer/Analyst:	
Biostatistician:	
Other Design Input:	
Protocol Classification *(select from drop-down list):*	Low Risk

Note: Higher-Risk protocol-based studies are those that assess outcomes related to Johnson & Johnson (JJ) branded products (comparative or non-comparative), compare outcomes related to interventions or technologies, and/or are generate evidence for regulatory activities (e.g., seeking a claim or indication)

Table of Contents

1. Protocol Synopsis

Title	Incidence and risk of heart failure in patients following metal-on-metal (MoM) hip arthroplasty
Study Objectives	Co-Primary: To estimate the incidence and evaluate the risk of heart failure among patients undergoing MoM arthroplasties of the hip compared with those with alternative types of arthroplasties (non-MoM) Co-Primary: To estimate the incidence and evaluate the risk of heart failure among patients undergoing MoM arthroplasties of the hip compared with age and gender similar Osteoarthritis (OA) cohort without arthroplasty
Data Sources	Medicare SAF
Study Design	Retrospective Cohort Study
Study Population	Patients are eligible if they are (1) $\geq$ 65 years, (2) undergo an elective, primary total hip arthroplasty (THA) performed in the inpatient setting between October 1, 2005, and December 31, 2017 (index procedure), and (3) enrolled in the data source for at least 365 days prior to index procedure (baseline period). Patient exclusions include a diagnosis of heart failure, THA/TKA arthroplasty, or metal implants during the baseline period or concurrent diagnosis of hip fracture during the index THA procedure.
Endpoints	$\geq$ 2 recorded Heart Failure-related diagnosis codes
Data Analyses	Descriptive statistics on baseline characteristics with comparison between exposure groups; Unadjusted incidence rate for heart failure; Propensity scores; Cox Regression to determine HRs with 95% CI

2. List of Abbreviations

Abbreviation	Definition
TKA	Total Knee Arthroplasty
THA	Total Hip Arthroplasty
MoM	Metal-on-Metal
HR	Hazard Ratio
CI	Confidence Interval
RA	Rheumatoid Arthritis
DMARDS	Disease-modifying antirheumatic drugs
OA	Osteoarthritis

3. Rationale and Background

It is estimated that the incidence of joint replacement is over 1 million total hip and total knee replacement procedures each year in the United States.[1] With the aging of the "baby boomers," higher rates of diagnosis and treatment of advanced arthritis, and growing demand for improved mobility and

quality of life, the annual procedure volumes are projected to increase considerably in the future, making joint replacements the most common elective surgical procedures in the coming decades.[2,3] The prevalence of total hip replacement in the United States was projected by Kremers et al in a 2015 publication.[4] The authors reported the 2010 prevalence of total hip replacement in the U.S. population was 0.83% for the overall population and 2.34% in those 50 years of age and older. The prevalence of hip replacement was higher among women (0.93%) than among men (0.72%) and increased with age, reaching 1.49%, 3.25%, and 5.26% at sixty, seventy, and eighty years, respectively. These estimates corresponded to 2.5 million individuals (1.4 million women and 1.1 million men) with total hip replacement in 2010.

A study published by Gillam et al.[5] in 2017 described a retrospective cohort study using data from the Australian Government Department of Veterans' Affairs health claims database on patients who received conventional THA for osteoarthritis between 2004 and 2012. The MoM THAs were classified into groups: Articular Surface Replacement (ASR) XL Acetabular System, other large-head (LH) (> 32 mm) MoM, and small-head (SH) (≤ 32 mm) MoM. The primary outcome was hospitalization for heart failure after THA and included 4,019 patients with no history of heart failure (56% women). Men with an ASR XL THA had a higher rate of hospitalization for heart failure than men with MoP THA (hazard ratio (HR) = 3.2, 95% CI: 1.6–6.5). No statistically significant difference in the rate of heart failure was found with the other LH MoM or SH MoM compared to MoP in men. There was no statistically significant difference in heart failure rate between exposure groups in women.

Another study published by in January of 2018[6] described a linkage study between the National Joint Registry, Hospital Episodes Statistics and records of the Office for National Statistics on deaths. Patients who underwent elective total hip arthroplasty between January 2003 and December 2014 with no past history of cardiac failure were included and stratified as having either a MoM (n = 53 529) or a non-MoM (n = 482 247) arthroplasty. The primary outcome measure was the time to an admission to hospital for cardiac failure or death. Analysis was carried out using data from all patients and from those matched by propensity score. The risk of cardiac failure was lower in the MoM cohort compared with the non-MoM cohort (adjusted hazard ratio (aHR) 0.901; 95% confidence interval (CI) 0.853 to 0.953). The risk of cardiac failure was similar following matching (aHR 0.909; 95% CI 0.838 to 0.987) and the findings were consistent in subgroup analysis.

Goodnough et.al. published a study[7] designed to compare the rate of onset of new cardiac symptoms in patients who have undergone MoM THA with those who have undergone metal-on-polyethylene (MoP) THA. Data from the Medicare Standard Analytics Files database for patients who underwent MoM THA between 2005 and 2012 was used. Bearing surface was selected using International Classification of Diseases ninth revision codes. Patients with a minimum five-year follow-up were selected. An age and gender-matched cohort of patients, who underwent MoP THA served as a comparison group. New diagnoses of cardiac disease including congestive heart failure were collected during the follow-up period. We identified 29 483 patients who underwent MoM THA and 24 175 matched patients who underwent MoP THA. Both groups had a mean Charlson comorbidity index score of 4. There were no statistically significant differences in 30 of 31 pre-existing comorbidities. Patients undergoing MoM THA had a slightly lower incidence of cardiac failure compared with those undergoing MoP THA at three years (6.60% versus 7.06%, odds ratio (OR) 0.93, 95% confidence interval (CI) 0.87 to 0.99) and four years (8.73% versus 9.49%, OR 0.91, 95% CI 0.86 to 0.97) postoperatively, with no difference in the incidence of new cardiac failure in between the groups at five years. There was no statistically significant difference in the incidence of arrhythmia, myocardial infarction and cardiomyopathy at any time between the two groups.

This study is being executed to elucidate the association between MoM vs non-MoM hip arthroplasties on subsequent diagnosis of heart failure. This study is device-agnostic in that all MoM and non-MoM devices, regardless of manufacturer, are being included.

4. Research Questions and Objectives

4.1 Research Question

Are patients with Metal-on-Metal arthroplasties of the hip at an increased risk of developing heart failure?

4.2 Research Objectives

4.2.1 Primary objective(s):

- To estimate the incidence and evaluate the risk of heart failure among patients undergoing MoM arthroplasties of the hip compared with those with alternative types of arthroplasties (non-MoM)
- To estimate the incidence and evaluate the risk of heart failure among patients undergoing MoM arthroplasties of the hip compared with an age and gender similar Osteoarthritis cohort without arthroplasty

4.2.2 Secondary objective(s):

- To describe and compare the baseline characteristics of the exposure groups and to identify important prognostic variables that should be balanced between the exposure groups and which should be included in the propensity score of the primary analysis.

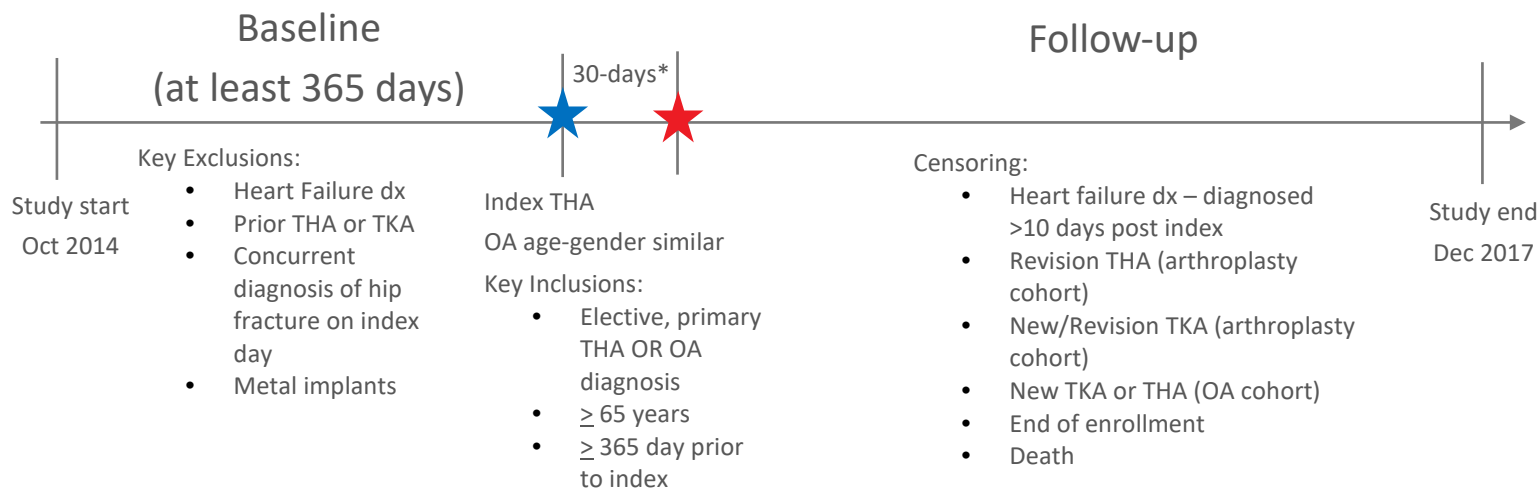
5. Research Methods

5.1 Data Source

The Medicare Database (Medicare SAF) captures the majority of the US population age 65 or older. The limited dataset that will be utilized for this analysis includes Medicare Part A and Part B claims which captures Fee-for-Service. Medicare Advantage Patients are not captured. Medicare Part A captures inpatient hospital visits and related claims including diagnosis (ICD-9), procedures, Medicare Severity Diagnosis Related Group (MS-DRG), dates of service, hospital provider number, and beneficiary demographic information. Medicare Part B is available for institutional outpatient providers only. Examples of institutional outpatient providers include hospital outpatient departments, rural health clinics, renal dialysis facilities, outpatient rehabilitation facilities, comprehensive outpatient rehabilitation facilities, and community mental health centers. Available data elements include diagnosis (ICD-9), Healthcare Common Procedure Coding System (HCPCS), dates of service, outpatient provider number, revenue center codes, and beneficiary demographic information. Once an individual enrolls in Medicare they generally remain enrolled until death; hence, this database is robust for longitudinal studies.

5.2 Study Design

This is a retrospective cohort study of patients undergoing total hip arthroplasty or have a diagnosis of OA without arthroplasty and meeting the inclusion and exclusion criteria between October 1, 2004, and June 30, 2018 (study period). The enrollment period (identification of index date) is between October 1, 2005 and December 31, 2017. The identified patients are longitudinally followed until a diagnosis of heart failure, THA revision (arthroplasty cohort only), new total knee arthroplasty (TKA) or THA, end of enrollment, death, or end of the study, whichever occurs first. The graphic below provides a visual representation of the study design.



*Heart failure diagnosed within 30-days of index date will be excluded to prevent cases of iatrogenic fluid overload due to the surgical procedure

5.2.1 Inclusion criteria

THA patients must meet ALL the following criteria to be included in study:

- Elective, primary THA performed in inpatient setting (first occurrence is the index date)
- ≥ 65 years
- Enrolled in the data source for at least 365 days prior to index procedure (baseline period)

Age and gender-similar OA patients must meet ALL the following criteria to be included in study:

- ≥ 2 recorded OA-related diagnosis codes:
  - Code list
- ≥ 65 years
- Enrolled in the data source for at least 365 days prior index procedure (baseline period)

5.2.2 Exclusion criteria

THA patients meeting any of the following during the 365-day baseline period will be excluded from the study:

- Diagnosis code for acute or chronic heart failure
- TKA or THA surgery (primary or revision)
- Concurrent (with index procedure) diagnosis of hip fracture

Age and gender-similar OA patients meeting any of the following during the 365-day baseline period will be excluded from the study:

- Diagnosis of acute or chronic heart failure
- TKA or THA surgery (primary or revision)
- Arthroscopic surgery

Exclusions for both study groups:

- Patients who have enrolled in Medicare due to disability
- Patients who have enrolled in Medicare due to end stage renal disease (ESRD)
- Patients enrolled in a HMO

- Patients with an orthopedic procedure requiring metal implants (e.g. knee, hip, shoulder, trauma plates, and spine) during baseline period

5.3 Variables

Final code lists for all variables will be included in the study report.

5.3.1 Primary Independent Variable(s) – Exposure Groups

- Group 1: Metal-on-Metal total hip arthroplasty
  - ICD-9: 00.75, hip bearing surface, metal-on-metal
  - ICD-10 Codes:
    - 0SRR01Z, Replacement of Right Hip Joint, Femoral Surface with Metal Synthetic Substitute, Open Approach
    - 0SRS01Z, Replacement of Left Hip Joint, Femoral Surface with Metal Synthetic Substitute, Open Approach
    - 0SRS019, Replacement of Left Hip Joint, Femoral Surface with Metal Synthetic Substitute, Cemented, Open Approach
    - 0SRS01A, Replacement of Left Hip Joint, Femoral Surface with Metal Synthetic Substitute, Uncemented, Open Approach
- Group 2: Non-Metal-on-Metal total hip arthroplasty
  - ICD-9 Codes
    - 00.74, hip bearing surface, metal-on-polyethylene (MoP)
    - 00.76, hip bearing surface, ceramic-on-ceramic (CoC)
    - 00.77, hip bearing surface, ceramic-on-polyethylene (CoP)
  - ICD-10 Codes:
    - 0SRR03Z, Replacement of Right Hip Joint, Femoral Surface with Ceramic Synthetic Substitute, Open Approach
    - 0SRS03Z, Replacement of Left Hip Joint, Femoral Surface with Ceramic Synthetic Substitute, Open Approach
    - 0SRS039, Replacement of Left Hip Joint, Femoral Surface with Ceramic Synthetic Substitute, Cemented, Open Approach
    - 0SRS03A, Replacement of Left Hip Joint, Femoral Surface with Ceramic Synthetic Substitute, Uncemented, Open Approach
- Age and gender-similar OA patients

Introduced in October 2005, ICD-9 bearing surface code identifiers (00.74 for Metal on p, 00.75 for M-M, 00.76 for C-C, 00.77 C-PE) are optional modifiers that can be reported in conjunction with the primary procedure code for total hip arthroplasty. A limitation on this data is that it has been shown to have both under-coding and misclassification when coded.

5.3.2 Subgroup/Stratification Variable(s)

- N/A

5.3.2.1 Patient Demographics

- Age at index
- Gender
- Race
- Calendar year
- Geographic region
- Insurance type
- BMI

5.3.2.2 Procedural Characteristics

- Year of index date
- Hospital length of stay (days)
- Medicare Severity Diagnosis Related Groups (MS-DRG) (Major Complication/Comorbidity, Complication/Comorbidity, No Complication/Comorbidity)

5.3.2.3 Patient Clinical Characteristics

- Deyo-Charlson Comorbidity Index (CCI): the CCI is an aggregate measure of comorbidity created by using select diagnoses associated with chronic disease (e.g., heart disease, cancer). Higher scores are indicative of greater comorbid burden. The CCI includes 19 medical conditions and weights these conditions from +1 to +6.
- Elixhauser comorbidity system: the Elixhauser comorbidity system is a set of 30 comorbidity indicators that is used for adjustment of comorbidity in observational studies. Van Walraven and colleagues developed a summary score for the Elixhauser comorbidities by modeling in-hospital mortality with inpatient admission data. The summary score is a weighted combination of the 30 Elixhauser comorbidities, where a larger comorbidity weight indicates a stronger association between the comorbidity and in-hospital mortality.
- Medicare Enrollment State Buy-In Status (Yes/No)
- Individual Elixhauser and Charlson comorbidity categories:
  - Specific CV comorbidities: dyslipidemia, hypertension, diabetes, peripheral vascular disease, TIA and obesity
- Other comorbidities that have been associated with increased mortality such as: chronic obstructive pulmonary disease, obstructive sleep apnea, cardiac arrhythmias, HIV, and cancer
- Rheumatoid Arthritis, Psoriatic Arthritis, Osteoporosis and Osteopenia
- Dislocation and instability – post index
- Metalosis – post index

5.3.2.4 Hospital & Provider Characteristics

- Hospital arthroplasty procedure volume for the specific arthroplasty type during BASELINE
- Surgeon arthroplasty procedure volume for the specific arthroplasty type during BASELINE
- Hospital: Bed size
- Hospital: Teaching status
- Hospital: Rural vs urban

5.3.3 Outcome(s) or Dependent Variable(s)

5.3.3.1 Outcomes for Primary Objective(s) – Primary Endpoint

- Heart failure cases diagnosed in the first 30-days post implantation (index date) will be excluded to prevent including cases of iatrogenic fluid overload due to the surgical procedure
- ≥ 2 recorded acute heart failure-related diagnosis codes

ICD-9-CM Code	*Code Description*
428.0	Congestive heart failure, unspecified
428.1	Left heart failure
428.20	Systolic heart failure, unspecified
428.21	Systolic heart failure, acute
428.23	Systolic heart failure, acute on chronic
428.30	Diastolic heart failure, unspecified
428.31	Diastolic heart failure, acute
428.33	Diastolic heart failure, acute on chronic

428.40	Combine systolic and diastolic heart failure, unspecified
428.41	Combine systolic and diastolic heart failure, acute
428.43	Combine systolic and diastolic heart failure, acute on chronic
428.9	Heart failure, unspecified

ICD-10-CM Code	***Code Description***
I50.20	Unspecified systolic (congestive) heart failure
I50.21	Acute systolic (congestive) heart failure
I50.23	Acute on chronic systolic (congestive) heart failure
I50.30	Unspecified diastolic (congestive) heart failure
I50.31	Acute diastolic (congestive) heart failure
I50.33	Acute on chronic diastolic (congestive) heart failure
I50.81	Right heart failure
I50.83	High output heart failure
I50.89	Other heart failure
I50.84	End stage heart failure
I50.82	Biventricular heart failure
I50.9	Heart failure, unspecified
I50.4	Combined systolic (congestive) and diastolic (congestive) heart failure
I11.0	Hypertensive heart disease with heart failure
I13.2	Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease
I13.0	Hypertensive heart and chronic kidney disease with heart failure and stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease

5.3.3.2 Outcomes for Primary Objective(s) – Secondary Endpoint

- Heart failure cases diagnosed in the first 30-days post implantation (index date) will be excluded to prevent including cases of iatrogenic fluid overload due to the surgical procedure
- ≥ 2 recorded acute or chronic heart failure-related diagnosis codes

ICD-9-CM Code	***Code Description***
428.0	Congestive heart failure, unspecified
428.1	Left heart failure
428.20	Systolic heart failure, unspecified
428.21	Systolic heart failure, acute
428.22	Systolic heart failure, chronic
428.23	Systolic heart failure, acute on chronic
428.30	Diastolic heart failure, unspecified
428.31	Diastolic heart failure, acute
428.32	Diastolic heart failure, chronic
428.33	Diastolic heart failure, acute on chronic
428.40	Combine systolic and diastolic heart failure, unspecified
428.41	Combine systolic and diastolic heart failure, acute
428.42	Combine systolic and diastolic heart failure, chronic
428.43	Combine systolic and diastolic heart failure, acute on chronic
428.9	Heart failure, unspecified

ICD-10-CM Code	*Code Description*
I50.20	Unspecified systolic (congestive) heart failure
I50.21	Acute systolic (congestive) heart failure
I50.22	Chronic systolic (congestive) heart failure
I50.23	Acute on chronic systolic (congestive) heart failure
I50.30	Unspecified diastolic (congestive) heart failure
I50.31	Acute diastolic (congestive) heart failure
I50.32	Chronic diastolic (congestive) heart failure
I50.33	Acute on chronic diastolic (congestive) heart failure
I50.81	Right heart failure
I50.83	High output heart failure
I50.89	Other heart failure
I50.84	End stage heart failure
I50.82	Biventricular heart failure
I50.9	Heart failure, unspecified
I50.4	Combined systolic (congestive) and diastolic (congestive) heart failure
I11.0	Hypertensive heart disease with heart failure
I13.2	Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease
I13.0	Hypertensive heart and chronic kidney disease with heart failure and stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease

5.3.3.3 Outcomes for Secondary Objective(s)

- Variables noted in sections above

5.3.3.4 Other Variables

N/A

5.3.4 Sample Size and Study Power

A previous analysis of the Medicare SAF database identified 18,521 patients with MoM hip implants between 2005 and 2015.

5.4 Data Analysis(es)

The goals of these analyses are to: 1) determine the characteristics of patients implanted with MoM and non-MOM hip implants and OA patients with arthroplasty, and 2) evaluate the risk of heart failure among patients with MoM implants compared to non-MOM implants or OA without arthroplasty.

5.4.1 Descriptive Statistics

Descriptive statistics will be calculated for both study cohorts. Categorical variables will be summarized by frequencies and proportions, and continuous variables will be summarized by means and standard deviations or medians and interquartile ranges. Differences between study cohorts will be assessed using Chi-square tests for categorical data and t-tests or Wilcoxon rank-sum tests for continuous data, as indicated.

5.4.2 Incidence Rate of Heart Failure

The number of new cases of heart failure will be determined. Person-time for each patient will be calculated from 30 days after index date to the first diagnosis code of heart failure (at-risk time interval). The incidence rate of heart failure will be determined for each study cohort as the number of new cases of heart failure during the observation period divided by the total person-time of observation among the patients at risk. The results will be reported as a point estimate (in cases/1000 person-years) and

95% CI. Confidence intervals will be based on asymptotic theory assuming the outcome follows a Poisson distribution.

5.4.3 Risk of Heart Failure Associated with MoM Implants

Cox proportional hazards regression will be performed to determine HRs of heart failure with 95% Cis in MoM implants versus non-MOM implant and MoM implants versus RA patients without arthroplasty. Propensity score matching or stratification will be used to control for confounding.

If a significantly higher risk of heart failure is identified for patients with MoM implants, Cox proportional hazards regression will be conducted to determine risk factors for a diagnosis of heart failure.

5.4.4 Sensitivity Analyses

- Limit outcome to hospitalization for heart failure
- Stratification by ICD-9 and ICD-10 codes (ICD-10 codes may be improved for ascertaining both MoM prostheses use and for heart failure as compare to ICD-9 codes)
- Stratification for non-MoM comparison (exclude MoP from the comparator group)

5.5 Quality Control

The study will be completed per the quality control guidance adopted by the individual/ champion evidence generation functions.

5.6 Limitations of the Research Methods

As with any database study, identification of medical events, such as heart failure or co-morbidities, is limited to data that are captured as part of the medical record or claims, which are not primarily collected for research purposes, and will rely on appropriate diagnostic codes to detect these events. Misclassification bias can result if study patients are not categorized correctly with regards to exposure or outcome. Limited patient follow-up time will hinder our ability to study the long-term risk of heart failure. The study results will be generalizable to patients meeting the inclusion and exclusion criteria.

6. Protecting the Confidentiality of the Data Obtained

Confidentiality of patient records will be maintained at all times. All study reports will contain aggregate data only and will not identify individual patients or physicians. At no time during the study will the Johnson & Johnson MD company receive patient identifying information except when required by law.

7. Management and Reporting of Complaints and Adverse Events

In this study, potential product complaints or safety signals cannot or will not be identified. Thus, the minimum criteria for reporting a product complaint or adverse event (i.e., suspect device manufacturer and event) will not be met.

8. Plans for Disseminating and Communicating Study Results

A final report will be created from study results which may be considered for publication in a peer reviewed publication according to the J&J Publication Policy.

9. References

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10. Appendices

1. Appendix I [Text goes here]
2. Appendix II [Text goes here]
3. Appendix III [Text goes here]
4. etc.

11. Major Amendments

#	Date	Section of study protocol	Amendment or update	Reason
1				
2				
3				

12. Project Milestones

This is illustrative. Please revise based on study timelines.

Task Name	Time to Completion (in weeks)
Develop JJ-format protocol	3 weeks from finalization of research proposal
Receive feedback from Stakeholder	1 week after provision of draft protocol
Finalize Protocol	1 week after receiving feedback from Stakeholder
Finalize Data Specification and Attrition File	1 week after finalization of protocol
Provide Patient Attrition Flow and Counts	1 week after finalization of data specification file
Build analytic file	6 weeks after attrition flow
Conduct analyses	Descriptive analyses: 2 weeks after completion of analytical file Multivariate analyses: 4 weeks after completion of analytical file
Prepare final report	Final report: 3 weeks after completion of analyses
Total Timeline till Final Report	**20 weeks from finalization of research proposal**
Additional Tasks	
Prepare abstract for conference submission	TBD based on timing of selected conference
Develop conference presentation or poster	TBD based on timing of selected conference
Prepare Journal Manuscript	TBD