Investigator Statement and Signature Page

Title: Post-Market Surveillance Study of the Wright Medical Technology Metal-on-Metal Total Hip System
Clinical Protocol Number: 11-LJH-001
Version: 1.1
Revision Date: 16Nov2017

I, _____, have read and understood the following study protocol and agree to conduct this study in accordance with the study protocol, all applicable regulations, all state and local laws, and in accordance with any applicable patient privacy laws.

Print Name: _____

Signature: _____

Date: _____

Post-Market Surveillance Study of the Wright Medical Technology Metal-on-Metal Total Hip System

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Version: 1.1
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I. ABBREVIATIONS/TERMINOLOGY

ADE – Adverse Device Effect

AE – Adverse Event

ALTR – Adverse Local Tissue Reaction

ALVAL – Aseptic Lymphocytic Vasculitis-Associated Lesions

IRB/EC – Institutional Review Board/Ethics Committee

EDC – electronic data capture system

FDA – Food and Drug Administration

HOOS - Hip disability and Osteoarthritis Outcome Score

ISO – International Organization for Standardization

MARS – Metal artifact reduction sequence

MoM – Metal-on-Metal

MPO – MicroPort Orthopedics Inc.

MRI – Magnetic resonance imaging

SADE – Serious Adverse Device Effect

SAE – Serious Adverse Event

THA – Total Hip Arthroplasty

UADE – Unanticipated Adverse Device Effect

USADE – Unanticipated Serious Adverse Device Effect

WMT – Wright Medical Technology Inc.

II. CLINCIAL PROTOCOL SYNOPSIS

Study Title	Post-Market Surveillance Study of the Wright Medical Technology Metal-on-Metal Total Hip System
Study Number/Revision	11-LJH-001 Ver.1.1
Study Type	Cross-sectional, multicenter study
No. Investigational Sites	Target 5 sites, with up to 7 sites total, for enrollment
Study Groups	**Group 1:** Subjects previously implanted with components of the Wright Medical Technology (WMT) Metal-on-Metal (MoM) Total Hip Arthroplasty (THA) System **Group 2:** Control, non-implanted subjects
No. Subjects	255 THAs (Group 1: 155 THAs, Group 2: 100 controls)
Follow-Up Schedule	**Group 1:** Subjects will be evaluated, during a single study visit, with a functional assessment (HOOS Score), an Environmental Assessment, past medical history, whole blood and serum cobalt and chromium metal ion levels, and MARS MRI. An additional 1-year Follow-Up Visit will be required *only* for subjects who were diagnosed with Adverse Local Tissue Reaction (ALTR) at the first study visit. If an ALTR subject has not undergone a revision of the enrolled hip prior to the end of the one-year period, they will be re-evaluated with the Hip disability and Osteoarthritis Outcome Score (HOOS), whole blood and serum cobalt and chromium metal ion levels, Metal artifact reduction sequence (MARS) MRI, and adverse event assessment during this additional study visit. **Group 2:** Subjects will be evaluated with an Environmental Assessment, past medical history, and whole blood and serum metal ion levels.
Subject Cross-sectioning	Subjects in **Group 1** previously implanted between 4 and 8 years prior to the study start date will be identified from Investigator records. Collected data will be evaluated in aggregate and cross-sectioned by year of implantation. Subjects will be cross-sectioned by the time that has elapsed between implantation and the initial visit (e.g. 4 years, 5 years) using contiguous visit windows (number of years $\pm$ 6 months). There will be 15 THAs collected for the Year 4 intervals and 35 THAs collected for the remaining intervals.
Primary Objective	The primary objective of the study is to determine the incidence of adverse local tissue reactions (ALTR) in each THA implanted with the WMT MoM THA System overall and for yearly cross-section interval from 4-year to 8-year post implant.
Secondary Objectives	The secondary objectives include: ▪ To determine whole blood and serum cobalt and chromium metal ion levels for subjects implanted with the WMT MoM THA System overall and for each defined cross-section interval ▪ To estimate baseline whole blood and serum cobalt and chromium metal ion levels for subjects not implanted with any metal implants, and compare the cobalt and chromium metal ion levels between the implanted subjects and controls (Group-1 vs. Group-2 subjects). ▪ To compare functional outcomes, as assessed by HOOS score, of subjects implanted with the WMT MoM THA System overall and for each defined cross-section interval in with and without ALTR (Group-1 subjects). ▪ To compare cobalt and chromium metal ion levels in subjects with and without confirmed ALTR (Group-1 subjects)

Inclusion Criteria	To be included in **Group 1**, subjects must meet all of the following criteria: 1. Has been implanted with appropriate components of the WMT MOM THA System for at least four years +/- six months (i.e., 3.5 years since implantation), but not longer than eight years and six months (i.e., 8.5 years since implantation) 2. Has previously undergone primary THA for any of the following: a. non-inflammatory degenerative joint disease including osteoarthritis, traumatic arthritis, or avascular necrosis; b. inflammatory degenerative joint disease including rheumatoid arthritis; c. correction of functional deformity. 3. Is willing and able to complete required study visit(s) and assessments 4. Plans to be available for the required study visit 5. Is capable of providing sufficient blood for sampling according to blood draw procedures 6. Is willing to sign the approved Informed Consent document Previously implanted bilateral subjects can have both THAs enrolled in the study provided: 1) the specified combination of components were implanted in both, 2) all other aspects of the Inclusion/Exclusion Criteria are satisfied, 3) enrollment does not exceed the subject count specified in the Clinical Trial Agreement and protocol enrollment strategy, and 4) the subject agrees to a second Informed Consent document and data collection specific to the second THA. Enrollment and treatment of a previously unimplanted hip is not permitted in this study. To be included in **Group 2**, subjects must meet all of the following criteria: 1. Does not have a metal implant (total hip, total knee, spinal, etc.) with the exception of dental implants 2. Is not an employee of the Investigator 3. Is willing and able to provide Informed Consent document 4. Is willing and able to attend the requested study visit(s) and assessments 5. Is capable of providing sufficient blood for sampling according to blood draw procedures
Exclusion Criteria	Subjects will be excluded from either study group if they meet any of the following criteria: 1. Subject is currently enrolled in another clinical investigation which could affect the endpoints of this protocol 2. Subject is unwilling or unable to sign the Informed Consent document 3. Subject has documented substance abuse issues 4. Subject has an emotional or neurological condition that would pre-empt their ability or willingness to participate in the study 5. Subject is currently incarcerated or has impending incarceration 6. **Group 1 only:** Subject has a condition or previously implanted medical device that contraindicates MRI (e.g. pacemaker, implantable defibrillator) 7. **Group 1 only:** Subject was skeletally immature (less than 21 years of age) at time of implantation

III. SCHEDULE OF EVENTS

The schedule of events for Study Groups 1 and 2 are shown in Tables 1 and 2, respectively.

Table 1. Schedule of events for Group 1

Event	**Study Visit + 4 weeks* (Visit 1)**	**1 year Follow-up Visit + 4 weeks, as needed[#] (Visit 2)**
Informed Consent	X	
Inclusion/Exclusion	X	
Medical History/Concomitant Medications	X	
Demographics	X	
Environmental Assessment	X	
Operative Information	X	
Device Information	X	
HOOS functional Scores	X	X
Blood Draw	X	X
MARS MRI	X	X
Adverse Event Assessment	X	X
Study Completion	X	

*The duration of subject participation will be limited to a single study visit (Visit 1) with multiple study activities. If all activities cannot be completed during the single visit due to scheduling logistics, subjects may have up to 4 weeks to complete the remaining activities.

[#]An additional 1-year Follow-up Visit (Visit 2) will be required *only* for subjects who were diagnosed with ALTR at Visit 1. Subjects diagnosed with ALTR will remain enrolled in the study for up to one year following Visit 1 or until revised, whichever comes first. If a subject has not undergone a revision of the enrolled hip prior to the end of the one-year period, they will be re-evaluated with the HOOS, whole blood and serum metal ion levels, MARS MRI, and adverse event assessment during this additional study visit. Subjects may have up to 4 weeks to complete the remaining activities due to scheduling logistics.

Table 2. Schedule of events for Group 2

Event	**Study Visit + 4 weeks* (Visit 1)**
Informed Consent	X
Inclusion/Exclusion	X
Medical History/Concomitant Medications	X
Demographics	X
Environmental Assessment	X
Blood Draw	X
Adverse Event Assessment	X
Study Completion	X

*The duration of subject participation will be limited to a single study visit (Visit 1) with multiple study activities. If all activities cannot be completed during the single visit due to scheduling logistics, subjects may have up to 4 weeks to complete the remaining activities.

IV. INTRODUCTION

This study is being initiated in response to the Food and Drug Administration (FDA) call to all manufacturers with 510(k) clearance for metal-on-metal (MoM) total hip arthroplasty (THA) devices to conduct postmarket surveillance studies. MicroPort has various acetabular shells, acetabular liners, fixation screws, femoral heads, femoral stems, modular necks, and proximal bodies currently cleared for MoM indications. Together these components comprise the Wright Medical Technology (WMT) MoM THA System. The primary objective of the study is to determine the incidence of adverse local tissue reactions (ALTR) in each THA implanted with the WMT MoM THA System overall and for each yearly cross-section from 4-year to 8-year post implant.

V. STUDY PURPOSE

Under Section 522 of the Federal Food, Drug, and Cosmetic Act, the FDA is authorized to "require manufacturers to conduct postmarket surveillance of any class II or class III devices meeting any of the following criteria: (1) its failure would be reasonably likely to have serious adverse health consequences; (2) it is expected to have significant use in pediatric populations; (3) it is intended to be implanted in the body for more than one year; or (4) it is intended to be a life-sustaining or life-supporting device used outside a device user facility."

FDA has used this authority to require all manufacturers of MoM THA devices, including MicroPort, to investigate these devices in a post-marketing surveillance setting. FDA has determined that "failure of these devices would be reasonably likely to cause pain, dislocation, or device loosening, leading to revision (any secondary surgical procedure), which would meet the definition of 'serious adverse health consequences.' In addition, since it is a permanent implant, it is intended to be implanted in the body for more than one year." These orders center on FDA's concern that "high ion concentrations of cobalt and chromium may be related to increased rates of adverse events."

To address these concerns, MicroPort will conduct a cross-sectional, multicenter investigation in accordance with the recommendations made by FDA in its call for these studies dated May 6, 2011. The primary objective of the study is to determine the incidence of adverse local tissue reactions (ALTR) in each THA implanted with the WMT MoM THA System overall and for each yearly cross-section from 4-year to 8-year post implant.

VI. COMPONENT DESCRIPTIONS

The WMT MoM THA System consists of various components including acetabular shells, acetabular liners, fixation screws, femoral heads, femoral stems, modular necks, and proximal bodies. These components can be utilized in a variety of configurations to assemble the final construct. Table 3 shows the various components that make up the WMT MoM Total Hip System and in turn are included in this study.

Table 3. Components of the WMT MoM Total Hip System

CONSERVE® Acetabular Components
DYNASTY® Acetabular Components
PROFEMUR® Femoral Components
PERFECTA® Femoral Components
PROFEMUR® Modular Necks
CONSERVE® Neck Sleeves

VII. INTENDED USE AND INDICATIONS FOR USE

The WMT MoM THA System is intended for use in THA for reduction or relief of pain and/or improved hip function in skeletally mature subjects (age ≥21 years).

Indications for Use:

1) non-inflammatory degenerative joint disease such as osteoarthritis, avascular necrosis, ankylosis, protrusio acetabuli, or painful hip dysplasia
2) inflammatory degenerative joint disease such as rheumatoid arthritis
3) correction of functional deformity, and
4) revision procedures where other treatments or devices have failed

Rough grit blast surfaces and the hydroxyapatite, titanium plasma spray, and calcium sulfate coatings applied to implant surfaces are intended for cementless fixation.

VIII. RISKS AND BENEFITS

A. Anticipated Clinical Benefits

All subjects previously underwent THA and did not have the procedure performed as part of the study. As a result, the anticipated clinical benefits will not be associated with the implantation of the THA devices. Instead, the anticipated clinical benefits will be associated with the information gained about the status of the subject's THA device as provided by the metal ion level measurements, their association with adverse events, functional scores, and imaging performed as part of the study.

B. Anticipated Adverse Events

All enrolled subjects previously underwent THA and did not have the procedure performed as part of the study. As a result, the anticipated adverse events due to participation in the study are limited to those associated with the blood draw and MRI.

The adverse events associated with the blood draw include:

- Pain
- Blood clots
- Bruising
- Blood loss (hemorrhage)
- Hematoma
- Allergic reactions to tape
- Seizure
- Damage to blood vessels
- Swelling at needle incision point
- Nerve damage
- Numbness
- Dizziness
- Fainting
- Nausea
- Vomiting
- Hyperventilation

Adverse events associated with MRI include:

- Malfunctioning of heart pacemakers, defibrillation devices and cochlear implants
- Reaction to contrast media

IX. STUDY OBJECTIVES

A. Primary Objective

The primary objective of the study is to determine the incidence of adverse local tissue reactions (ALTR) in each THA implanted with the WMT MoM THA System overall and for yearly cross-section intervals from 4-year to 8-year post implant.

B. Secondary Objective

The secondary objectives include:

- To determine whole blood and serum cobalt and chromium metal ion levels for subjects implanted with the WMT MoM THA System overall and for each defined cross-section interval
- To estimate baseline whole blood and serum and serum cobalt and chromium metal ion levels for subjects not implanted with any metal implants, and compare the cobalt and chromium metal ion levels between the implanted subjects and controls (Group-1 vs. Group-2 subjects).
- To compare functional outcomes, as assessed by HOOS score (Hip disability and Osteoarthritis Outcome Score), of subjects implanted with the WMT MoM THA System overall and for each defined cross-section interval in subjects with and without ALTR (Group-1 subjects).
- To compare cobalt and chromium metal ion levels in subjects with and without confirmed ALTR (Group-1 subjects).

X. STUDY DESIGN

A. Study Design

This is a cross-sectional, multi-center study to evaluate outcomes in subjects previously implanted for between 4 and 8 years prior to the study start date. A target of 5 sites, with up to 7 sites total, will participate in this study. Subjects will be identified from Investigator records. Collected data will be evaluated in aggregate and cross-sectioned by year of implantation according to the time that has elapsed between implantation.

B. Sample Size and Subject Cross-Sectioning

There will be two groups of subjects in this clinical study: **Group 1** will consist of subjects previously implanted with the WMT MoM THA System; **Group 2** (i.e., Control Group) will consist of control subjects not implanted with any other metallic devices (excluding dental implants).

The sample size for **Group 1** is 155 THAs that must have been implanted between 4 and 8 years prior to enrolling in this study. This sample size will allow for 35 THAs to be included at each 1-year interval between Years 5 and 8 and 15 THAs to be included in the Year 4 interval (Table 4).

For each cross-section year, a sample size of 35 hips will give us a two-sided 95% confidence interval for the incidence rate of ALTR with a width no greater than 0.346. With the entire Group-1 cohort (n=155), the width of such a confidence interval will be no wider than 0.163.

The sample size for **Group 2** is 100 control subjects.

Subjects will be identified from Investigator records. Collected data will be evaluated in aggregate and cross-sectioned by year of implantation. Subjects will be cross-sectioned

by the time that has elapsed between implantation and the initial visit (e.g. 4 years, 5 years) using contiguous visit windows (number of years ± 6 months).
As subject enrollment will be carried out in at least 5 sites, enrollment will begin with Group-1. Group-2 subjects will be matched by age and gender to Group-1 to achieve a more balanced distribution between the two groups. To minimize the potential of over-enrollment, the study team will generate enrollment summaries and inform the sites if enrollment targets are reached for any given cross-sectioned year or for Group-2.

Table 4. Group 1 enrollment stratification based on time lapse from MoM THA implantation date to initial study visit.

Group 1	Year 4 ± 6m	Year 5 ± 6m	Year 6 ± 6m	Year 7 ± 6m	Year 8 ± 6m
N (hips)	15	35	35	35	35

In comparing metal-ion levels between Group-1 and Group-2, we will have 90% power to detect a 0.65 standard-deviation unit difference as significant with 5% Type-1 error rate in each cross-sectioned year assuming that the ion levels in Group-1 and Group-2 will have similar variability. With the comparison of the entire Group-1 with Group-2, we can detect 0.4 standard-deviation unit difference as significant with 90% power and 5% Type-1 error rate.

Due to potentially enrolling both hips of a given patient, whenever data is collected for the patient, not for each hip, the data analysis for that particular study objective will be carried out at the patient level. If the data is collected for each hip for a given study objective, the data analysis will be carried out for each hip assuming that the hips are independent.

C. Primary Endpoint

The primary endpoint is an estimate of the incidence of ALTR in each THA implanted with the WMT MoM THA System overall and for each yearly defined cross-section interval.

D. Secondary Endpoints

The secondary endpoints include:

- Estimates of whole blood and serum cobalt and chromium metal ion levels for subjects implanted with the WMT MoM THA System overall and for each defined cross-section interval. Here, we will also categorize patients enrolling only one hip and patients enrolling both hips, and estimates of whole blood and serum cobalt and chromium metal ion levels by this classification will be obtained as well.
- An estimate of baseline whole blood and serum cobalt and chromium metal ion levels subjects not previously implanted with metal implants (Group-2 subjects) compared to subjects previously implanted with metal implants (Group-1 subjects).
- Full descriptions of functional outcomes, as assessed by HOOS scores, of subjects implanted with the WMT MoM THA System overall and for each defined cross-section interval in subjects with and without ALTR (Group-1 subjects).
- A comparison of cobalt and chromium metal ion levels in subjects with and without confirmed ALTR (Group-1 subjects).

E. Follow-Up Time Points

Follow-up for **Group 1** will consist of a single study visit (Visit 1) in which they will be evaluated with a functional assessment (HOOS Score), an Environmental Assessment, past medical history, whole blood and serum cobalt, and chromium metal ion levels and MARS MRI. Group-1 subjects who are diagnosed with ALTR will be required to complete a 1-year follow-up visit (Visit 2) or until they are revised, whichever comes first. Therefore, they will be followed for 1-year or until any revision surgery at which point the subject will be taken off study.

Follow-up for **Group 2** will consist of a single study visit (Visit 1) in which they will be evaluated with an Environmental Assessment, past medical history, and whole blood and serum cobalt and chromium metal ion levels. The subjects will be taken off study immediately after this single visit.

F. Study Duration

The total study duration from final approval of the study protocol until the submission of the final report is expected to be 42 months.

G. Duration of Subject Participation

The duration of subject participation will be limited to a single study visit with multiple study activities (Visit 1). If all activities cannot be completed during the single visit due to scheduling logistics, subjects may have up to 4 weeks to complete the remaining activities.

An additional 1-year Follow-up Visit (Visit 2) will be required *only* for subjects in **Group 1** who were diagnosed with ALTR at Visit 1. Subjects diagnosed with ALTR will remain enrolled in the study for up to one year following Visit 1 or until revised, whichever comes first. If a subject has not undergone a revision of the enrolled hip prior to the end of the one-year period, they will be re-evaluated with the HOOS, cobalt and chromium metal ion levels, MARS MRI, and adverse event assessment during this additional study visit. Subjects may have up to 4 weeks to complete the remaining activities due to scheduling logistics.

H. Estimated Enrollment Period

The estimated time required to complete subject enrollment is 24 months.

XI. STATISTICAL ANALYSIS PLAN

Subjects will be assigned to a follow-up cohort depending upon the time that has elapsed between implantation and the initial clinical visit of the study (e.g., 4 year cross-section, 5 year cross-section, etc.) using contiguous visit windows (number of years $\pm$6 months).

Interim Data Looks will include, but is not limited to, the following:

- Report the incidence of adverse local tissue reactions (ALTR) in hips implanted with the WMT MoM THA System overall and for each defined cross-section interval.
- Report whole blood and serum cobalt and chromium metal ion levels for subjects implanted with the WMT MoM THA System overall and for each defined cross-section interval.
- Report the baseline whole blood and serum cobalt and chromium metal ion levels for subjects not implanted with any metal implants.
- Report the functional outcomes, as assessed by HOOS score, of subjects implanted with the WMT MoM THA System overall and for each defined cross-section interval.
- Report cobalt and chromium metal ion levels in subjects with and without confirmed ALTR.
- Report MRI results for study subjects.
- Report functional outcomes in subjects with and without confirmed ALTR.
- Report Adverse Events observed in study subjects.

Categorical variables will be summarized with the number and percent of subjects in each group. Continuous variables will be summarized with the mean, standard deviation, median, minimum, and maximum values. 95% confidence intervals will be calculated for the primary and secondary endpoints.

The Interim Data Looks will be provided to FDA beginning six months after the final protocol is approved and every six months for the first two years. Interim reporting will be provided annually beginning Year 3 until study completion.

A final study report will be provided to FDA following study completion and final data analysis.

XII. SUBJECT SELECTION

A. Inclusion Criteria

To be included in **Group 1**, subjects must meet all of the following criteria:

1. Has been implanted with appropriate components of the WMT MOM THA System for at least four years +/- six months (i.e. 3.5 years since implantation) , but not longer than eight years and six months (i.e. 8.5 years since implantation)
2. Has previously undergone primary THA for any of the following:
    a. non-inflammatory degenerative joint disease including osteoarthritis, traumatic arthritis, or avascular necrosis;
    b. inflammatory degenerative joint disease including rheumatoid arthritis;
    c. correction of functional deformity.
3. Is willing and able to complete required study visit(s) and assessments
4. Plans to be available for the required study visit
5. Is capable of providing sufficient blood for sampling according to blood draw procedures
6. Is willing to sign the approved Informed Consent document

Previously implanted bilateral subjects can have both THAs enrolled in the study provided: 1) the specified combination of components were implanted in both, 2) all other aspects of the Inclusion/Exclusion Criteria are satisfied, 3) enrollment does not

exceed the subject count specified in the Clinical Trial Agreement and protocol enrollment strategy, and 4) the subject agrees to a second Informed Consent document and data collection specific to the second THA. Enrollment and treatment of a previously unimplanted hip is not permitted in this study.

To be included in **Group 2**, subjects must meet all of the following criteria:

1. Does not have a metal implant (total hip, total knee, spinal, etc.) with the exception of dental implants
2. Is not an employee of the Investigator
3. Is willing and able to provide Informed Consent document
4. Is willing and able to attend the requested study visit
5. Is capable of providing sufficient blood for sampling according to blood draw procedures

B. Exclusion Criteria

Subjects will be excluded from either study group if they meet any of the following criteria:

1. Subject is currently enrolled in another clinical investigation which could affect the endpoints of this protocol
2. Subject is unwilling or unable to sign the Informed Consent document
3. Subject has documented substance abuse issues
4. Subject has an emotional or neurological condition that would pre-empt their ability or willingness to participate in the study
5. Subject is currently incarcerated or has impending incarceration
6. **Group 1 only:** Subject has a condition or previously implanted medical device that contraindicates MRI (e.g. pacemaker, implantable defibrillator)
7. **Group 1 only:** Subject was skeletally immature (less than 21 years of age at time of plantation)

C. Point of Enrollment

Subjects will be considered enrolled in the study when they have been informed of all aspects of the study, had ample time to review the Informed Consent document, signed the Informed Consent document, and satisfied the Inclusion/Exclusion Criteria.

D. Subject Withdrawal or Discontinuation

Subjects maintain the right to discontinue their participation in the study at any point. If a subject exercises this right, the Investigator will make every effort to ascertain and document the reason for withdrawal.

E. Subjects Lost to Follow-Up

If a subject is not able to complete the study after being enrolled, the Investigator will document the last contact with the subject. This is only for subjects in Group-1. All attempts to contact the subject will be documented in the source documentation.

XIII. PROCEDURES

A. Enrollment Procedures

As the subject enrollment will be carried out in at least 5 sites, the enrollment of subjects will be done according to the following criteria within each site:

- Enrollment will start with Group-1 subjects.

- After enrolling the first Group-1 subject, if there is a Group-2 candidate available then he/she can be enrolled if he/she
    - meets the Inclusion/Exclusion Criteria, and
    - is ±10 years of the previously enrolled Group-1 subject, and
    - same gender of the previously enrolled Group-1 subject.
- Each site should alternate enrollment between Group-1 and Group-2 as described above. This will generate a more balanced age and gender distribution.
- Group-1 enrollment will not be limited due to lack of eligible Group-2 subjects.
- Each site can continue enrolling to Group-1 and Group-2 until the enrollment targets are reached for each cross-sectioned year and for Group-2, or until instructed by MPO.

Group 1: Investigators will attempt to identify potential subjects from those they have previously implanted at their individual practices. Investigators will review their records for consecutive subjects starting with those implanted closest to 8 years from the protocol approval date with the study components and moving forward in time. The Investigator should not skip any potential subject implanted with the appropriate combination of components. Potential subjects will be cross-sectioned using the methods described above. The Investigator should attempt to contact any previously implanted subject that satisfies the Inclusion/Exclusion Criteria until there is a total of 35 subjects enrolled collectively at all sites for each year window (± 6 months).

Please note: previously implanted subjects with a pending revision of the WMT MoM components are eligible for enrollment and will need to be screened.

If a subject has appropriate WMT MoM components implanted in both hips, both can be enrolled in the study, as long as both hips satisfy the Inclusion/Exclusion Criteria. Subjects will be asked to sign two consent forms and complete two sets of questionnaires, one for each hip, but have only one blood draw and one MRI, if sufficient. Each THA will be assigned to the appropriate cross-sectioning interval (e.g. the two THAs may be in different intervals if bilateral THAs were not performed simultaneously).

Group 2 (Control Subjects): Investigators will attempt to identify potential control subjects from their individual practices as long as the subjects satisfy the Inclusion/Exclusion Criteria. Each subject can only be enrolled one time (see above for Group-2 enrollment guidelines).

Group 1 & 2: The Investigator will inform potential subjects of all aspects of the study, including all potential risks and benefits. Potential subjects will be allowed ample time to consider and ask questions about the information they have been provided. If after being informed the potential subject still wishes to participate, they will be asked to sign an Informed Consent document. Once the subject has signed the Informed Consent document and has met the Inclusion/Exclusion Criteria, they will be considered enrolled in the study. Any subject who signs the Informed Consent document and fails to satisfy the Inclusion/Exclusion Criteria will be considered a screen failure. Screen failures will be captured in the electronic data capture (EDC) system.
At screening, the subject will be assigned a seven digit subject identification number. The first three digits will be the code assigned to the Investigation Site. The second

three digits will correspond to the order the subject was enrolled (i.e. the first subject enrolled at each site will be 001). The last digit will be an “L” or “R” corresponding to the left or right hip. Control subjects will have a “C” assigned as the last digit (instead of “L” or “R”). This seven digit code will be used to identify the subject in the EDC.

B. Subject Medical History, Concomitant Medications, and Demographics (Both Groups 1 and 2)

Subject medical history and demographic information will be collected from the medical record **in both groups.** Data will come from the time of the primary THA surgery and recorded for **Group 1** subjects. **Group 2** data will come from the current medical records. The following information will be collected on these forms:

- Date of birth
- Gender
- Height
- Weight
- Status of other joints that affect ambulation **(Group 1 only)**
- Past medical events including significant diagnoses and major medical events and/or THA related Serious Adverse Events (SAEs)
- Concomitant medications

An Environmental (Metal Ion) Assessment form will also be completed by subjects in both Groups 1 and 2 to document environmental exposure to metal ions. Bilateral subjects with both THAs enrolled will be asked to complete one Environmental Assessment form which will be entered into the database for both enrolled THAs.

C. Operative Events (Group 1 only)

All of the following Operative information will be collected for all subjects in **Group 1**. Bilateral subjects with both THAs enrolled will have operative information completed separately for each THA.

i. Primary THA Procedure Information (Group 1 only)

The following information related to the subject’s primary THA operation will be obtained from the medical record and recorded for all subjects in **Group 1**.

- Date of admission
- Primary diagnosis for index THA procedure
- Previous treatments of the operated hip (osteotomy, resection, fracture fixation, or fusion)
- Date of operation
- Operative side
- Cement usage
- Bone graft usage
- Intraoperative complications
- Date of discharge

ii. Device Information (Group 1 only)

The product description, eight-digit product code, and lot number for each implanted component will be recorded for all subjects in **Group 1**. The number of acetabular screws used, if any, will also be recorded.

D. Whole Blood and Serum Metal Ion Levels (Both Groups 1 and 2)
Whole blood and serum cobalt and chromium metal ion levels will be collected in accordance with the Blood Draw Protocol for each subject **in both groups**. Bilateral subjects with both THAs enrolled will have a single blood draw and results will be used for both which will be entered into the database for both enrolled THAs.

E. HOOS Scores (Group 1 only)
HOOS Scores will be collected and recorded for each subject in **Group 1**. Bilateral subjects with both THAs enrolled will be asked to complete a separate HOOS Score for each THA.

F. MARS MRI (Group 1 only)
MARS MRI will be collected in accordance with the Imaging Protocol for each subject in **Group 1**. Bilateral subjects with both THAs enrolled may have a single MARS MRI, if sufficient for both THAs. Each side will be reviewed separately.

G. Adverse Events (both Groups 1 and 2)
Adverse events will be recorded in accordance with the Adverse Event Section below.

H. Revisions (Group 1 only)
Any enrolled THAs revised prior to the closure of the last site will have their WMT MoM THA System components explanted and analyzed in accordance with the Retrieval Analysis Protocol. Additionally, periprosthetic tissue and synovial fluid samples will be collected, as available, and analyzed in accordance with the Retrieval Analysis Protocol.

Please note: although a revision procedure is not considered a study-related activity, MPO will analyze and report the findings of the retrieval analyses resulting from revisions during the study period.

I. Additional Follow-up Study Visit (Group 1 subjects diagnosed with ALTR only)
An additional 1-year Follow-up Visit (Visit 2) will be required *only* for **Group 1** subjects who were diagnosed with ALTR at the first Study Visit (Visit 1). Subjects diagnosed with ALTR will remain enrolled in the study for up to one year following Visit 1 or until revised, whichever comes first. If a subject has not undergone a revision of the enrolled hip prior to the end of the one-year period, they will be re-evaluated with the HOOS, whole blood and serum metal ion levels, MARS MRI, and adverse event assessment during Visit 2. Subjects may have up to 4 weeks to complete the remaining activities due to scheduling logistics.

XIV. ADVERSE EVENTS AND ADVERSE DEVICE EFFECTS

A. Definitions

Adverse Event (AE) [1]
Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medical device. This includes events related to the investigational device and procedures involved.

Adverse Device Effect (ADE) [1]
AE related to the use of a medical device. This includes events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This includes any event resulting from use error or from intentional misuse of the investigational medical device.

Serious Adverse Event (SAE) [1]
AE that:

1) Led to death;
2) Led to serious deterioration in the health of the subject, that either resulted in
    a. A life-threatening illness or injury, or
    b. A permanent impairment of a body structure or a body function, or
    c. In-patient or prolonged hospitalization, or
    d. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function; or
3) Led to fetal distress, fetal death, or a congenital abnormality or birth defect

This includes device deficiencies that might led to a serious adverse event if (A) suitable action had not been taken or (B) intervention had not been made or (C) if circumstances had been less fortunate; and a planned hospitalization for pre-existing condition.

Serious Adverse Device Effect (SADE) [1]
Any ADE that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Adverse Device Effect (UADE)/ Unanticipated Serious Adverse Device Effect (USADE) [2,3]
Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

B. Relationship of Adverse Events to Device
Investigators will assign and document the likelihood each AE was **related to the implanted devices** using the following definitions.

- **None:** Any event that is associated with the device by timing and physiology, and was NOT caused or contributed to by the device
- **Possible:** Any event that is associated with the device by timing and physiology, and there is a possibility that it may have been caused or contributed to by the device
- **Probable:** Any event that is associated with the device by timing and physiology, and there is a good chance that it may have been caused or contributed to by the device
- **Definite:** Any event that is associated with the device by timing and physiology, and was caused or contributed to by the device

C. Relationship of Adverse Events to Surgical Procedure
Investigators will assign and document the likelihood each AE was **related to the surgical procedure** using the following definitions.

- **None:** Any event that is associated with the device by timing and physiology, and was NOT caused or contributed to by the surgical procedure
- **Possible:** Any event that is associated with the device by timing and physiology, and there is a possibility that it may have been caused or contributed to by the surgical procedure
- **Probable:** Any event that is associated with the device by timing and physiology, and there is a good chance that it may have been caused or contributed to by the surgical procedure
- **Definite:** Any event that is associated with the device by timing and physiology, and was caused or contributed to by the surgical procedure

D. Severity of Adverse Events
Investigators will assign and document their assessment of the severity of the AE using the following definitions. Severity is not the same as seriousness and is defined in terms of mild, moderate, and severe.

- **Mild:** The AE is noticeable to the subject but does not interfere with routine activity and does not require medical treatment
- **Moderate:** The AE interferes with routine activity but responds to symptomatic therapy or rest. Usually requires medical treatment.
- **Severe:** The AE requires removal of the implant. The subject is at risk of death or loss of a limb.

E. Recording and Reporting Adverse Events
SAEs must be reported to MPO as soon as possible but no later than **10 calendar days** of the Investigator (or site personnel) becoming aware. This includes:

- All primary THA procedure related SAEs from time of THA implantation to the enrollment, and through subjects' study completion or withdrawal.
- If unable to provide as instructed, the Investigator (or site personnel) will notify Clinical Data Management at MPO (contact information listed in the Study Binder).

If a follow up report is required for a unresolved SAE it must be reported as soon as possible but no later than **10 calendar days** of the Investigator (or site personnel) becoming aware of additional information.

ADEs, UADEs , SADEs and USADEs must be reported to MPO as soon as possible but no later than **10 calendar days** of the Investigator (or site personnel) becoming aware. This includes:

- All UADEs, SADEs, and USADEs from the **time of THA implantation** through subjects' study completion or withdrawal.
- If unable to provide as instructed, the Investigator will notify Clinical Data Management at MPO (contact information listed in the Study Binder).

If a follow up report is required for unresolved UADEs , SADEs or USADEs it must be reported as soon as possible but no later than **10 calendar days** of the Investigator (or site personnel) becoming aware of additional information.

Upon MPO's request, the Investigator must supply any additional information related to the safety reporting of any event.

F. Adverse Event Status Update

The Investigator will follow subjects who experience an Adverse Event until it is resolved or the Investigator assesses them as chronic or stable or until the subject's participation in the study ends. Prior to completion of the study, the Investigator will document the resolution date. If surgical intervention is required to treat the AE, the Investigator will document the details of the intervention.

Any surgical interventions will be classified as follows:

- **Reoperation with no revision:** Reoperation without revision would include procedures such as irrigation and debridement to treat infection
- **Revision of one or more components:** Revision is a procedure that adjusts or in any way modifies the original component configuration
- **Removed:** Removal is a procedure that removes the original components
- **Non Sponsor Device:** Reoperation that modifies, adjusts, removes or adds non-sponsor components.
- **Other:** Any other kind of surgery that does not revise or remove the components

Clinical Data Management should be notified prior to performing a surgical intervention that removes any of the implanted components (contact information can be found in the Study Binder). MPO will provide instructions on the appropriate methods for returning explanted devices to MPO. Any MPO component removed during a surgical intervention will be sent back to MPO for investigation.

G. Anticipated Adverse Events

Anticipated device and THA procedure related adverse events include [4]:

- Osteolysis (progressive bone resorption);
- Particulates leading to increased wear rates necessitating early revision;
- Allergic reactions to materials; metal sensitivity that may lead to histological reactions, pseudotumor, and aseptic lymphocytic vasculitis-associated lesions (ALVAL);
- Delayed wound healing; deep wound infection (early or late) which may necessitate removal of the prosthesis; on rare occasions, arthrodesis of the involved joint or amputation of the limb may be required;
- A sudden drop in blood pressure intra-operatively due to the use of bone cement;
- Damage to blood vessels or hematoma;
- Temporary or permanent nerve damage, peripheral neuropathies, and subclinical nerve damage as possible result of surgical trauma resulting in pain or numbness of the affected limb;
- Cardiovascular disorders including venous thrombosis, pulmonary embolism, or myocardial infarction;
- Fatigue fracture of the prosthetic component can occur as a result of trauma, strenuous activity, improper alignment, incomplete implant seating, duration of service, loss of fixation, non-union, or excessive weight;
- Dislocation, migration, and/or subluxation of prosthetic components from improper positioning, trauma, loss of fixation, and/or muscle and fibrous tissue laxity;

- Periarticular calcification or ossification, with or without impediment to joint mobility;
- Trochanteric non-union due to inadequate reattachment and or early weight bearing;
- Trochanteric avulsion as a result of excess muscular tension, early weight bearing, or inadvertent intraoperative weakening;
- Traumatic arthrosis of the knee from intraoperative positioning of the extremity;
- Inadequate range of motion due to improper selection or positioning of components, by femoral impingement, and periarticular calcification;
- Femoral or acetabular perforation or fracture; femoral fracture while seating the device; femoral fracture by trauma or excessive loading, particularly in the presence of poor bone stock;
- Undesirable shortening or lengthening of the limb;
- Aggravated problems of the affected limb or contralateral extremity by leg length discrepancy, excess femoral medialization, or muscle deficiency;
- Pain.

XV. AMENDMENTS TO CLINICAL PROTOCOL

Amendments cannot be made to the clinical protocol without the written consent of MPO. Since this is an FDA-ordered study, amendments to the protocol will only be enacted after receiving approval from FDA. Additionally, amendments to the protocol must be approved by the Institutional Review Board/Ethics Committee (IRB/EC) prior to their implementation. Statistical Analysis Plan will be also updated according to the protocol amendments as necessary.

XVI. DEVIATIONS FROM CLINICAL PROTOCOL

Investigators will not deviate from the clinical protocol except to deliver emergency care or to eliminate an immediate hazard to the subject. Investigators must report all deviations from the clinical protocol to MPO or its designated representatives as soon as possible. All deviations with the potential to affect subject safety, rights, or well-being must also be reported as required by the IRB/EC.

XVII. STUDY ETHICS

A. Ethics Committee Approval

It is the responsibility of the Investigator to obtain prospective approval of the clinical protocol, any clinical protocol amendments, Informed Consent document, and any other relevant documents from the IRB/EC. All correspondence with the IRB/EC will be retained in the Investigator Site File. Copies of IRB/EC approvals must be forwarded to MPO or its designated representative prior to enrolling subjects. The Investigator must immediately report to MPO or its designated representative if the IRB/EC withdraws its approval of the study for any reason.

B. Statements of Compliance

The study will be conducted in accordance with any applicable local, regional, or national subject privacy laws. Each site must have written approval from their respective IRB/EC prior to enrolling subjects.

C. Financial Disclosures

All Investigators must complete, sign and date the Financial Disclosure form prior to their participation in the study. Each Investigator must notify MPO or its designated representative if any relevant changes occur during the course of the study and for one

year following the completion of the study. Copies of the Financial Disclosure form for each Investigator will be maintained in MPO's investigational files.

XVIII. SPONSOR DISCONTINUATION CRITERIA

MPO reserves the right to terminate a non-performing site. Reasons for considering early termination or suspension of an individual site may include, but are not limited to:

- Site non-compliance with the clinical protocol or failure to comply with government or local regulations;
- Failure to submit data in a timely manner;
- Failure to comply with or act upon findings;
- Failure to take action to protect the rights and safety of human subjects;
- Failure to maintain pace to complete enrollment.

MPO reserves the right to discontinue the study at any time. After such a decision, the Investigator must also notify their respective EC of the discontinuation of the study. The Investigator must then contact all participating subjects to notify them of this decision and its impact on their follow-up per the guidance of the EC.

XIX. STUDY COMPLETION

A. Subject Completion

Individual subject participation will conclude once the subject has completed all required clinical visits and all outcome measurements required by the clinical protocol. The date of last follow-up, the date of study withdrawal, or date subject was determined to be lost to follow-up will be recorded.

B. Study Closeout Activities

The study will be considered complete once the last subject at the site has completed all clinical visits and all outcome measurements required by the clinical protocol. Additionally, the following activities must be completed at each site before the study is considered complete:

- All essential documents are complete and up to date
- Case report forms have been completed, entered into the electronic data capture (EDC) system, reviewed by the monitor, and all queries answered with related data updated, as applicable
- Current status or resolution of all ongoing SAEs and ADEs is documented
- Arrangements are made for archiving and record retention according to local and any regulatory requirements and the investigator agreement
- Documentation of disposition of any remaining clinical study materials is completed
- All IRB/ECs have been notified of the conclusion of the study
- All AEs have been entered and the outcome verified and/or updated, as applicable
- FDA has been notified of the conclusion of the study

XX. REFERENCES

[1] ISO-14155: Clinical investigation of medical devices for human subjects - Good clinical practice, 2011.
[2] Code of Federal Regulations 21 CFR Part 812
[3] MEDDEV 2.7/3 Clinical Investigations: Serious Adverse Event Reporting
[4] MicroPort Orthopedics Inc. Hip System Package Insert 136288-7, 2012.

XXI. APPENDICES

APPENDIX 1: Draft Informed Consent Document – Group 1
APPENDIX 2: Draft Informed Consent Document – Group 2
APPENDIX 3: Draft Case Report Forms (all Groups)
APPENDIX 4: Blood Draw and Metal Ion Analysis Protocol
APPENDIX 5: Imaging Protocol