



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

("MoM Post-Market Study")

Protocol Number: 11-LJH-001

**Radiographic Evaluation Protocol
Revision E**

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CONFIDENTIALITY STATEMENT

The information contained in this document is confidential and proprietary and should not be made available to those not directly associated with the study. Authorized recipients of this information include investigators and co-investigators, contract research organizations, reviewers, and other health care personnel necessary to conduct the study.

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SIGNATURE PAGE

By signing this document, the individuals named below agree that they have read and approved this protocol. Further, MicroPort Orthopedics, Inc. (Sponsor) and Medical Metrics, Inc. (Imaging Core Lab) agree to follow the procedures outlined in this protocol.

Protocol Title	Post-market Surveillance Study of Wright Medical Technology Metal-on-Metal Total Hip System	
Protocol Revision / Date	Rev E / 09-Oct-2018	
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HISTORY OF REVISIONS

The following table summarizes the history of revisions to this protocol:

Revision	Release Date	Significant Revisions Since Previous Version
A	23-Feb-2012	N/A
B	21-Aug-2012	<ul style="list-style-type: none"> Revised the 'Study Design and Purpose' and 'Imaging Objectives' sections to ensure consistency with the Clinical Protocol Provided clarification on the use of U/S imaging as a screening tool Added several MR assessments to aid in characterizing ALTR and Peri-prosthetic Soft Tissue Masses Refined the MARS MRI protocol to permit better sensitivity (Appendix 3) Added Ultrasound Image Acquisition Protocol (Appendix 4) Added additional literature citations Applied minor formatting changes to content Updated Appendices to ensure consistency with the body of the protocol
C (DRAFT)	09-Aug-2013	<ul style="list-style-type: none"> Added assessments of <i>Joint Effusion</i> and <i>Synovial Fluid Characterization</i> Combined the assessments of Presence of ALTR and Severity of ALTR into a single assessment; severity is graded as a qualifier when ALTR is present Revised the assessment titled "Low Signal Capsule" to "Low Synovium Signal" to better clarify the target anatomy for this assessment Divided the single, multi-grade assessment of 'Peri-Prosthetic Soft Tissue Mass' into three separate, absent/present assessments for clarity: Simple Fluid Collection, Complex Fluid Collection and Predominantly Solid Mass Revised the assessment of Location(s) of Peri-Prosthetic Soft Tissue Mass to identify the location of the largest simple, largest complex fluid, and largest predominantly solid mass observed and facilitate intuitive adjudication of disagreements amongst readers
D	09-June-2016	<ul style="list-style-type: none"> Update sponsor information Remove ultrasound and x-ray imaging and assessments Add follow-up MRI for non-revised subjects with ALTR Update REP to follow current processes at MMI

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E	09-Oct-2018	<ul style="list-style-type: none">• Update signature page• Modify visit intervals to 5 to 11 years post-implantation
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ABBREVIATIONS

ALTR	Adverse Local Tissue Reaction
ALVAL	Aseptic Lymphocytic Vasculitis-Associated Lesions
AP	Antero-Posterior
ARMD	Adverse Reaction to Metal Debris
DICOM	Digital Imaging and Communications in Medicine
FSE	Fast Spin Echo
FTP	File Transfer Protocol
ITF	Image Transmittal Form
kVp	Peak Kilo Volts
mAs	Milli-Ampere Second
MARS	Metal Artifact Reduction Sequence
MMI	Medical Metrics, Inc.
MoM	Metal on Metal
MRI	Magnetic Resonance Imaging
PD	Proton Density
SID	Source to Image Distance
SOP	Standard Operating Procedures
STIR	Short Tau Inversion Recovery
TE	Time of Echo (or Echo Time)
THA	Total Hip Arthroplasty
TR	Time of Repetition (or Repetition Time)
TSE	Turbo Spin Echo

1 STUDY DESIGN AND PURPOSE

This is a cross-sectional, multi-center clinical investigation designed to assess metal ion concentrations, incidence of revision and prevalence of symptomatic non-malignant, non-infective adverse local tissue reactions (ALTR) in Metal on Metal (MoM) primary total hip arthroplasty (THA) subjects.

Please refer to the main study protocol (11-LJH-001) for additional information on the study design and purpose.

2 IMAGING OBJECTIVES

The primary endpoint of the study is an evaluation of adverse local tissue reactions (ALTR^{*)}.

- Incidence of anticipated and unanticipated adverse events
- Incidence of ALTR in implanted subjects with and without pain and/or functional symptoms

The imaging assessments planned for this study are summarized in **Appendix 1**.

3 IMAGING SCHEDULE

Imaging will be performed at the time intervals specified in the study protocol. Implanted subjects will be evaluated using metal artifact reduction sequence (MARS) magnetic resonance imaging (MRI).

Table 1: Initial Screening Visit Imaging Summary for the three study cohorts.

Implant Status		MARS MRI (Study visit: 5 to 11 years postop)	MARS MRI (Post-Study visit: 12 months after initial study visit)
Non-implanted		-	-
Implanted	Non-revised	×	×*
	Revised	×	-

* Only implanted, non-revised subjects diagnosed with ALTR at the original study visit will have an additional MR visit 12 months after the initial MRI exam.

MARS MRI will be performed at the time intervals specified in the study protocol to assess the local tissue for evidence of fracture, osteolysis or loss of fixation, palpable mass, or potential metal hypersensitivity. MARS MRI will be collected using the protocol described in **Appendix 2** on subjects implanted a minimum of 5 years to a maximum of 11 years at the time of enrollment. For the purpose of this study, the following visits will be defined: Year 5, Year 6, Year 7, Year 8, Year 9, Year 10, and Year 11. MARS MRI will be evaluated for quality before assessments are conducted.

* Note that “Adverse Local Tissue Reaction (ALTR)” and “Adverse Reaction to Metal Debris (ARMD)” are used interchangeably.

Source: <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/MetalonMetalHipImplants/ucm241604.htm>

Subjects diagnosed with ALTR will remain enrolled in the study for up to one-year following the study visit or until they are revised, whichever occurs first. If a subject is not revised prior to the end of the one-year period, they will undergo an additional MARS MRI exam.

4 ASSESSMENT METHODS

4.1 Data Collection and Transmittal

Investigational Sites will produce the imaging identified in accordance with the study protocol. The Investigational Sites will send all images to Medical Metrics, Inc. (MMI), the imaging core lab for this study. The digital images will be maintained by MMI in a secure, clinical database.

The Investigational Sites will transfer the images to MMI in accordance with the image transfer protocol, a sample of which is included in **Appendix 3**. An image transmittal form will be attached with the digital images. This form will provide the following information to identify each shipment of radiographic images: Subject Number, Visit Designation, and Visit Date.

Access to images and associated study data will be restricted to authorized personnel only. All data and materials will be considered the exclusive, confidential property of MICROPORT. All image analysis and data management will be performed by MMI in accordance with their established and audited Standard Operating Procedures (SOPs).

4.2 Independent Image Review

Two independent radiographic reviewers and a tie-breaker will participate in this investigation. The reviewers will be board-certified, fellowship-trained, practicing, musculoskeletal radiologists with extensive clinical experience in image-based assessments of THA. The reviewers will have no financial interest in MICROPORT. The reviewers will be paid consultants to MMI and will be assigned to the study for its duration.

The radiographic reviewers will be trained on the schedule of imaging assessments and grading systems for recording each assessment. The reviewers will also be trained on the features of the treatments, their modular design and their indications for use. All training will be conducted with the aid of case examples, training atlases and/or graphical illustrations depicting key observations. All training will be conducted under the supervision of MMI's Chief Scientist. The reviewers will not have access to clinical outcomes data during the study.

Reviewer training will be conducted in accordance with MMI's SOPs. All training will be conducted and documented prior to commencing the reads. Each reviewer will be required to confirm via electronic signature that he or she has been trained *before* conducting the evaluation. Any changes to the radiographic evaluation protocol will require re-training and documentation before further work can be performed.

The MRI assessments will be performed by two primary, independent radiographic reviewers and a third reviewer to adjudicate disagreements. To maximize the reliability of the review, a pre-review training meeting will be conducted to establish consensus on interpretation of the classification criteria, with particular emphasis on the MRI review. During this process, the reviewers will evaluate and discuss images and information obtained from the scientific literature regarding soft-tissue reactions and changes following THA.^{1,2,3,4,5,6,7,8,9,10,11}

There are many cases presented in the literature describing soft tissue reactions following THA, and consensus review of these cases will facilitate uniformity in the detection and interpretation of peri-prosthetic soft-tissue reactions. Anderson et al. and Mistry et al. have shown substantial agreement between observers when differentiating the presence and extent of soft-tissue reactions based on a lesion size of 5 cm^{1,11}. It is expected that consensus review of cases will improve agreement between reviewers. Agreement statistics will be calculated for the two primary reviewers during the course of the study if a sufficient number of positive findings are available to allow for reliable agreement statistics.

Inter-reader variability will be documented following periodic blinded review of duplicate MRI exams by the primary reviewers. MMI will obtain observer agreement statistics appropriate to each assessment (including adjusted percentage agreement, weighted / unweighted kappa, ICC, etc). Reader reliability will be assessed under the supervision of MMI's Chief Scientific Officer. Unexplained differences in reliability will be addressed through re-training where appropriate.

4.3 Qualitative Assessment of Images

The following qualitative, visual assessments will be performed as described below. Assessments with a disagreement will be resolved by the third reviewer based on a majority-rules determination.

Assessment	Modality
MR Image Interpretability	MRI
Presence / Severity of ALTR (Adverse Local Tissue Reaction)	MRI
Low Synovium Signal	MRI
Simple Fluid Collection (Presence and Location)	MRI
Complex Fluid Collection (Presence and Location)	MRI
Predominantly Solid Mass (Presence and Location)	MRI
Joint Effusion	MRI
Synovial Fluid Characterization	MRI
Additional MRI Observations	MRI

A detailed classification system for each qualitative assessment is provided below. In cases where an assessment cannot be made from the available images due to technical/confounding factors (such as obscured anatomy, poor contrast or imaging artifact) the assessment will be graded as 'Ind' (Indeterminate). If an assessment cannot be made due to missing images or inadequate field of view (FOV), it will be graded as 'UA' (Unable to Assess). In cases where an assessment is not applicable to the subject/visit it will be graded as 'NA' (Not Applicable). And finally, assessments that are not required at select time points will be reported as 'NR' (Not Required).

4.3.1. MR Image Interpretability

MR Image Interpretability will be graded as 'Optimal', 'Adequate', 'Suboptimal' or 'Poor or Non-Diagnostic' in accordance with the following definitions (adapted from White et al.¹²):

0. **Optimal:** Clear depiction of peri-prosthetic tissue with no impact on diagnostic scoring
1. **Adequate:** Artifact present with minimal impact on diagnostic scoring
2. **Suboptimal:** Artifact present with moderate impact on diagnostic scoring
3. **Poor or Non-Diagnostic:** Artifact prevents diagnostic scoring of images

Clarifying remarks regarding the effect and characteristics of the observed artifact(s) will be documented at the radiologist's discretion.

4.3.2. Presence / Severity of Adverse Local Tissue Reaction (ALTR)

Presence of Adverse Local Tissue Reaction will be graded as 'Normal', 'Acceptable', 'Abnormal – Not suggestive of ALTR', 'Abnormal – Suggestive of ALTR' or 'Too Small to Characterize' in accordance with the following definitions^{1,4}. When ALTR (Grade 3) has been noted, its severity will be qualified as 'Mild', 'Moderate', or 'Severe'.

0. **Normal:** Normal post-operative appearance
1. **Acceptable:** Acceptable post-operative appearance, including seromas, hematomas and atrophy of the short external rotators. Also includes bone marrow edema in the proximal femur in the absence of other changes.
2. **Abnormal – Not suggestive of ALTR:** Peri-prosthetic soft tissue abnormalities typical of a disease other than metal-on-metal reaction including infection and bursitis. Appearance may include fluid collections with low T1 signal and high T2 signal with homogenous signal within the fluid and thin smooth wall, and/or inflammatory changes in soft tissue with or without the presence of bone marrow edema.
3. **Abnormal – Suggestive of ALTR:** Peri-prosthetic soft tissue abnormalities with features typical of a local adverse tissue reaction to metal debris, including solid masses or fluid collections. Typical

appearance is a fluid signal collection extending from and surrounding the bearing and demarcated by a very low-signal capsule (rim) on T2, commonly with debris and heterogeneous signal within the fluid and/or presence of wall thickening or irregularity.

1. **Mild:** Peri-prosthetic fluid collection(s) 1 to 5 cm in diameter with cyst wall < 3 mm in thickness
2. **Moderate:** Predominantly solid mass(es) 1 to 5 cm in diameter in which wall thickness is > 50% of the maximum cross sectional diameter; fluid collection(s) \geq 5 cm in diameter; or fluid collection(s) with any of the following features: wall thickness \geq 3 mm, muscle atrophy or edema in any muscle other than short external rotators, or bone marrow edema
3. **Severe:** Predominantly solid mass(es) > 5 cm in which wall thickness is > 50% of the maximum cross sectional diameter
4. **Too Small to Characterize:** Any solid or cystic mass measuring less than one cm in largest diameter

This is an overall assessment of the presence of an adverse local tissue reaction as well as soft tissue abnormalities *not* related to metal debris. A 'normal' versus 'acceptable' post-operative appearance will be documented to flag observations for further monitoring (e.g. seroma, hematoma) that may overlap with metal-on-metal fluid collections. Assessments of peri-prosthetic tissue masses can be difficult to characterize, particularly when smaller than one cm. Therefore lesions less than one cm will be classified as "too small to characterize".

ALTR is an umbrella term for metallosis, adverse reaction to metal debris (ARMD), aseptic lymphocytic vasculitis-associated lesions (ALVAL) and pseudotumor / soft tissue mass¹³. Common features of ALTR on MRI include presence of low signal capsule, wall thickening, wall irregularity, peri-prosthetic solid masses and fluid collections.

The assessment of the severity of ALTR is based on grading schemes reported in publications from Anderson et al (2011)**Error! Bookmark not defined.**, Wynn Jones et al (2011)**Error! Bookmark not defined.** and a more recent publication from Hauptfleisch et al (2012)¹⁴. The proposed grading scale uses a combination of lesion size and relative wall thickness of the soft tissue mass. As it is recognized that the proposed scale is based on limited published data to support these severity thresholds, quantitative data on size and wall thickness will be quantitatively measured to refine the severity scoring system as data accumulates. The measurements are defined in section 4.5.

The size of the soft tissue mass will be measured in three anatomic planes. For cystic masses (fluid collections), lesion severity will be differentiated by size < 5 cm and \geq 5 cm. This is based on the reliability of similar assessments reported by Anderson et al^{**Error! Bookmark not defined.**} who showed that there was good agreement above this size threshold. Results from Hauptfleisch et al¹⁸ suggest cystic masses with a wall thickness of > 3 mm are associated with greater severity of symptoms than those with wall thickness < 3 mm. Predominantly solid masses are generally larger in size than cystic ALTR lesions, and typically present with more severe symptoms. Based on these results, cystic lesions with

> 3 mm wall thickness will be graded as moderate severity and predominantly solid lesions > 5 cm will be graded as severe ALTR.

4.3.3. Low Synovium Signal

Low Synovium Signal will be graded as 'Absent' or 'Present' in accordance with the following definitions:

0. **Absent:** No evidence of signal loss in the interior lining of the joint capsule (synovium) and pericapsular tissues that may be due to metal particle deposition
1. **Present:** Presence of low signal in the interior lining of the joint capsule and pericapsular tissues that may be due to metal particle deposition

The joint capsule should normally have low signal, with a synovial lining that typically cannot be easily resolved in a clinical MRI exam. The assessment of Low Synovium Signal evaluates signal loss due to metal particle deposition in the synovium or lining of the extra-articular pseudo-capsule (as an indicator of metallosis) on non-fat suppressed T2 weighted Turbo Spin Echo (TSE) / Fast Spin Echo (FSE) images. Theoretically, the presence of metal in the soft tissues (metallosis) should cause decreased signal in the tissues due to the metal, which may be seen as low signal in the lining of the synovium or pseudo-capsule. Signal loss may be most obvious in sequences with long TEs, such as T2-weighted images. Attention will be paid to the presence of characteristic signal loss at sites of metal particle deposition, including the joint capsule rim.

4.3.4. Simple Fluid Collection

Simple Fluid Collection will be graded as 'Absent' or 'Present' in accordance with the following definitions. When one or more simple fluid collections are observed, the location of the *largest* collection will be documented as a qualifier as indicated.

0. **Absent:** No evidence of simple peri-prosthetic fluid collection(s)
1. **Present:** Presence of simple peri-prosthetic fluid collection(s) generally characterized by low T1 / high T2 signal and a thin smooth wall measuring < 3 mm in thickness. Minimal fine (hairline) septations may be present.
 1. **Anterior Medial:** Presence of a simple, peri-prosthetic fluid collection in the anterior medial quadrant
 2. **Anterior Lateral:** Presence of a simple, peri-prosthetic fluid collection in the anterior lateral quadrant
 3. **Posterior Medial:** Presence of a simple, peri-prosthetic fluid collection in the posterior medial quadrant
 4. **Posterior Lateral:** Presence of a simple, peri-prosthetic fluid collection in the posterior lateral quadrant

When present, the reviewer will provide clarifying remarks regarding the nature of the collection(s) observed, including whether infection is suspected. The specific

muscle(s) within the affected quadrant may be identified at the reviewer's discretion. The reviewer will document in the comments when multiple simple fluid collections are observed.

4.3.5. Complex Fluid Collection

Complex Fluid Collection will be graded as 'Absent' or 'Present' in accordance with the following definitions. When one or more complex fluid collections are observed, the location of the largest collection will be documented as a qualifier as indicated.

0. **Absent:** No evidence of complex peri-prosthetic fluid collection(s)
1. **Present:** Presence of complex fluid collection(s) characterized by irregular wall, a wall thickness ≥ 3 mm, numerous or thick septations and/or internal debris. Signal characteristics may be variable on T1- and T2-weighted sequences.
 1. **Anterior Medial:** Presence of a peri-prosthetic fluid collection in the anterior medial quadrant
 2. **Anterior Lateral:** Presence of a peri-prosthetic fluid collection in the anterior lateral quadrant
 3. **Posterior Medial:** Presence of a peri-prosthetic fluid collection in the posterior medial quadrant
 4. **Posterior Lateral:** Presence of a peri-prosthetic fluid collection in the posterior lateral quadrant

When complex fluid collections are observed, the reviewer will provide clarifying remarks regarding the nature of the collections. The specific muscle(s) within the affected quadrant may be identified at the reviewer's discretion. The reviewer will document in the comments when multiple complex fluid collections are observed.

4.3.6. Predominantly Solid Mass

Predominantly Solid Mass will be graded as 'Absent' or 'Present' in accordance with the following definitions. When one or more solid masses are observed, the location of the largest solid mass will be documented as a qualifier as indicated.

0. **Absent:** No evidence of solid or predominantly solid mass(es) in which wall thickness is $> 50\%$ of the maximum cross sectional diameter
1. **Present:** Presence of peri-prosthetic solid mass(es) or complex fluid collection(s) characterized by thick irregular wall in which the wall thickness is $> 50\%$ of the maximum cross sectional diameter.
 1. **Anterior Medial:** Presence of a peri-prosthetic solid mass in the anterior medial quadrant
 2. **Anterior Lateral:** Presence of a peri-prosthetic solid mass in the anterior lateral quadrant
 3. **Posterior Medial:** Presence of a peri-prosthetic solid mass in the posterior medial quadrant

4. **Posterior Lateral:** Presence of a peri-prosthetic solid mass in the posterior lateral quadrant

When present, clarifying remarks regarding the nature of the mass(es) will be documented. The specific muscle(s) within the affected quadrant may be identified at the reviewer's discretion. The reviewer will document in the comments when multiple, solid masses are noted.

Solid masses of concern are typically characterized by low to intermediate signal on T2 and intermediate signal on T1, and may appear slightly higher than normal muscle. Mature heterotopic ossification having signal characteristics of bone will not be classified as a peri-prosthetic mass.

4.3.7. Joint Effusion

Joint Effusion will be graded as, 'None', 'Mild', 'Moderate', or 'Severe' in accordance with the following definitions:

0. **None:** Normal physiological synovial volume
1. **Mild:** Evidence of mild increase in synovial fluid volume, < 33% distention
2. **Moderate:** Evidence of moderate increase in synovial fluid volume, 33% - 66% distention
3. **Severe:** Evidence of severe increase in synovial fluid volume, > 66% distention

This assessment intends to capture the presence of any increased synovial fluid and corresponding joint distention, if present.

4.3.8. Synovial Fluid Characterization

Synovial Fluid Characterization will be assessed as, 'Fluid', 'Debris', 'Mixed', 'Other' or 'Fluid not Visible' in accordance with the following definitions:

0. **Fluid:** High signal Intensity with a thin (< 5 mm) intermediate to low signal intensity pseudocapsule
1. **Debris:** Intermediate to low signal intensity debris
2. **Mixed:** Fluid signal intensity and intermediate to low signal intensity debris
3. **Other:** Pattern not described
4. **Fluid not Visible:** Synovial fluid not sufficiently visible for characterization

This assessment is based on that as proposed in Hayter, et al¹⁵. and is intended to provide insight on the visual appearance of the synovial fluid. T2 sequences are intended be used in this assessment.

4.3.9. Additional Observations (MRI)

Additional observations will be documented in the comments section. These may include observations of the presence/extent of peri-prosthetic bone and soft tissue edema, bone marrow replacement, muscle atrophy, tendon avulsion or rupture, bursitis, etc. Observations may also include lymphadenopathy, necrosis, tumor and clarifying remarks regarding solid masses and fluid collections observed, including indications of infection and osteolysis. Standard commenting criteria and keywords will be developed for clarity and to facilitate rapid identification of noteworthy observations.

4.4 Quantitative Assessment of Images

There will be two quantitative assessments made from MR images, which are described below.

4.4.1. Size of Peri-Prosthetic Soft Tissue Mass

The following measurements will be produced to assess the size of the largest predominantly solid mass observed, if any. The dimensions of the mass in each of three principal directions will be reported in millimeters (mm) as follows:

1. **Predominantly Solid Mass – Maximal Axial-Plane Dimension**
2. **Predominantly Solid Mass – Maximal Coronal-Plane Dimension**
3. **Predominantly Solid Mass – Maximal Sagittal-Plane Dimension**

Additionally, the following measurements will be produced to assess the size of the largest simple and complex fluid collection observed, measured from outer wall to outer wall in millimeters (mm):

1. **Simple Fluid Collection – Maximal Axial-Plane Dimension**
2. **Simple Fluid Collection – Maximal Coronal-Plane Dimension**
3. **Simple Fluid Collection – Maximal Sagittal-Plane Dimension**
1. **Complex Fluid Collection – Maximal Axial-Plane Dimension**
2. **Complex Fluid Collection – Maximal Coronal-Plane Dimension**
3. **Complex Fluid Collection – Maximal Sagittal-Plane Dimension**

When no simple fluid, complex fluid, and/or predominantly solid lesion is observed, the relevant assessments will be reported as 'NA' (Not Applicable).

4.4.2. Wall Thickness of Peri-Prosthetic Soft Tissue Mass

The wall thickness of the largest fluid collection and solid mass will be measured at the site of greatest cross sectional diameter on an axial image as described by Hauptfleisch et al.¹⁴ For cases with multiple lesions, the largest lesion will be used to measure wall thickness. The following measurements will be produced:

1. **Predominantly Solid Mass – Maximal Axial-Plane Wall Thickness**
2. **Simple Fluid Collection – Maximal Axial-Plane Wall Thickness**
3. **Complex Fluid Collection – Maximal Axial-Plane Wall Thickness**

When no simple fluid, complex fluid and/or predominantly solid lesion is observed, the relevant assessments will be reported as 'NA' (Not Applicable).

5 DATA MANAGEMENT AND QUALITY CONTROL

MMI will ensure that all finished results undergo thorough quality control procedures and have been checked for accuracy and validity prior to shipment to MICROPORT and/or their designee.

MMI will use best efforts to ensure optimal accuracy by:

1. Documenting poor image quality in cases where it may impact the reliability of the analysis.
2. Conducting reproducibility studies, as needed, to ensure minimum variation in the results.
3. Verifying TR, TE, TI (as applicable), echo train lengths, receiver bandwidths, etc. for various MR sequences.
4. Ensuring that MRI quality is sufficient to permit quantitative analysis; this includes inspecting images for susceptibility, motion, flow, and off-resonance artifacts.
5. Performing sensitivity studies to investigate the effects of intra- and inter-site variation in MRI acquisition parameters, etc.
6. Inspecting image meta-data in DICOM headers to verify that acquisition is performed in compliance with the recommended image acquisition protocol.
7. Providing sites with regular feedback on image acquisition and transfer protocol compliance
8. Commenting on image quality in cases where it may compromise the accuracy of the results.
9. Conducting observer reproducibility studies, as needed, to ensure minimum variation in the analysis results across observers.
10. Conducting routine in-process and final inspection of analysis results and data.

MMI will provide an image acquisition protocol to ensure acquisition of best-quality images. The proposed protocol is summarized in **Appendix 2** (MARS MRI Protocol). The protocol includes:

1. Procedures and scanner settings for acquiring magnetic resonance Imaging data
2. Instructions for ensuring that MRI are of high quality with minimal artifacts

MMI will use best efforts to ensure the accuracy of the data received from the sites. MMI will reconcile receipt of images with transmittal information and will validate received image information to ensure database consistency. This will include:

1. Verifying the content and labeling of all received images, including subject ID, site ID and treatment location.
2. Verifying the visit dates to ensure that all images are dated correctly per study schema.
3. Verifying image receipt logs to ensure that each set of images is stored uniquely in the database and that no duplicate images have been submitted.

MMI will maintain compliance with all standard operating procedures and data management practices including:

1. Restricting access to digital information and images to authorized personnel only.
2. Maintaining audit trails of modifications made to the client data (such as corrections to the subject demographics and/or visit information).
3. Performing routine quality audits and process inspection.
4. Performing routine data backup and data validation procedures.
5. Maintaining all images in a secure manner while in MMI's possession.
6. Promptly returning digital media to the clinical sites.

A validated software system will be used to produce the measurements, record the reviewer's assessments, store the data and images, and produce the deliverables.

1. Quantitative and qualitative image assessments will be captured through a validated software interface. The assessments will be digitally signed and dated at the time the assessments are produced.
2. User authentication will validate the identity of the software operator.
3. Automated error detection tools will assist in error avoidance.
4. The radiographic assessments will be stored in a proprietary database and linked with the images used to produce the assessments.
5. Electronic audit trails of modifications made to the data will be recorded in accordance with good clinical practices and the provisions of 21 CFR Part 11.
6. During the production of deliverables, data will be automatically extracted from the database using a validated software tool that produces summary electronic deliverables in a standard format.
7. A set of quality control checks will be applied to the deliverable to confirm accuracy of the reported data.
8. Each electronic deliverable will be password-protected against subsequent editing prior to shipment to MICROPORT and/or their designee.

Interim deliverables will be subject to change until a final deliverable containing locked data has been reported. Changes to data could occur, for example, if the assessments are performed using an initial set of images that are later supplemented with additional images sent from the site. Receipt of additional imaging may cause an assessment to change in some scenarios. Changes may also occur if images are mislabeled with respect to the subject ID and/or visit ID which are later corrected. The reviewers may also in some cases revise their assessments after new images at later time points are received. Whenever changes to data occur, the reason for the change will be documented. Data will be "locked" against further changes at the time final deliverable is submitted.

MMI will regularly submit a monthly inventory report of images received to date to MICROPORT. Each interim report shall include a list of images received by subject and image type (modality and view / sequence). Each report will be cumulative and up-to-date. MMI will support database queries related to each inventory report as requested.

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- ¹³ Haddad FS, Thakrar RR, Hart AJ, et al. Metal-on-Metal Bearings: The Evidence So Far. *J Bone Joint Surg [Br]* 2011;93-B:572-9
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APPENDIX 1: RADIOGRAPHIC ASSESSMENT SUMMARY

Qualitative Assessments (MRI)	Evaluations/Comparisons
1. MR Image Interpretability	<ul style="list-style-type: none"> • This assessment documents of the effect of metal artifact on diagnostic image quality • MR Image Interpretability will be graded as 'Optimal', 'Adequate', 'Suboptimal' or 'Poor or Non-Diagnostic'
2. Presence / Severity of Adverse Local Tissue Reaction (ALTR)	<ul style="list-style-type: none"> • This is an overall assessment of the presence of reaction to metal wear debris as well as an assessment of lesions, such as large fluid collections, that may not be due to metal debris. • Presence of ALTR will be graded as 'Normal', 'Acceptable', 'Abnormal – Not suggestive of ALTR', 'Abnormal – Suggestive of ALTR' or 'Too Small to Characterize' • When present, the severity of ALTR will be qualified as 'Mild', 'Moderate', or 'Severe'.
3. Low Synovium Signal	<ul style="list-style-type: none"> • Low Synovium Signal will be assessed for the presence of low signal in the interior lining of the joint capsule and pericapsular tissues that may be due to metal particle deposition • Low Synovium Signal will be graded as 'Absent' or 'Present'
4. Simple Fluid Collection	<ul style="list-style-type: none"> • Simple Fluid Collection will be assessed for the presence and location of "simple" fluid collections • Simple Fluid Collection will be graded as 'Absent', 'Present' • When Present, the location of the largest observed lesion will be recorded as 'Anterior Medial', 'Anterior Lateral', 'Posterior Medial', 'Posterior Lateral' • The presence of multiple collections will be documented in the comments
5. Complex Fluid Collection	<ul style="list-style-type: none"> • Complex Fluid Collection will be assessed for the presence and location of "complex" fluid collections • Complex Fluid Collection will be graded as 'Absent', 'Present' • When Present, the location of the largest observed lesion will be recorded as 'Anterior Medial', 'Anterior Lateral', 'Posterior Medial', 'Posterior Lateral' • The presence of multiple collections will be documented in the comments
6. Predominantly Solid Mass	<ul style="list-style-type: none"> • Predominantly Solid Mass will be assessed for the presence and location of "predominantly solid" soft tissue masses • Predominantly Solid Mass will be graded as 'Absent', 'Present' • When Present, the location of the largest observed lesion will be recorded as 'Anterior Medial', 'Anterior Lateral', 'Posterior Medial', 'Posterior Lateral' • The presence of multiple solid masses will be documented in the comments
7. Joint Effusion	<ul style="list-style-type: none"> • Joint Effusion will assess the extent of any increased fluid levels and the corresponding joint distention • Joint Effusion will be graded as 'None', 'Mild', 'Moderate', or 'Severe'

8. Synovial Fluid Characterization	<ul style="list-style-type: none"> • Synovial Fluid Characterization will describe the MR appearance of the synovial fluid • Synovial Fluid Characterization will be graded as 'Fluid', 'Debris', 'Mixed,' 'Other', or 'Fluid not Visible'
9. Additional MRI Observations	<ul style="list-style-type: none"> • Additional observations may include but are not limited to presence/extent of peri-prosthetic bone and soft tissue edema, bone marrow replacement, muscle atrophy, tendon avulsion or rupture, bursitis, etc. Observations may also include lymphadenopathy, necrosis, tumor and clarifying remarks regarding solid masses and fluid collections observed, including indications of infection and osteolysis.
Quantitative Measures (MRI)	Evaluations
10. Size of Peri-Prosthetic Soft Tissue Mass	<ul style="list-style-type: none"> • The maximum dimensions of the largest observed soft tissue mass, simple fluid, and complex fluid collection will be recorded in each imaging plane from MRI • The following measurements will be produced and reported in mm <ul style="list-style-type: none"> ○ Predominantly Solid Mass – Maximal Axial-Plane ○ Predominantly Solid Mass – Maximal Coronal-Plane ○ Predominantly Solid Mass – Maximal Sagittal-Plane ○ Simple Fluid Collection – Maximal Axial-Plane ○ Simple Fluid Collection – Maximal Coronal-Plane ○ Simple Fluid Collection – Maximal Sagittal-Plane ○ Complex Fluid Collection – Maximal Axial-Plane ○ Complex Fluid Collection – Maximal Coronal-Plane ○ Complex Fluid Collection – Maximal Sagittal-Plane
11. Peri-Prosthetic Soft Tissue Mass Wall Thickness	<ul style="list-style-type: none"> • The maximum wall thickness of the largest solid mass, simple fluid, and complex fluid collection (cystic mass) will be measured at the site of greatest cross sectional diameter on axial MR images as described by Hauptfleisch et al • The following measurements will be produced and reported in mm <ul style="list-style-type: none"> ○ Predominantly Solid Mass – Maximal Axial-Plane Wall Thickness ○ Simple Fluid Collection – Maximal Axial-Plane Wall Thickness ○ Complex Fluid Collection – Maximal Axial-Plane Wall Thickness

APPENDIX 2: MARS MRI ACQUISITION PROTOCOL

MRI Acquisition Protocol

Application: Metal-on-Metal Hip Prosthesis

General Guidelines for the Radiologist/MRI Technologist

Hardware

- An MRI scanner of 1.5T field strength is required. Some variation in recommended acquisition parameters is to be expected depending on field strength, scanner manufacturer, software version, release number, and hardware configuration.
- A higher field strength scanner should not be used due to susceptibility artifacts from the metal implant.
- The MRI scanner must be approved for clinical use.
- Use of a Phased Array Body Coil is required.

Subject and Positioning

- Please administer standard safety questionnaire prior to imaging the subject.
- Please instruct subjects to remain still during the MRI exam to minimize motion artifacts.
- The subject should be supine, in the “head-first” position.
- Subjects should be positioned with the legs in approximately 15 degrees of rotation and knees in about 10 degrees of flexion to improve consistency.
- A strap may be used to secure the surface coil when in use. Padding under the knees may be used as necessary to ensure subject comfort.

Imaging Anatomy

- The initial sequences will use a large (around 34 cm) Field of View (FOV), followed by imaging of the affected (treated) hip(s), which will be conducted using a smaller FOV.
- The imaging slab should remain unchanged across sequences acquired in the same orientation. This means that the slices for all axial series should be collected at the same location, i.e. without repositioning the slab. The same applies for sagittal and coronal acquisitions also.

Image Acquisition

- Please use Auto Shim for all acquisitions, manual shimming is not necessary for this protocol.
- Please do NOT use any parallel imaging methods for acquisition as this is likely to utilize non-uniform RF fields.
- Please ensure that the anatomy is centered in the FOV.
- Use the largest bandwidth possible to reduce the signal distortion due to the presence of the implant.
- For any return visits, please use subjects’ **baseline scans** as reference for visual guidance in determining FOV extent, slice positioning, and angulation. This will aid in the accuracy of image analyses and help comparative review of the anatomy.
- Changes to TR may be necessitated by specific absorption rate (SAR) limits imposed by the scanner console. Such changes are acceptable provided TR remains within the limits prescribed by this protocol. The technologist or supervising

radiologist may chose to utilize phase oversampling and/or modify the number of slices to accommodate an altered scan TR.

- Additional imaging sequences may be added at the supervising radiologist's discretion or if they are routinely performed as 'standard-of-care' sequences.

Other Notes

- All MRI Images should be sent to the Medical Metrics, Inc. (Houston, TX, USA), the study core lab, in DICOM format. These may be burned to media with an image viewer, where possible.
- No contrast-based sequences are prescribed in this MRI protocol.

1.5T MR Acquisition Sequences

1. 3 PLANE LOCALIZER

Purpose: Anatomic Scout for FOV placement	Imaging Mode: 2D/Multi-slice
Pulse Sequence: Localizer 3-Plane	Scan Region: Hip/Pelvis
TR/TE/Flip angle: Default scanner settings	Measurements: 1
FOV: 40 cm x 40 cm	Matrix: 256 x 512 or higher
Number of Slices: 20/direction	Slice Thickness/Gap: 5 mm/1 mm

Notes: This sequence may be run per site protocols, more than once if required. Additional calibration scans (field map, parallel coil reference scans, etc.) should be run after a suitable localizer scan is acquired.

2. CORONAL T1 WEIGHTED SEQUENCE

Purpose: 2D Anatomic Imaging	Imaging Mode: 2D/Multi-slice
Pulse Sequence: 2D-Fast Spin Echo (FSE)	Echo Train Length: 4
TR/TE/Flip angle: 450-700/10-15/NA	Matrix: 320 x 320 or higher
FOV: 34 cm x 34 cm	Slice Thickness/Gap: 5.0 mm/0 mm
Number of Measurements: 2	

Notes: It is recommended that the phase encode be set in the Head-Foot direction. The coverage should span the tensor fasciae latae, which is generally accomplished by using an FOV in the 32-36 cm range. The goal is to achieve an optimal pixel resolution of approximately 400-500 microns, which may be achieved by increasing the matrix size.

3. CORONAL STIR SEQUENCE

Purpose: 2D Anatomic Imaging	Imaging Mode: 2D/Multi-slice
Pulse Sequence: 2D-FSE-IR	Echo Train Length: 7-8
TR/TE/TI: 3800-4400/18-25/130ms	Matrix: 256 x 256 or higher
FOV: 34 cm x 34 cm	Slice Thickness/Gap: 5.0 mm/0 mm
Number of Measurements: 2	

Notes: It is recommended that the phase encode be set in the Head-Foot direction. The goal is to achieve an optimal pixel resolution of approximately 600-700 microns, which may be achieved by increasing the matrix size.

4. AXIAL T1 WEIGHTED SEQUENCE

Purpose: 2D Anatomic Imaging

Pulse Sequence: 2D-FSE

TR/TE/Flip angle: 450-700/10-15/NA

FOV: 20 cm x 20 cm

Number of Measurements: 2

Imaging Mode: 2D/Multi-slice

Echo Train Length: 3-4

Matrix: 384 x 384 or higher

Slice Thickness/Gap: 5.0 mm/0 mm

Notes: Imaging coverage should span the entire hip prosthesis on the affected (treated) side. It is recommended that the phase encode be set in the Right-Left direction. The goal is to achieve an optimal pixel resolution of approximately 400-500 microns. For subjects with bi-lateral implants, use 2 axial scans (one per side) to avoid loss of SNR.

5. AXIAL T2 WEIGHTED SEQUENCE

Purpose: 2D Anatomic Imaging

Pulse Sequence: Fast Spin Echo (FSE)

TR/TE/Flip angle: 4500-5500/40-50/ NA

FOV: 20 cm x 20 cm

Number of Measurements: 2

Imaging Mode: 2D/Multi-slice

Echo Train Length: 13-16

Matrix: 384 x 384 or higher

Slice Thickness/Gap: 5.0 mm/0 mm

Notes: Imaging coverage should span the entire hip prosthesis on the affected (treated) side. It is recommended that the phase encode be set in the Right-Left direction. It is recommended that the same imaging slab be used as the Axial T1 weighted sequence. For subjects with bi-lateral implants, use 2 axial scans (one per side) to avoid loss of SNR.

6. SAGITTAL T2 WEIGHTED SEQUENCE

Purpose: 2D Anatomic Imaging

Pulse Sequence: Fast Spin Echo (FSE)

TR/TE/Flip angle: 4500-5500/40-50/NA

FOV: 32 cm in the SI direction

Number of Measurements: 2-3

Imaging Mode: 2D/Multi-slice

Echo Train Length: 13-16

Matrix: 448 x 448 or higher

Slice Thickness/Gap: 5.0 mm/0 mm

Notes: It is recommended that the phase encode be set in the Antero-Posterior (AP) direction. A rectangular FOV may be used as the AP dimension need not be 32 cm.

7. AXIAL STIR SEQUENCE

Purpose: 2D Anatomic Imaging

Pulse Sequence: 2D-FSE-IR

TR/TE/Flip angle: 3800-4400/18-25/130ms

FOV: 20 cm x 20 cm

Number of Measurements: 2

Imaging Mode: 2D/Multi-slice

Echo Train Length: 7-8

Matrix: 384 x 384 or higher

Slice Thickness/Gap: 5.0 mm/0 mm

Notes: Imaging coverage should span the entire hip prosthesis on the affected (treated) side. It is recommended that the phase encode be set in the Right-Left direction. It is recommended that the same imaging slab be used as the Axial T1 weighted sequence. The goal is to achieve an optimal pixel resolution of approximately 500-600 microns. For subjects with bi-lateral implants, use 2 axial scans (one per side) to avoid loss of SNR.

APPENDIX 3: IMAGE TRANSFER PROTOCOL

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Instructions for submitting images to MMI are provided below. Any questions regarding the image transfer process for this study should be directed to the study's Project Manager at MMI:

David Kennedy
 Project Manager
 Medical Metrics, Inc.
 +1 (713) 850-7500 x204
dkennedy@medicalmetrics.com

Image Preparation

Subject Identification Code

All subject-identifying protected health information (PHI) should be removed from the images and/or metadata before being transferred to MMI. This includes the subject's Name, Birthdate, Age, Weight, Medical Record Number, etc. Sequence-specific details, such as the Series Description, Study Description, Protocol Name, Image Date, etc., must not be removed.

Subjects will be identified using a unique subject identification code consisting of a site number and subject number. The format of this identification code is provided below:



Site #
Subject #
Right (R) or Left (L)

Examples: 001–001R 999–998L

Notes: Include leading zeroes in the site and subject numbers
 MMI will not be collecting subject initials

File Naming Conventions for Digital Images

Digital images must be organized in a standard folder structure that clearly and uniquely identifies the subject ID and visit designation.

All images stored in DICOM format must use the following folder structure:

Format: .\[Subject ID] _ [Visit Designation] \ [Modality] \ [* .dcm files]

Example: .\123-456L_Year5\XR\image.dcm
 .\123-456L_Year5\MR\image.dcm

In this example, Year 5 images for subject 123-456L are organized within a folder "123-456L_Year5". The images are stored within a subfolder to identify them by modality, in this case, "XR" and "MR".

Notes: An underscore should separate the subject ID and Visit ID
 Use standard visit IDs (Year 5, Year 6, etc.)

Include leading zeroes in the subject ID
Use descriptive modality names, MR, CT etc.

Image Transmittal Form

An **Image Transmittal Form** (ITF) must accompany all images sent to MMI via courier or file transfer protocol (FTP) client. The ITF provides an inventory of the images contained within the shipment and a mechanism for documenting the receipt and return of the images. A project-specific ITF template is provided on the following page. An electronic version of the form will also be provided.

For transfers via courier, the ITF must be included in the shipping parcel.

For transfers via FTP, the ITF must be faxed or emailed to MMI.

For transfers via web-portal, the ITF is completed online and a separate form is not required.

Enter only one subject/visit designation per row. Multiple subjects can be included on the form. All fields should be completed for each transfer.

Sites must promptly submit all images to MMI to ensure timely receipt and inspection of images. Image receipt and inspections cannot begin until the images arrive at MMI.

Visit Designations:

- Year 5
- Year 6
- Year 7
- Year 8
- Year 9
- Year 10
- Year 11
- Post-Study Visit

MicroPort MoM Post-Market Study (553)

Sent Date:
(dd-mmm-yyyy)

Site Number:



Method of Transfer:

Tracking #:

FTP
 Courier

Person Preparing Shipment/Transfer:

Email:

Phone:

Fax:

Subject ID - Site - Subject R/L	Visit Designation	Visit Date (DD-MMM-YY)	Treatment Side
			<input type="checkbox"/> Right <input type="checkbox"/> Left
			<input type="checkbox"/> Right <input type="checkbox"/> Left
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Courier Transfer (Discs and Films):



Medical Metrics, Inc.
2121 Sage Road, Suite 300
Houston, Texas 77056
P 713-850-7500
www.medicalmetrics.com

Attn: MicroPort MoM Post-Market Study (553)

Address to Return Discs and/or Films:

FTP Transfer:

Click the "Send to MMI" button below to submit the transmittal form.

Alternatively, send this form to either of the following:

Fax: +1 (713) 850-9996
Email: tf@medicalmetrics.com

(To Be Completed by Medical Metrics Personnel)

Date of Return: ____ - ____ - ____ (dd-mmm-yyyy) Fax #: ____ Return Prepared By: _____

Image Transfer Options

The following image transfer options are available for this study:

- CD/DVD
- FTP
- Web-Portal using Medidata® Medical Imaging

CD/DVD Transfer

Sites that prefer to transfer images to MMI via CD/DVDs must send them to the following address using a courier service (e.g. FedEx, UPS or DHL) that support electronic tracking of shipments:

Medical Metrics, Inc.
Attn: MicroPort MoM Post-Market Study (553)
2121 Sage Road, Ste 300
Houston, TX 77056, USA

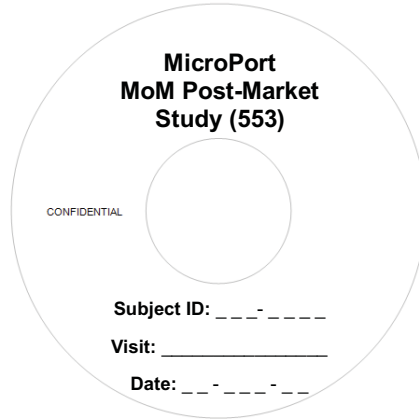
Phone: +1 (713) 850-7500
Fax: +1 (713) 850-9996

An **Image Transmittal Form** (ITF) must accompany each shipment. The ITF provides an inventory of all images in the shipment and must be placed within the packing container. The study ITF can be found in the section above.

Images for a specific subject visit should be stored on a single CD or DVD. **If possible, a single CD/DVD should contain only the images obtained during a single visit for a single subject.** Placing digital images for multiple subjects and/or multiple visits on a single CD or DVD should be avoided. All images must be stored to CD/DVD in DICOM format.

CD/DVD Disc Label

If needed, sites will be provided round disc labels that can be placed directly on the disc. The CD/DVD Disc Label is a permanent-adhesive label with pre-printed fill-in-the-blank and check-box information. The label is used to identify the subject ID, visit designation, and visit date of images on the CD or DVD. A ball-point pen should not be used on the label after it has been affixed to the disc, as this may corrupt the disc.



Disc Sleeve Label

CDs and DVDs must be contained within a sleeve or jewel case to protect the disc during shipment. A **Disc Sleeve Label** must be affixed to the CD/DVD sleeve or jewel case. The label should not be attached to the CD or DVD itself, which will obstruct the center hole, and render the disk unusable. The Disc Sleeve Label is a permanent-adhesive label with pre-printed fill-in-the-blank and check-box information. The label is used to identify the subject ID, visit designation, visit date, and type(s) of images on the CD or DVD.

An example **Disc Sleeve Label** is provided below:

MicroPort MoM Post-Market Study (553) – Disc Sleeve Label		
Subject ID:	____ - ____	_____
	Site #	Subject #
Visit Designation:	_____	
Visit Date:	____ - ____ - ____	
	dd	mmm yy

Notes: Include leading zeroes in the site and subject numbers
Use DD-MMM-YY date format (e.g. 01-Jan-14)

FTP Transfer

Sites that prefer to upload images via FTP will receive a file transfer account that is specific to the site and project, along with the username and password. A completed ITF must be faxed or emailed to MMI once the images have been uploaded.

The fax number is: +1 (713) 850-9996

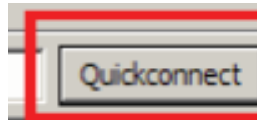
The email address is: tf@medicalmetrics.com

When MMI receives the transmittal form by fax or email, the images identified on the form will be moved off of the FTP site to indicate that they have been processed. The transmittal form will then be verified and faxed or emailed back to the site for their records. Any gaps or discrepancies will be marked on the transmittal form.

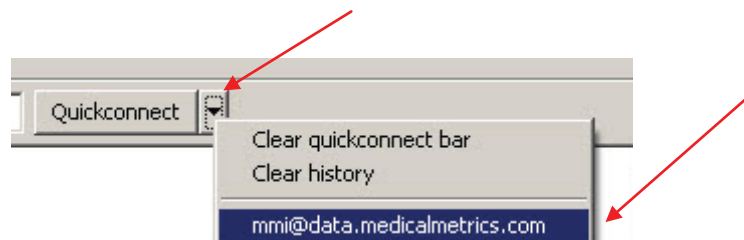
MMI recommends FileZilla for FTP file transfers, which is freely available from the website below. FileZilla is a free FTP transfer client and is recommended, though not required if your facility has an existing FTP client available for use.

NOTE: If FileZilla is not available to the site, or if installation / use of the client software is not permitted, an alternative software-based client should be used. Web-based FTP transfers are not recommended (ex. using Internet Explorer). The software used for FTP transfer should support the following features: unattended transfers, resuming interrupted / paused transfers (without restarting), multiple concurrent transfer sessions, and support for slow and / or lengthy transfers.

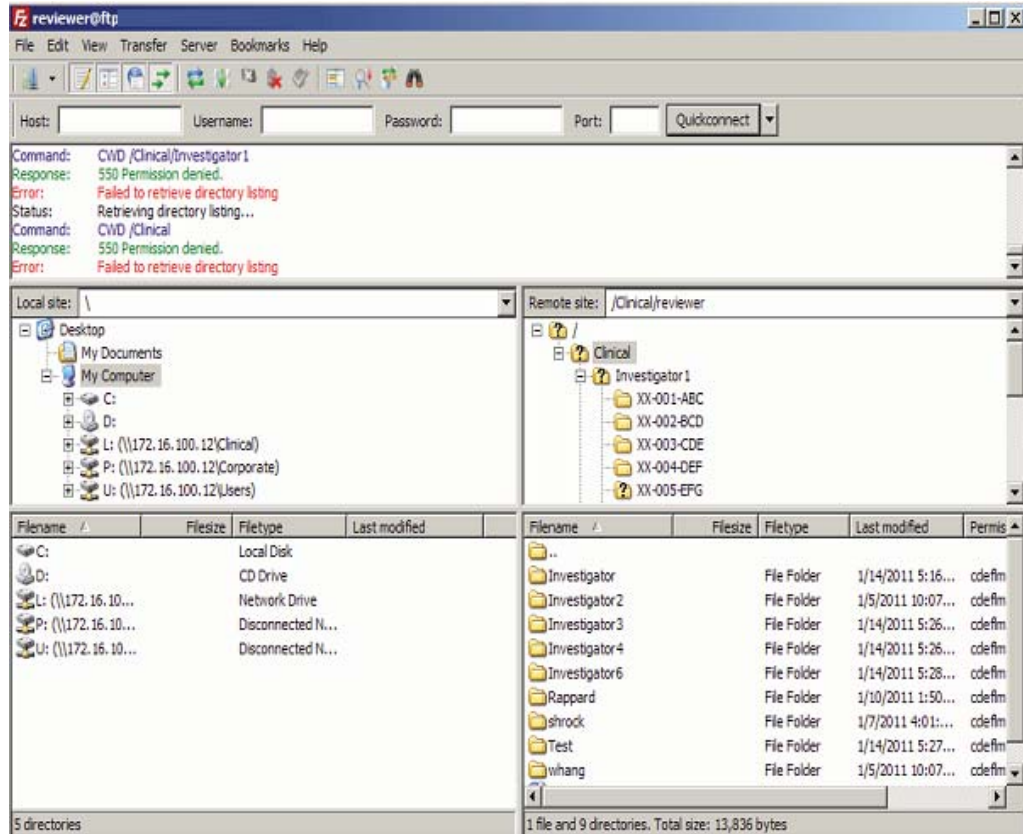
1. Load / Install FileZilla (<http://filezilla-project.org>)
 - Follow instructions to download FileZilla → **“Client”**
 - Select the proper download file according to your operating system (e.g., Windows FileZilla_3.5.1_win32-setup.exe [recommended])
2. Launch FileZilla and enter the following information:
 - Host: data.medicalmetrics.com
- or -
 - Secure Host: ftpes:\\data.medicalmetrics.com
 - Username: assigned by MMI (your project-specific FTP username)
 - Password: assigned by MMI (your project-specific FTP password)
 - Port: <empty>
3. Select "Quickconnect"



4. Click the Quickconnect arrow and select "mmi@data.medicalmetrics.com"



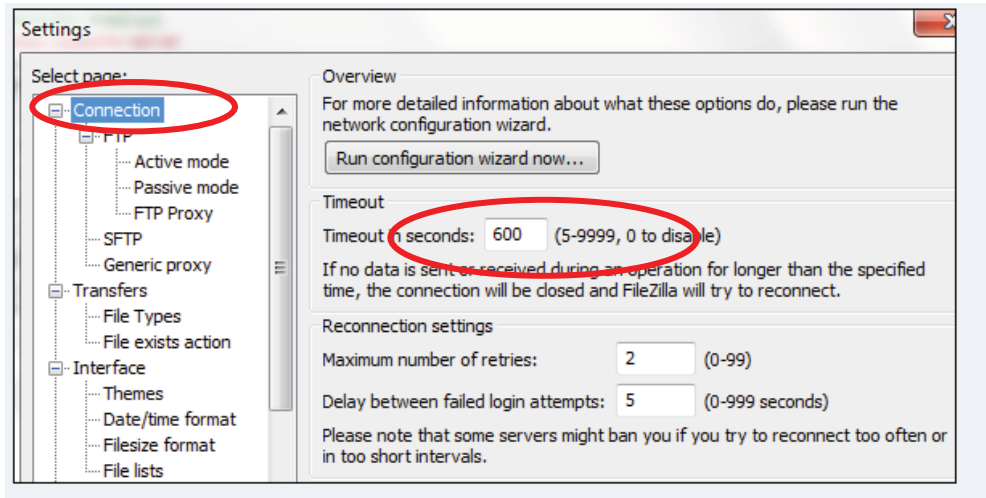
5. The files on **your** computer are in the 'Local Site' pane (left panel). The files on **MMI's FTP** site are in the 'Remote site' pane (right panel).



- Place a copy of the images you wish to transfer to MMI in descriptively-named folders using the folder-naming conventions described in section C1 above.
- Place all of these folders into a parent folder named with the subject ID, e.g., 123-456L. The complete folder path should look like this:
.\ [Subject ID] \ [Subject ID] _ [Visit Designation] \ [Modality] \ [file.dcm]
- In the left-hand pane of the FileZilla window, navigate to the new parent folder (i.e., 123-456L) on the local computer
- In the right-hand pane of the FileZilla window, select the location / directory on the ftp server that you wish to transfer the selected parent directory into (as seen in the example above, with the 'Clinical' directory selected).
- Right-click the selected directory on the left, and select 'Upload' to transfer into the chosen location on the ftp site.
- You will now see the file in the right pane – the file is being transferred (copied onto the FTP site). Large files (CT or MRI) may take several minutes to transfer.
- Fax the completed transmittal form to: +1 (713) 850-9996 or email the completed form to: tf@medicalmetrics.com

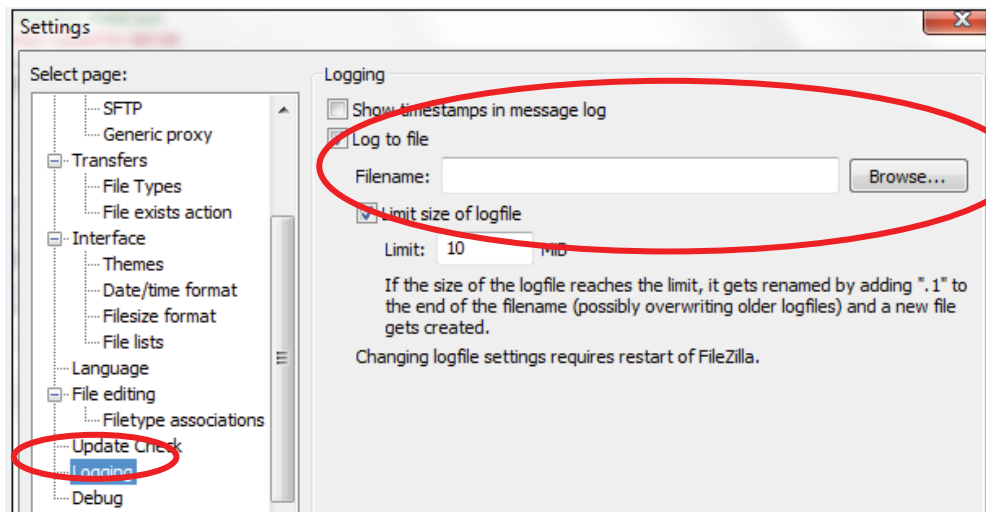
Additional Instructions & Tips:

After installing FileZilla, go to **Edit** → **Settings** → **Connection** to increase the timeout from 120 to at least 600 seconds. This will prevent the software from automatically disconnecting if there is ever a period of inactivity due to stepping away from the computer for a while.



You can also enable a logging record for your account audit trail. This can be used to record a history of your transfers for record-keeping purposes.

- **Edit** → **Settings** → **Logging** → **Log to file**.
- Click browse, specify a location, and save



For questions regarding FTP transfer process, please contact the study Project Manager at MMI.

For issues related to installation and setup of FileZilla, please contact MMI's technical support at: support@medicalmetrics.com

Web Portal Transfer

Sites that prefer to upload images via Medidata® Medical Imaging will find instructions in **Appendix A**. Each site electing to use this option will also be trained on how to use the portal.

Logistics Overview & Handling of Images at MMI

Image Quality Control

Upon receipt at MMI, the images will undergo at least two layers of quality control:

- **Image Labeling Inspection (ILI):** conducted to ensure there are no discrepancies in the subject ID, visit designation, visit date, or any other study information.
- **Image Quality Evaluation (IQE):** conducted to ensure the imaging parameters are compliant with the Image Acquisition Protocol and that the image quality is sufficient for use in the study.

Additional review may be required depending on the complexity of any noted issues.

Discrepancy Handling

All discrepancies identified during the image quality control process will be relayed promptly after identification via email notification to the site. MICROPORT will be carbon-copied (CC'd) on the email.

Each discrepancy will be tracked using a Discrepancy ID number which will be included in the discrepancy notification email. The Discrepancy ID number should always be referenced when responding to discrepancy notifications.

MMI does not store or destroy any image media. All films and CDs/DVDs will be returned to the site once discrepancies are resolved, along with the marked-up transmittal form(s). Images transferred via FTP will *not* be returned to the site, only the associated transmittal form(s) will be returned.

Appendix A: Medidata® Medical Imaging User Guide



Medidata[®] Medical Imaging Clinical Trial Platform

Site User Guide

Version 1.3
May 22, 2017



Welcome

Welcome to the Medidata® Medical Imaging Clinical Trial Platform Site User Guide. This platform will allow you to quickly and compliantly upload medical images and data related to your clinical trial so they can be accessed by the study sponsor or core lab (**Medical Metrics, Inc., MMI**). This User Guide contains detailed instructions on using the Medidata® Medical Imaging platform and a Quick Reference Sheet with step-by-step instructions for the most common actions you will perform within the system.

This document was developed by Medical Metrics, Inc. (MMI) for trials that use the Medidata® Medical Imaging Clinical Trial Platform. The document describes the features, functionality and workflow of the platform as designed for use with MMI processes. The information contained in this document is confidential and proprietary and should not be made available to those not directly associated with the trial.

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Workstation Setup

Choose your operating system

The Medidata Medical Imaging platform supports both Windows® and Mac® OS workstations. The preferred internet browser for both operating systems is Google Chrome®.

Regardless of the browser used, no software needs to be installed to use the Medidata platform to upload images. However, some browsers may require a plug-in to be enabled with the latest version of Java in order to upload medical images. Google Chrome is the preferred Windows browser since it uses HTML 5 and does not require Java or any other browser plug-ins.

If you are using Internet Explorer on a Windows workstation, an optional piece of software called the Transfer Agent may be installed as an alternative to Chrome or the Java-based upload. This software requires a small installation (<https://www.intelegrid.com/upgrade/>), which optimizes the upload process and may significantly reduce upload times. The Transfer Agent is not available for Mac OS.

Set up your workstation

Windows or Mac – Google Chrome (Recommended)

- a. If you do not have Chrome, download it by opening another internet browser and navigating to <https://www.google.com/chrome/browser/desktop/>

Windows – Internet Explorer (Alternate)

- a. Verify you have the most recent version of Internet Explorer
- b. Verify you have the most recent version of Java by going to <http://java.com/en/download/installed.jsp> and clicking the 'Verify Java Version' button.
- c. Click Start, and run. Then type “configure java” (without quotation marks). From the Java Control Panel, click on the Security tab. Under the Exception Site List box, click the Edit Site List button. Click the Add button and enter <https://web.intelegrid.com>
- d. Optionally, download and install the Transfer Agent at <https://www.intelegrid.com/upgrade/transferagent.html>

Receive your login information

Once site training is complete and Medical Metrics has confirmed that your site will be using the Medidata® platform, an email will be sent to you with login instructions. Contact your Medical Metrics project manager if you are ready to send your first images and have not received login instructions.

Using the Medidata Platform

Log in for the first time

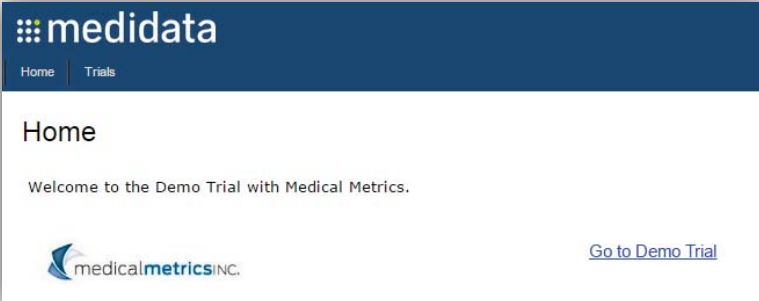
After configuring your browser settings and receiving your login credentials from Medical Metrics, you are ready to use the Medidata platform.

- a. Open your Internet browser
- b. Go to www.clinicaltrialimaging.com
- c. Enter your email address
- d. You will be asked to create a password the first time that you log in
- e. Once you login, click on the desired clinical trial to begin work

Note: If you are a part of more than one clinical trial that uses the Medidata® platform, all available trials will be shown on your home screen.



The screenshot shows the 'Sign In Medidata Imaging' page. It features the Medidata logo in the top right corner. Below the logo, there are two input fields: 'Email Address:' and 'Password:'. To the right of the password field is a link that says 'Forgot Password?'. Below the password field is a 'Login' button. A 'Secure Connection' indicator is visible at the bottom left of the form area. A link for 'Having trouble? Contact Support' is located to the right of the input fields.



The screenshot shows the 'Home' page of the Medidata platform. It features a dark blue header with the Medidata logo and navigation links for 'Home' and 'Trials'. Below the header, the text reads 'Home' and 'Welcome to the Demo Trial with Medical Metrics.' At the bottom left, there is the Medical Metrics logo. At the bottom right, there is a link that says 'Go to Demo Trial'.

Forgot password

If you forget your password, go to the website www.clinicaltrialimaging.com, enter your registered email address, and click the 'Forgot Password?' button. An automatic email will be sent to your email account with instructions to reset your password.

Navigate the Home Screen

The Home Screen is the first screen that is displayed after you log in and select your trial. From here, you will be able to add new Subjects to your trial, and access Subjects that have been enrolled by your Site.

The screenshot shows the Medidata Home Screen interface. At the top, there is a dark blue header with the Medidata logo and navigation links for 'Home' and 'Trials'. On the right side of the header, there is a user profile section with the email 'echan@medicametrics.com' and links for 'Profile', 'Help', and 'Sign Out'. Below the header, there is a white area with the 'medicalmetricsINC.' logo and navigation links for 'Back to Trials', 'Home', and 'Documents'. The main content area is titled 'Home' and features a 'Subjects' table. The table has columns for 'Site Name', 'Subject Name', 'Screening Name', 'Initials', 'Date of Birth', and 'Status'. There are four rows of data, each representing a subject. To the right of the table, there is a 'View' section with search options for 'Search Subjects' and 'Search Visits', and an 'Actions' section with an 'Add Subject' button. A 'Refresh' button is located below the table. Callouts with blue lines point to various elements: the 'Home' link in the header, the 'Subjects' table, the 'Initials' column, the 'Date of Birth' column, the 'Add Subject' button, the 'Search Subjects' and 'Search Visits' options, the 'Refresh' button, and the 'Subject Name' column.

Click here to go back to a list of clinical trials you have access to

Subjects currently enrolled in the trial from your Site

You can search for Subjects by any of the listed fields

Click to navigate back to the current trial Home page

Click to edit your profile or change your password

Home

Trials

echan@medicametrics.com Profile Help Sign Out

medicalmetricsINC.

Back to Trials Home Documents

Home

Site Name	Subject Name	Screening Name	Initials	Date of Birth	Status
002	002-001	Unknown	Unknown	Unknown	✓
002	002-111	Unknown	Unknown	Unknown	✓
002	002-003	Unknown	Unknown	Unknown	✓
002	002-952	Unknown	Unknown	Unknown	✓

(4 results in 1 pages)

Refresh

View

- Search Subjects
- Search Visits

Actions

- Add Subject

Sites are identified by a unique ID

Access existing subjects and visits by clicking on the appropriate Subject ID

Hit 'Refresh' to view recently created subjects

Add a new Subject to the trial

Search by Subject or Visit

Create a subject in your trial

Each subject you create will be associated with your site and searchable by other users at your site. Medical Metrics has carefully configured the data you are required to enter when creating each subject, and edit checks are in place to ensure that the data you enter is formatted correctly.

To create a subject:

- Click the 'Add Subject' button on the Home screen
- Fill in the Subject ID and any other required data on the Add Subject screen
 - If you are a part of more than one Site, you will be able to choose under the 'Site Selection' header
- Click 'Save'

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Add Subject

Step 1: Select the site you want to add a subject to.
Step 2: Complete subject details and click 'Save'.

Site Selection	Subject Details
Site Name <input type="text" value="002"/>	Please provide subject details below: Site: <input type="text" value="002"/> Number: <input type="text"/> Treated Side: <input checked="" type="checkbox"/> Left <input type="checkbox"/> Right
<input type="button" value="Save"/> <input type="button" value="Cancel"/>	

After creating the subject, you will automatically be taken to the subject-level view.

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Subject: 002-002

Subject Details			
Subject Name	002-002	Screening Name	Unknown
Treated Side	Left	Status	Active

Subject Details		
Subject Name	002-002	
Screening Name	Unknown	
Status	Active	

Actions

- Add Unscheduled Visit

Visits

Visit Name	Complete	Img Reqs
Pre-Op	✗	0
1-Year	✗	0
Post-Op	✗	0

Complete a visit requirement

When a subject is added in the platform, a visit calendar for that subject is automatically created. Each visit contains requirements (medical imaging or file uploads) for you to complete. Access the individual visits by clicking on the visit name in the right navigation panel. After fulfilling all of the requirements for a visit, you will submit the visit for review.

Requirements that are mandatory for the visit are initially highlighted in **red** whereas optional requirements are not highlighted. After you complete a mandatory requirement, the highlight will change from **red** to **green**. Some trials offer the ability to 'override' certain requirements for a visit, so that you can identify required imaging that was not taken or is otherwise permanently unavailable.

To complete a visit requirement:

- Click on the desired 'Subject' from the Home screen, or create a new subject
- Click on the desired 'Visit' for the subject from the navigation panel on the right
- Click on a command next to the desired 'Requirement' to fulfill the requirement

From the requirement-level view, there are 2 possible types of requirements that you may be asked to complete: 1) medical image exams (usually DICOM files) and/or 2) file uploads (non-DICOM files). See the following page for more details on each requirement type.

The screenshot displays the 'Subject: 002-003' page. It features a 'Pre-Op Visit Details' section with a table showing the visit name, status (Active), and date (Unknown). Below this is a 'Pre-Op Visit Requirements' table with columns for Type, Info, Requirement, and Commands. The requirements are: 1 exam (CT), 1 exam (Procedure Form), and 1 exam (X-Rays). The X-Rays requirement is highlighted in red, indicating it is mandatory and not yet completed. The CT requirement is highlighted in green, indicating it is optional and completed. The Procedure Form requirement is highlighted in green, indicating it is optional and completed. The 'Commands' column for the X-Rays requirement shows 'Upload Exams' and 'Override'. A 'Submission Problems (3):' section lists three errors: 1. X-Rays: Requires an upload or override. 2. Visit date is required. 3. CT: No upload supplied. A red error message at the bottom states: 'The Pre-Op visit has not satisfied all required items. Please submit all required exams and files to mark complete!'. On the right side, there is a 'Subject Details' panel with a 'Close' button, and a 'Visits' table showing the status of various visits. The 'Pre-Op' visit is highlighted in blue and shows a red 'X' in the 'Complete' column and '1' in the 'Img Reqs' column. The '1-Year' and 'Post-Op' visits also show red 'X' marks in the 'Complete' column and '0' in the 'Img Reqs' column. A 'View' section on the right includes 'View Subject' and 'Add Unscheduled Visit'. A 'Visits' table at the bottom right shows the status of various visits. A 'Select a visit for the subject' callout points to the 'Visits' table. A 'Fulfill requirements by clicking on the commands here' callout points to the 'Commands' column in the requirements table. An 'Errors in red must be addressed before a visit can be submitted.' callout points to the red error message.

medicalmetrics INC. Back to Trials Home Documents

Subject: 002-003

Pre-Op Visit Details

Visit Name	Pre-Op	Visit Date	Unknown
Status	Active		

Pre-Op Visit Requirements

Type	Info	Requirement	Commands
Exam	CT	1 exam	Upload Exams
Exam	Procedure Form	1 exam	Upload Exams Comment
Exam	X-Rays	1 exam	Upload Exams Override

Submission Problems (3):

Errors:

- X-Rays: Requires an upload or override.
- Visit date is required

Warnings:

- CT: No upload supplied.

✖ The Pre-Op visit has not satisfied all required items. Please submit all required exams and files to mark complete!

Exam

Preview	Requirement	Details	Modality	Study Date	Images / Series	Upload Date	Upload By	Actions
	Procedure Form		SC	18-Feb-2016 5:47 PM	4 / 1	18-Feb-2016 5:47 PM	pnewman@medicalmetrics.com	Preview

Subject Details

Subject Name 002-003
Screening Name Unknown
Status Active

View

View Subject

Actions

Add Unscheduled Visit

Visits

Visit Name	Complete	Img Reqs
Pre-Op	✖	1
1-Year	✖	0
Post-Op	✖	0

Select a visit for the subject

Fulfill requirements by clicking on the commands here

Errors in red must be addressed before a visit can be submitted.

Upload medical images or files

To upload an image or exam for a requirement, click on the command 'Upload Exam' next to the requirement. Depending on the requirement, you may be asked to select whether the upload file is a DICOM or Non-DICOM file.

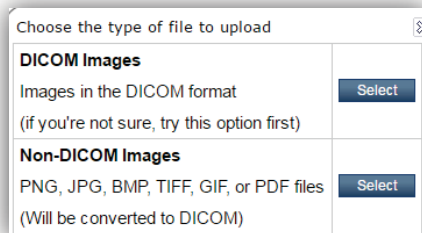
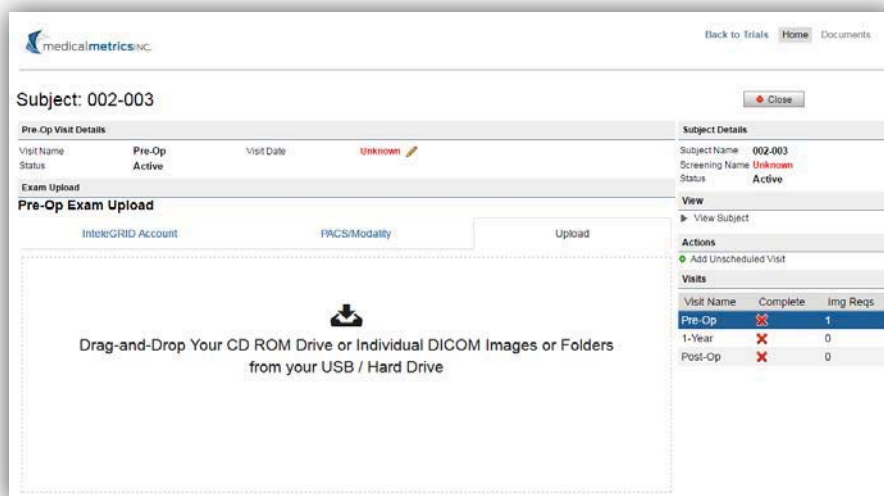


Image Uploads (DICOM)

To upload an image, drag and drop images or folders from a CD/DVD, USB drive, or the computer hard drive into the web browser window. All images/exams in the directory will subsequently be displayed on the screen, where you can specify which studies should be uploaded to the image requirement at that visit.



Note: The interface may prompt you to browse for the images rather than drag-and-drop depending on the internet browser and whether you are using the Transfer Agent described on Page 3.

Tip: You can review studies you uploaded by going to the Visit-level view and pressing the 'Preview' icon next to the study. This will launch an image viewer of the uploaded file within your Internet browser (no software installation required).

Exam								
Preview	Requirement	Details	Modality	Study Date	Images / Series	Upload Date	Upload By	Actions
	Procedure Form		SC	18-Feb-2016 5:47 PM	4 / 1	18-Feb-2016 5:47 PM	pnewman@medicalmetrics.com	Preview

For study-related questions, please contact your MMI project manager.
For technical support regarding the image transfer platform, please contact helpdesk@mdsol.com.

File Uploads (Non-DICOM)

File uploads may be used for non-image files (e.g. documents). To upload non-image files:

- Select 'Choose File' and navigate to the file that you want to upload
- Click 'Open'. The selected filename will appear in the list for upload
- Once all desired files have been selected to fulfill the requirement, click 'Complete Image Upload'

medicalmetrics INC. Back to Trials Home Documents

Subject: 002-003 Close

Pre-Op Visit Details		Subject Details													
Visit Name	Pre-Op	Visit Date	Unknown												
Status	Active	Subject Name	002-003												
Pre-Op File Upload [Procedure Form]		Screening Name	Unknown												
Choose File No file chosen		Status	Active												
File Name		View													
098_21-118-L-N_Longitudinal_XR_Lat Timebased.gif		View Subject													
098_19-212-MMR_PreOp_MR_Axial T2 Series_Axial MR (12.000).jpg		Actions													
Action		Add Unscheduled Visit													
	Remove	Visits													
	Remove	<table border="1"> <thead> <tr> <th>Visit Name</th> <th>Complete</th> <th>Img Reqs</th> </tr> </thead> <tbody> <tr> <td>Pre-Op</td> <td></td> <td>1</td> </tr> <tr> <td>1-Year</td> <td></td> <td>0</td> </tr> <tr> <td>Post-Op</td> <td></td> <td>0</td> </tr> </tbody> </table>		Visit Name	Complete	Img Reqs	Pre-Op		1	1-Year		0	Post-Op		0
Visit Name	Complete	Img Reqs													
Pre-Op		1													
1-Year		0													
Post-Op		0													
Series Name Procedure Form															
Complete Image Upload		Cancel													

Submit a visit for review

Once all of the requirements for a visit have been satisfied, a blue 'Submit Visit' button will appear and you will be able to submit that visit for review. This action will automatically alert Medical Metrics that a visit has been completed and will transfer the images to Medical Metrics. To submit a visit:

- Click on the desired 'Subject' from the Home screen
- Click on the desired 'Visit'
- Confirm that there are no error messages or missing information in **red**
- Click on the blue 'Submit Visit' button

After submission of the visit, you will receive a message that indicates the images have been submitted and are under review. In addition, the **x** on the Visit Calendar will be replaced with a **✓**, which will be visible the next time you load the subject-level or visit-level views.

Note: Before completing the last requirement for a visit, the Medidata® platform may ask you if you would like to submit automatically. If you would like to do so, the system will submit the visit once the requirement has been fulfilled. If you do not fulfill the requirement, the visit will not be submitted.

The screenshot displays the Medical Metrics interface for Subject 002-003. The 'Post-Op Visit Details' section shows the visit name, status (Active), and date (05-Sep-2015). The 'Post-Op Visit Requirements' table lists one requirement: '1 exam' of type 'Exam' and info 'Ultrasound', with a 'Commands' link 'Upload Exams'. A blue 'SUBMIT VISIT' button is visible. The 'Visits' table shows the following data:

Visit Name	Complete	Img Reqs
Pre-Op	✘	1
1-Year	✘	0
Post-Op	✘	0

Once all requirements have been met, you must click 'Submit Visit' to transfer images to Medical Metrics.

The **x** next to the submitted visit will change to **✓** once a visit has been successfully submitted.

Perform a Test Transfer to MMI

Each site should submit a test image to Medical Metrics in the actual trial platform to confirm that the images can be transferred as intended. After your user account has been activated, send a test image to Medical Metrics by following these instructions:

- a. Click on 'Add Subject' to create a new subject
 - In the Subject ID/number field, enter 'TEST'
 - Fill out any other required information, and click 'Save'
- b. Select any visit in the navigation panel on the right for the test transfer
- c. Click on the command next to each 'Requirement' to fulfill the requirement(s)
- d. Once all requirements are fulfilled, click the blue 'Submit Visit' button

Once the test transfer is complete, Medical Metrics will notify you only *if* there were any issues with the transfer. Otherwise, if the dialog indicates the transfer was completed successfully, you may begin submitting study images.

The screenshot shows the Medical Metrics interface for a subject named '002-TEST'. The interface includes a header with the Medical Metrics logo and navigation links. The main content area is divided into several sections:

- Subject: 002-TEST**: A callout box (1) points to the subject ID field.
- Post-Op Visit Details**: A table showing visit information. A callout box (3) points to the 'Commands' column, which contains an 'Upload Exams' link.
- Post-Op Visit Requirements**: A table with columns for Type, Info, Requirement, and Commands. The 'Requirement' column shows '1 exam' in a green box. A callout box (4) points to the 'SUBMIT VISIT' button below this section.
- Subject Details**: A sidebar on the right showing subject information. A callout box (2) points to the 'Visits' section, which contains a table of visit details.

The 'Visits' table in the sidebar is as follows:

Visit Name	Complete	Img Reqs
Pre-Op	✗	1
1-Year	✗	0
Post-Op	✗	0

Frequently Asked Questions

Is Intelemage the same as the Medidata Medical Imaging platform?

Yes, Intelemage was acquired in 2016 by Medidata and the platform has been rebranded as the Medidata® Medical Imaging platform.

Is the Medidata Medical Imaging Platform secure?

Yes, the Medidata infrastructure is a secure platform to transfer medical images. The platform is 21 CFR Part 11 compliant, SOC-2 Type II Certified, designed to enable users to meet all HIPAA obligations, and fully validated with redundant data centers for optimal data security.

How do I get a Medidata account?

Medical Metrics will email you with your log-in credentials after it has been confirmed that your site will be using the Medidata platform and site training has been completed.

Do I need to de-identify medical images before upload?

For DICOM files, the Medidata® platform automatically removes all PHI stored in DICOM tags when you upload a study. For non-DICOM files, it is the site's responsibility to mask any PHI that is 'burned' into the pixel data of an image prior to uploading to the Medidata® platform.

What happens if I upload a scan by mistake?

You will not be able to remove scans that have already been submitted. Contact your Medical Metrics project manager, and they will remove the incorrect scan for you.

If our site cannot use the Medidata platform, what other options do we have?

There are other methods of transferring images to Medical Metrics. Contact your Medical Metrics project manager if your site is unable to use the Medidata image transfer platform.

Do I need to follow-up with Medical Metrics to ensure the imaging was received?

No, Medical Metrics will receive an automatic notification that a new visit has been submitted, so no additional follow-up is required. However, you should confirm that the 'Submit Visit' button was clicked, and that a green checkmark (✓) is visible next to the submitted visit. If you see a red "x" (✗), the visit was not submitted correctly, and you should go through the submission process again.

I forgot my password. What do I do?

Go to the website www.clinicaltrialimaging.com, enter your email address, and click the 'Forgot Password?' button. You will receive an automatic email with instructions to reset your password.

Quick Reference Guide

Workstation Setup

1. Launch Google Chrome.
2. If not using Google Chrome, Update Java™ by going to <http://www.java.com/en/download/installed.jsp> on your browser and clicking 'Verify Java'

Using the Medidata Platform

1. Log in
 - a. Go to www.clinicaltrialimaging.com
 - b. Enter your email and password
 - c. Click on the desired clinical trial
2. Navigate the Home Screen
 - a. From the Home Screen, you can create new Subjects, search for previously created Subjects, or search for specific Subject-Visits
3. Create a Subject
 - a. Click the 'Add Subject' button on the Home Screen
 - b. Fill in the Subject ID and any other required data
 - c. Click 'Save'
4. Complete Visit requirement(s)
 - a. Click on the desired 'Subject' from the Home Screen
 - b. On the Subject screen, click on the desired 'Visit' from the navigation panel on the right
 - c. On the Visit screen, click on the command next to the desired 'Requirement' to fulfill the requirement
5. Submit a Visit for review
 - a. Once all requirements are fulfilled for a visit, click the blue 'Submit Visit' button on the Visit screen