

# Explant, Tissue, and Fluid Collection and Analysis Summary

## 1 INTRODUCTION

The United States Food and Drug Administration (FDA), has issued Section 522 Orders for formal post market surveillance studies to Zimmer for 510(k) cleared metal on metal hip implants. The orders cover legacy Zimmer devices as well as those acquired through Implex and Centerpulse. Part of the post-market surveillance includes the study of explanted retrievals when made available after medically necessary surgical intervention. The analysis requested by the FDA is to be focused on identifying the “modes and causes of failure”, and “should include, but not be limited to, analysis of taper/trunion involvement” in the failure [1]. The explant analysis should also identify clinical and demographic factors that may be “associated with device failure,” [1].

This document describes the steps to be taken to collect explanted devices, tissue and joint effusion samples as appropriate, and patient clinical data. The steps Zimmer is asking the health care providers to perform are described in Section 2. Flowcharts that summarize the activities in Section 2 have also been generated. Please read the detailed instructions in Section 2, and use the Flowcharts to guide you through the device, tissue, fluid, and data collection activities. These instructions do not address the safety issues associated with these activities. Only those trained in handling infectious substances should perform these procedures. Additionally, these activities should only be performed to the extent that they do not adversely affect patient safety.

This document makes reference to an “explant kit” (available by calling Zimmer 1-877-946-2761). This kit includes:

1. A brown box which contains materials for collecting and shipping tissue and fluid samples including:
  - a) 12 tissue cartridges
  - b) 4 small jars
  - c) 4 large jars
  - d) 1 marker and 1 pencil
  - e) 2 clear biohazard bags
  - f) 2 sheets of absorbent material
  - g) 2 white biohazard envelopes
  - h) 1 SafTpak box for Diagnostic Specimens
  - i) 1 pre-addressed FedEx label
2. A white box which contains materials for shipping explanted components (cup, head, etc) including:
  - a) 4 padded envelopes
  - b) 8 clear biohazard bags
  - c) 1 pre-addressed FedEx label

Sections 3 and 4 of this document summarize the analyses that Zimmer and Zimmer’s contract laboratory, Exponent (Philadelphia, PA), will perform on the explanted devices and any tissue or fluid samples obtained. Sections 3 and 4 do not contain any activities to be performed by health care providers, but are included for informational purposes only.

## 2 Explant, Tissue, and Fluid Collection

### 2.1 Pre-Operative (Flowchart 1)

- 1) The revising surgeon should obtain consent forms from [www.522.zimmer.com](http://www.522.zimmer.com) and follow their standard procedures for obtaining consent from the patient to be included in this study. Zimmer recognizes the patient has the right to refuse to be included in the study. However, if the patient does not consent to the study, Zimmer requests that the occurrence of a revision still be reported through a Product Experience Report (PER). Zimmer sales representatives can assist with the PER process. Being included in the study means the patient agrees that:
  - a) their explanted device can be sent to Zimmer for analysis (including potentially destructive analysis);
  - b) tissue and fluid samples may be obtained as medically appropriate and sent to Exponent for analysis (Exponent is a laboratory Zimmer has contracted with for the purpose of tissue and fluid analysis); and
  - c) medical records regarding the index and revision surgery will be sent to Zimmer, which is a non-HIPAA entity.
- 2) At least two days prior to surgery, please contact the Zimmer Call Center at 1-877-946-2761 to request an explant and tissue shipping kit. This kit will contain materials and detailed instructions for collecting and shipping explants and tissue and fluid samples. At the time of this call, a unique identification number (CPTXXXXXXXXXX) will be assigned to track the explanted device.
- 3) Obtain the patient's medical records for the index surgery. In particular please obtain:
  - a) the pre-index surgery imaging;
  - b) the quality of the index surgery;
  - c) reasons for revision;
  - d) patient experience with the implant;
  - e) clinical performance;
  - f) original diagnosis;
  - g) date of implantation; and
  - h) patient's age, sex, height, weight.

### 2.2 Day of Surgery (Flowchart 2)

- 1) Ensure camera, formalin, and the explant shipping kit are available.
- 2) Prior to actual removal of the device from the patient, obtain *in situ* photographs that show localized identifiable features of the devices (such as etch content) as well as allow the *in situ* orientation of the devices to be determined. If possible, mark the superior portion of the shell and the inferior portion of the head with an indelible, but non-destructive technique, such as a marker.

- 3) Inspect for, and describe instances of:
  - a) soft tissue damage/destruction via metallosis;
  - b) bony destruction (osteolysis);
  - c) muscle attachment destruction;
  - d) nerve damage; and/or
  - e) presence of pseudotumors or lymphocytic masses.Record the description in the surgical notes or on Data Sheet 1 (attachment)
- 4) If joint effusion is observed, take a sample of the fluid and place it in one of the small jars provided in the explant kit. Label the outside of the small jar to identify it as containing joint effusion using the marker provided. Do not add formalin to the sample of the joint effusion.
- 5) In cases without an obvious cause of failure such as early loosening (<3 months), osteolysis or fracture, excise a sample of any pseudotumor type periprosthetic tissue, metal stained tissue, and any necrotic bone or tissue as long as patient safety is not adversely affected. Collected tissue samples should be placed in individual tissue cartridges with one tissue location sample per cartridge. Be careful not to over-stuff the tissue cartridge. If the tissue sample is too large for a cartridge, place the tissue sample directly into a small jar. Do not mix the tissue samples with any joint effusion samples.
- 6) Number each individual tissue sample in the cartridges (with pencil) or small jars (with marker). The location for each tissue sample can then be identified by writing the tissue sample numbers on the anatomical images on Data Sheet 2, and then a description can be provided on the lines below the image. Alternately, directly label the cartridges or jars with the location and/or description of the tissue.
- 7) Place the tissue cartridges into the small jars provided. Do not over-stuff the small jars. Each small jar should be able to fit 2 to 3 tissue cartridges. Add 10% formalin to each small jar containing tissue (do not add formalin to joint effusion). Add enough formalin so the entire tissue sample is covered, but do not exceed more than 30 mL per small jar. Formalin should be available from the hospital.

### **2.3 Post-Operative (Flowcharts 2, 3, 4)**

- 1) Inspect the explanted devices shortly after explantation and document damage known to have been caused during extraction via a written description, sketches, and/or photographs. This inspection and documentation should be performed in the presence of, or with the consultation of the operating surgeon. Sketches are provided for recording damage on Data Sheets 3 and 4
- 2) Rinse and decontaminate the explanted devices. Only cold decontamination techniques should be used. Potential methods include soaking in 10% neutral buffered formalin for 12 hours, or soaking in STERIS' Spor-Klenz® according to the manufactures' instructions
- 3) Obtain the patient's medical records for the revision surgery. In particular please obtain:

- a) the pre-revision surgery imaging;
  - b) the quality of the revision surgery;
  - c) date of revision;
  - d) main observations at revision;
  - e) other mitigating factors; and
  - f) device part number and lot number.
- 4) (**Flowchart 3**) Ship the retrieved components to Zimmer using the pre-addressed white box and the associated packaging materials. Each individual component should be sealed in a plastic biohazard bag and then placed into and sealed in a second biohazard bag. The double bagged component should then be placed into a padded envelope. All components, in padded envelopes, should then be placed in the white box along with any completed Data Sheets or paper medical records and shipped to Zimmer. Please ship all components from one subject per white box, and ensure all envelopes, boxes, documents, etc. are labeled with the CPT number, patient initials and revision date, or other information that will ensure subsequent identification.

When handling, packaging and shipping the retrieved components, avoid putting all the retrieved components in the same container without separating packaging. Ideally, each retrieved component should be individually wrapped and stored in its own padded envelope, then placed in the white box with all the other retrieved components. This will prevent further damage to the explants, which can be difficult to distinguish from *in situ* damage.

- 5) (**Flowchart 4**) Ship any tissue samples and joint effusion to Exponent using the pre-addressed brown box and the associated packaging materials. Ensure the lids of all the small jars are screwed on tightly. Then place the small jars in the large jars and ensure the lids of the large jars are screwed on tightly. Ensure all large jars are labeled with the CPT number, patient initials and revision date, or other information that will ensure subsequent identification.

Place the two large tissue jars and 1 sheet of absorbent material in one clear biohazard bag. Repeat for the other two large tissue jars. Seal each clear biohazard bag and place it into a white biohazard envelope. To close the envelope, please follow the directions printed on the envelope. Place all white envelopes for an individual patient into the black nylon retrieval kit and zip it up. Place the black nylon retrieval kit in the brown SafTpak Box.

- 6) Send all electronic data (such as electronic copies of medical records, or digital pictures taken during surgery) to [zimmer.per@zimmer.com](mailto:zimmer.per@zimmer.com). Include the Zimmer issued “CPT” identification number in the e-mail.

### 3 Summary of Explant Analysis

When the explanted components and clinical information are received by Zimmer, the collected data will be reviewed for missing information, and the hospitals and/or surgeons where the device was implanted and explanted will be asked to provide any missing clinical

information and/or for an explanted device that is not returned. All received explanted devices will then be analyzed using methods from ASTM F561 [2] and as described below:

- 1) All received devices will be inspected for the features in Table 1 (articulating surface), Table 2 (taper) and Table 3 (non-articulating surfaces).

**Table 1. Articulating Surfaces**

1. Wear	8. Edge damage/subluxation
2. General scratches	9. Equatorial contact wear
3. Sizable 3rd body damage	10. Stripe wear formations (superior and inferior)
4. Surface corrosion	11. Evidence of, or exclusion of, a polished main wear zone
5. Embedded particles	12. Surface pitting
6. Discoloration or staining	13. Wear Scars exceeding to the cup rim and beyond
7. Impingement	

**Table 2. Taper Surfaces**

1. Wear	4. Embedded particles
2. Fretting	5. Discoloration or staining
3. Corrosion	6. Surface pitting

**Table 3. Non-articulating Surfaces**

1. Cup front face damage	3. Backside damage, i.e. any damage to the backing of the cup (e.g. removal of porous beading/coating) or bottom face of the femoral head
2. Cup edge/rim damage, both superior and inferior edges	4. Fretting damage caused by fixation screws, if present.

- 2) The fracture surface of all devices with mechanical fracture will be inspected for evidence of the phenomena listed in Table 4. Unique fracture surfaces will be examined for the phenomena in Table 5 using scanning electron microscopy (SEM) as appropriate.

**Table 4. Fracture Surfaces**

1. Static-overstress, causing plastic deformation	5. Impact
2. Shear	6. Stress corrosion or environmental cracking
3. Fatigue	
4. Torsion	7. Corrosion-fatigue

**Table 5. Fracture Surface Phenomena**

1. Presence of fatigue striations	3. Evidence of significant ductile overload
2. Fraction of surface with ductile overload	4. Defects associated with crack initiation

- 3) Cups that were well-positioned *in situ* and associated with adverse tissue reactions, or with obvious high wear/damage will be measured with a three-dimensional coordinate measuring machine (CMM) to measure changes in device radius of curvature of both worn and unworn surfaces. Estimations of volumetric wear will then be determined based on fitting the surfaces of the worn and un-worn regions and computationally determining the volume of the worn region. Available heads that articulated with well positioned cups *in situ* and associated with adverse tissue reactions or with obvious high/wear damage will have the same volumetric wear measurements and calculations performed.
- 4) All tapers that have greater than 30% of the surface discolored or with obvious high magnitudes of fretting will be measured with the CMM and have volumetric loss calculations performed using a process comparable to that used for the articular surfaces.
- 5) All devices (cups) that were not significantly malpositioned or did not loosen at less than three months will be subject to a detailed wear map analysis. This mapping consists of identifying wear, transitional wear, and other areas of interest and then taking images of each area of interest optically, with interferometry, or scanning electron microscopy using the method and magnification that allows the area of interest to be characterized. Damaged and undamaged surfaces will also undergo surface roughness measurements. These cups will also be sectioned to perform hardness, average grain size and carbide volume fraction measurements.

## 4 Summary of Tissue Analysis

The excised tissue will be dehydrated, embedded, and sectioned. The tissue will then be stained with hematoxylin and eosin, and a detailed histological analysis of the tissue will be performed. The presence and extent of giant cell activity, white blood cell infiltration, blood cell death, and presence/absence of germinal centers will be noted. The tissue samples will be scored according to the following:

### Surface tissue necrosis [3]

Type 1: surfaces that show intact synovial surface epithelium.

Type 2: surfaces where there was a loss of the synoviocyte layer without fibrin deposition.

Type 3: surfaces associated with fibrin deposition;

Type 4: surfaces where there was extensive necrosis with loss of architecture.

### Width of lymphocytic cuffs [4]

Grade 1: cuffs <0.25 mm thick

Grade 2: cuffs 0.25 to 0.5 mm thick

Grade 3: cuffs 0.5 to 0.75 mm thick

Grade 4: cuffs >0.75 mm thick

Status of blood vessels

- A: no vasculitis
- B: early vasculitis
- C: late vasculitis

Chronic lymphocytic infiltrate present [4]

- A: diffuse synovitis
- B: lymphoid aggregate synovitis
- C: germinal centre containing synovitis

Status of inflammatory cells [5]

- 0: Minimal inflammatory cell infiltrates
- 1: Predominantly macrophages, occasional lymphocytes may occur
- 2: Mix of macrophages and lymphocytes, either diffuse and/or small (<50% of hpf) perivascular aggregates
- 3: Mix of macrophages and lymphocytes, large (>50% hpf) perivascular aggregates may occur
- 4: Predominantly lymphocytes, mostly in multiple, large (>50% hpf) perivascular aggregates, follicles may be present

Loss of synovium [5]

- 0: Intact synovial lining
- 1: Focal loss of synovial surface, fibrin attachment may occur
- 2: Moderate to marked loss of synovial surface, fibrin attachment
- 3: Complete loss of synovium, abundant attached fibrin and /or necrosis of lining tissue

General tissue organization [5]

- 0: Normal tissue arrangement
- 1: Mostly normal tissue arrangement, small areas of synovial hyperplasia, focal necrosis may occur
- 2: Marked loss of normal arrangement, appearance of distinct cellular and acellular zones, thick fibrous layers may occur
- 3: Perivascular lymphocytic aggregates mostly located distally, thick acellular areas may occur

If there is a tissue sample with metal staining, approximately 1 g of tissue (if available) will be digested in acid and analyzed for the presence of cobalt, chromium, molybdenum, and titanium using inductively coupled plasma mass spectrometry (ICP-MS). A second 1 g portion of metal stained tissue (if available) will be enzymatically digested, filtered and evaluated for particle number and size distributions. Metal stained joint fluid will also be evaluated for particle number and size distribution.

## 5 REFERENCES

- [1.]JPS110093 letter, received from FDA, 6 May 2011, as an example.
- [2.]ASTM F561-05a “Standard Practice for Retrieval and Analysis of Medical Devices, and Associated Tissues and Fluids,” Reapproved 2010, ASTM International, West Conshohocken, Pennsylvania.



- [3.] Davies AP, et al. An unusual lymphocytic perivascular infiltration in tissues around contemporary metal on metal joint replacements. *J Bone Joint Surg Am* 2005;87:18-27
- [4.] Natu S, et al, “Adverse reactions to metal debris: histopathological features of periprosthetic soft tissue reactions seen in association with failed metal on metal hip arthroplasties,” *J Clin Pathol* 2012;65:409-418.
- [5.] Campbell P, et al, “Histological Features of Pseudotumor-like Tissues From Metal-on-Metal Hips,” *Clin Orthop Relat Res* (2010) 468:2321–2327



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# Data Sheet 1: Intra-Op Explant Damage: CPT \_\_\_\_\_

Description of instances of:

a) soft tissue damage/destruction via metallosis \_\_\_\_\_

\_\_\_\_\_

b) bony destruction (osteolysis) \_\_\_\_\_

\_\_\_\_\_

c) muscle attachment destruction \_\_\_\_\_

\_\_\_\_\_

d) nerve damage \_\_\_\_\_

\_\_\_\_\_

e) presence of pseudotumors or lymphocytic masses. \_\_\_\_\_

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# Data Sheet 2: Tissue Retrieval Data Form

## CPT \_\_\_\_\_

**Known metal sensitivities:**

\_\_\_\_\_

**Tissue Description:**

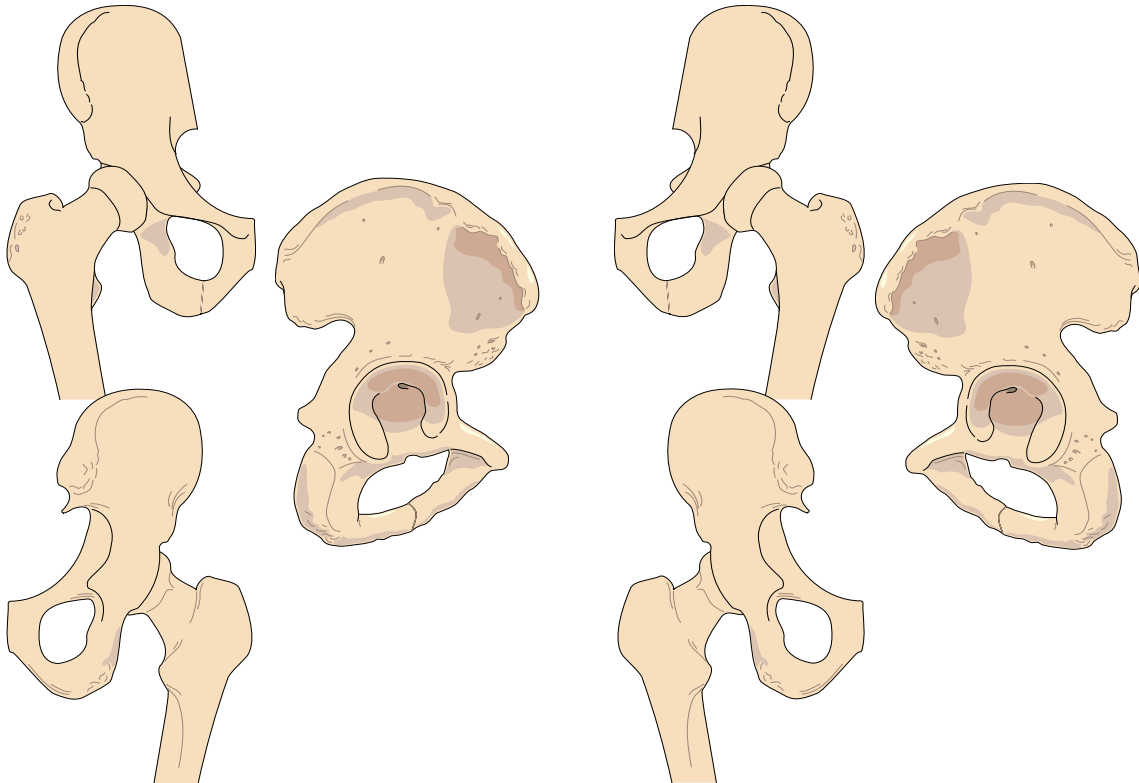
\_\_\_\_\_

\_\_\_\_\_

**Please indicate the location(s) of retrieved tissues.**

**Right**

**Left**



**Additional Information (anything that might be useful for tissue analysis including color of tissue, complications during removal):**

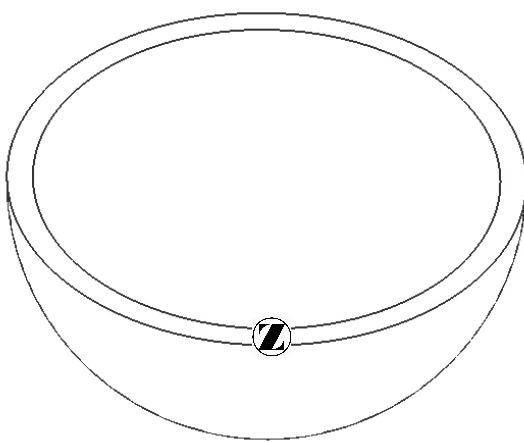
\_\_\_\_\_

\_\_\_\_\_

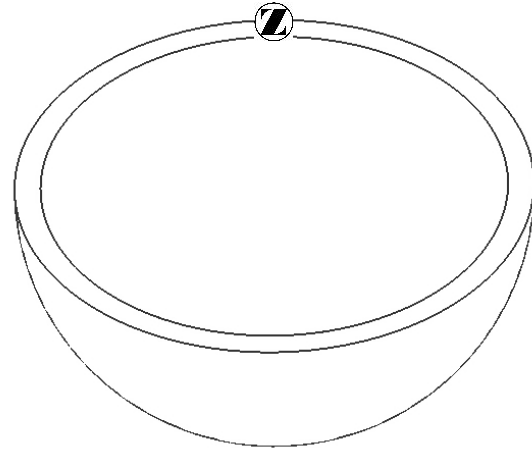
\_\_\_\_\_

## Data Sheet 3: Intra-Op Explant Damage: CPT \_\_\_\_\_

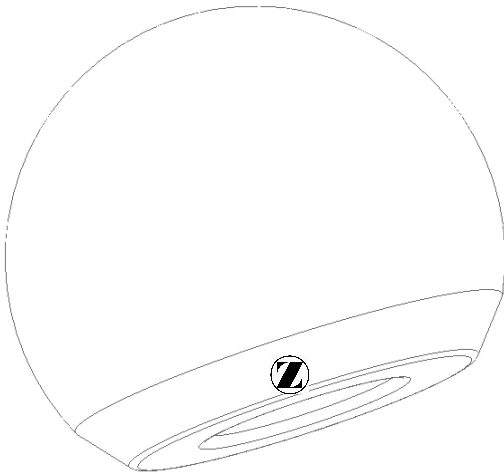
Please orient the components as shown and sketch the damage caused during device removal.



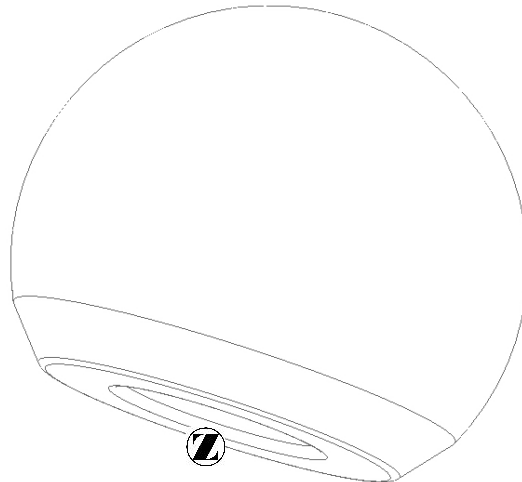
Cup with 'circle Z' etch on near side.



Cup with 'circle Z' etch on far side.



Head with 'circle Z' etch on near side.



Head with 'circle Z' etch on far side.

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## Data Sheet 4: Intra-Op Explant Damage: CPT \_\_\_\_\_

