# <A PROSPECTIVE MULTI-CENTER RANDOMIZED STUDY ON TOTAL HIP REPLACEMENT WITH E1>

**PROTOCOL NUMBER (Study ID): INT.CR.GH2**

**PROTOCOL VERSION: v 1.0 (Feb. 29, 2012)**

**NCT01883492**

## Table of Contents

## STUDY SUMMARY

| | |
|---|---|
| **TITLE** | A PROSPECTIVE MULTI-CENTER RANDOMIZED STUDY ON TOTAL HIP REPLACEMENT WITH E1 |
| **DESIGN** | PROSPECTIVE, RANDOMIZED, MULTI-CENTER |
| **PURPOSE** | Evaluate E1 wear, clinical outcomes and quality of life on patients who received THA with E1 |
| **POPULATION** | 160 hips |
| **DURATION** | EXPECTED DURATION OF THE PATIENT RECRUITMENT IS 1 YEAR. LAST FOLLOW-UP IS AT 10-YEAR AND THE EXPECTED COMPELETION DATE FOR THE LAST ENROLLED DATE IS 11 YEARS AFTER THE FIRST ENROLLMENT. |

# 1. INTRODUCTION

## 1.1. BACKGROUND

Total hip arthroplasty (THA) is one of the most successful surgical procedures in general. Yet, a few problems remain unsolved, and aseptic loosening is probably the most important of them. One of the main reasons for aseptic loosening in THA is the foreign body reaction caused by the wear particles. Since the late 1990s, the orthopedic industry has been developing highly crosslinked polyethylene (HXLPE) materials to capitalize on the increased wear resistance. In 2007, E1® Antioxidant Infused Technology was developed to reduce wear rate, maintain mechanical properties and prevent oxidative degradation. In late 2010, E1® Acetabular Liners was introduced and has been used widely in Japan.

Also alumina ceramic was introduced as a bearing surface in the 1971 as an alternative to the metal on-polyethylene couplings. Since then, alumina ceramic has been used in THA successfully for more than 35 years. BIOLOX®Delta is designed with improved fracture toughness, further reduces the risk of fracture and also extends the design flexibility of the material.

However, there are a few clinical data collected on wear and performance of E1® Liners available for Caucasian population and no data for Japanese today. There is no clinical data of BIOLOX®Delta femoral head articulating against E1® Liner. Therefore, it is needed to collect clinical data to support marketing and validate design of E1® Liners in terms of its safety and efficacy.

## 1.2. DEVICE DESIGN AND DESCRIPTION*

All patients will receive the vitamin E treated polyethylene "E1® Liners". Short-term femoral head penetration and long-term steady state wear of the polyethylene will be measured using software.
The investigational group, Ceramic-on-Polyethylene (CoP) total hip prosthesis, consists of BIOLOX® Delta ceramic modular femoral head articulating against E1® Liner. The ceramic femoral head is attached to a conventional femoral stem to complete the CoP total hip prosthesis device configuration.
The control group, Metal-on-Polyethylene (MoP) hip prosthesis, consists of the commercially available cobalt chrome (CoCr) femoral head articulating against E1® Liner. The metal femoral head is attached to a conventional femoral stem to complete the MoP total hip prosthesis device configuration.

- E1® Acetabular Liners: flat (MaxRom, MaxRom+) and hi-wall (Hi-Wall, Hi-wall+) style liner used for both the investigational (CoP) and control (MoP) cohorts.
  - 28, 32 and 36mm inner diameters are available and 40mm will be available in mid CY 2012.
- BIOLOX®Delta femoral heads: used for the investigational cohort. The BIOLOX® Delta ceramic femoral heads are manufactured from BIOLOX® delta, an alumina composite matrix.
  - 28, 32, 36 and 40mm head diameters will be available in mid CY 2012.
- Biomet cobalt-chrome femoral heads used for the control cohort
  - 28, 32, 36 and 40mm head diameters are available
- Any Biomet Femoral Component (Hip Stem) used for both the investigational and control cohorts
- RingLoc® PPS® or Ringloc+® Regenerex® Acetabular Shell System used for both the investigational and control cohorts.

### 1.3. RATIONALE FOR CURRENT STUDY

E1® Acetabular liners received approval in Japan in 2010. BIOLOX®Delta femoral heads has not been approved and estimated the approval in mid CY 2012. Currently there is no clinical data on E1® Acetabular liners implanted in Japanese population. There is a need to collect clinical data to investigate how this hip system performs in Japanese population.

### 1.4. PURPOSES

The primary objectives of this pilot clinical study include:

• Evaluate E1 Wear including early bedding-in process, clinical outcomes on patients who received THA with E1

• Compare E1 wear used with CoCr and Biolox Delta heads

## 2. STUDY DESIGN

### 2.1. OVERALL DESIGN

This study is a prospective, multi-center randomized controlled study and will be conducted in Japan at a maximum of 5 sites.

The study will consist of two phases, over a period of 11 years. Phase 1 will collect data on penetration rate recognized as “early bedding-in” and patients will be followed at immediate post-op, 6 months and 1

year, 2 years, 3 years. Phase 2 will collect data on penetration rate recognized as “steady-state wear” after 5 years, 7years and 10 years post-op.

## 2.2. NUMBER OF SITES AND SUBJECTS/PROCEDURES

Total of 160 hips will be enrolled in the study.

## 2.3. PRIMARY AND SECONDARY ENDPOINTS

| ***PHASE 1*: Immediate post-op to 3 years** | |
|---|---|
| **Primary endpoints** | Early bedding in |
| **Secondary endpoints** | **At all follow-up visits:**<br>Survivorship up to 3 years<br>JOA<br>Radiographic Assessment<br>Complications including revisions |
| ***PHASE 2*: 5 to 10 years** | |
| **Primary endpoints** | Steady-state wear |
| **Secondary endpoints** | **At all follow-up visits:**<br>Survivorship up to 10 years<br>JOA<br>Radiographic Assessment<br>Complications including revisions |

## 2.4. ASSESSMENT PROCEDURE

### 2.4.1. ASESSMENT PARAMETERS AND METHODS

Medical History and Demographic Data

Demographic information will be collected, a detailed medical history will be obtained and a physical examination will be performed (including height, weight).

Clinical Assessments

An operative record will be completed to record details of each operative procedure and of the used implants.

Data to determine the clinical and functional performance of the device will be collected. Pre-operative and post-operative analysis will be compared using recognized and validated systems (JOA Score).

Radiographic Assessments (including Radiographic Assessment protocol)

A radiographic assessments including polyethylene wear analysis and cup inclination angle will be completed at each follow-up period.

The X-rays must be taken according to the Martell technique*, which requires an A/P pelvis view centered over the pubis. See attachment for radiographic technique.

For the polyethylene wear analysis, all Radiographic images will be determined and the penetration rate will be measured by Hip Analysis Suite (software program, Dr. John Martel at Chicago University).

### 2.4.2. ASEESMENT TIMELINES/SCHEDULE

Example of Tabulated Assessment Schedule

| | | | ***PHASE 1*** | | | | | | ***PHASE 2*** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **PRE-OP** | **SURGERY** | **IMMEDIATE POST-OP** | **6 WK** | **6 MO** | **1 YR** | **2 YR** | **3 YR** | **5 YR** | **7 YR** | **10 YR** |
| Informed Consent | **X** | | | | | | | | | | |
| Demographic and Historical Record | **X** | | | | | | | | | | |
| Operative Record | | **X** | | | | | | | | | |
| Radiographic Assessment | | | **X** | **(X*)** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |
| JOA | **X** | | | | **X** | **X** | **X** | **X** | **X** | **X** | **X** |
| Complications including Revisions | | **ANYTIME** | | | | | | | | | |

* Baseline for bedding in and total penetration rate

#### 2.4.3. ALLOWED WINDOW OF EACH SCHEDULE

| PHASE | Evaluation Schedule | | |
|---|---|---|---|
| | **Interval** | **Follow-Up Window** | **Months Post-Op Range** |
| *PHASE 1* | Immediate Post-Op | ± 2 weeks | Immediate post-op < 2 weeks |
| | 6 weeks | ± 2 weeks | 4-8 weeks |
| | 6 month follow-up | ± 1 month | 5-7 months |
| | 1 year follow-up | ± 2 months | 10-14 months |
| | 2 year follow-up | ± 3 months | 19-27 months |
| | 3 year follow-up | ± 3 months | 33-39 months |
| *PHASE 2* | 5 year follow-up | ± 3 months | 57-63 months |
| | 7 year follow-up | ± 3 months | 81-87 months |
| | 10 year follow-up | ± 3 months | 117 – 123 months |

## 2.5. Randomization

Patients will be randomized to receive Delta Ceramic Head (investigational group), or CoCr Head (control group). Patients have an equal opportunity of being assigned to the investigational group or control group. Specifically:

In case of unilateral patients, the affected side of hip will be randomized to one of two groups. In case of bilateral patients, both sides of hip will be randomized to the same device (Delta Ceramic or CoCr).

The randomization will occur via a random number generator (manual or computer). Block randomization will be used. Blocks of K patients will be created where K = 4.

The possible sequences are AABB, BBAA, ABAB and BABA. Two sets of randomization blocks will be followed by unilateral and bilateral patients respectively.

For unilateral patients, A or B represents the device assigned to affected side of the hip. For bilateral patients, A or B represents the device assigned to both affected sides of the hip.

The doctor or other health care professional does not choose the participants for each group. For Patients satisfying inclusion criteria, randomization will occur by retrieving the next randomly generated group assignment.

### 2.6. DURATION OF THE STUDY

Expected duration of recruitment period would be 1 year after the first case is enrolled. Each subject is to be followed-up to 3 years post-op for phase 1 and 10 years post-op for phase 2.

## 3. SELECTION AND WITHDRAWAL OF SUBJECTS

All subjects, regardless of sex, race, or geographic location, must fit into the scope of the Inclusion / Exclusion criteria to be eligible for the study. If required per applicable regulations, all participants must sign an Informed Consent to be enrolled into the study.

### 3.1. INCLUSION CRITERIA

In accordance with approved Indications for Use E1 liner and Delta Ceramic and CoCr femoral head hip system specifically:

Patients suitable for primary Total Hip Replacement

Patients with degenerative joint disease (inflammatory or non-inflammatory) or any of the composite diagnoses of:

a. Osteoarthritis
b. Avascular necrosis
c. Legg Perthes
d. Rheumatoid Arthritis
e. Diastrophic variant
f. Fracture of the pelvis
g. Fused hip
h. Slipped capital epiphysis
i. Subcapital fractures
j. Traumatic arthritis

Patients aged over 20

Patients with limited co-morbidity – ASA I – III

Patients must be able to understand instructions and be willing to return for follow-up

### 3.2. EXCLUSION CRITERIA

In accordance with approved Absolute and Relative Contraindications for use in participating countries for E1 liner and Delta Ceramic and CoCr femoral head hip system System.

Absolute contraindications include: infection, sepsis, and osteomyelitis.

Relative contraindications include:

1) uncooperative patient or patient with neurologic disorders who are incapable of following directions,

2) osteoporosis,

3) metabolic disorders which may impair bone formation,

4) osteomalacia,

5) distant foci of infections which may spread to the implant site,

6) rapid joint destruction, marked bone loss or bone resorption apparent on roentgenogram, and

7) vascular insufficiency, muscular atrophy, or neuromuscular disease.

8) pregnancy

### 3.3. SUBJECT WITHDRAWAL

It is recognized that the subject's participation in this trial is entirely voluntary, and that she/he may refuse to participate and may withdraw from participation at any time without jeopardy to any future medical care. It is also recognized that the investigator, at his/her discretion, may withdraw a subject from this study based upon his/her professional judgment. In event of subject withdrawal, applicable local procedures should be followed.

## 4. ADVERSE EVENT MANAGEMENT AND REPORTING

A record of all adverse events relating to subjected device (see Risk Analysis Section) and operative procedure, including details of the nature, onset, duration, severity, will be made on the

relevant section(s) of the subject's CRF. The subject will be questioned about any adverse event(s) at each subsequent follow-up assessment visit.

# 5. STATISTICAL ANALYSIS PLAN

## 5.1. Sample Size Calculation

The study population is calculated based on the primary endpoint of Poly wear at 10 year postop. A total of 160 hips will be recruited the study and randomly assigned to either CoCr or Ceramic head group. Each site is required to use the same stem and cup for both CoCr and Ceramic groups.

Significance Level = 5 % (95% confidence)

d = 0.5 mm Clinically significant difference in wear.

ξ = 0.07 Estimate standard deviation of wear.

N = 63

Take into consideration of Lost-to-Follow-up Rate = 20% for 10 year

**Final N = 80 hips per group**

## 5.1. Data Analyses

### 5.1.1. INTERIM

An interim data analyses will be conducted when all patients reach 1, 2, 3, 5 and 7 yr post-op follow-up.

### 5.1.2. FINAL

A final data analysis will be conducted upon study's completion.

# 6. DATA COLLECTION, HANDLING AND RETENTION

## 6.1. SOURCE DOCUMENTATION REQUIREMENTS

Source documentation for this study will be maintained to document the treatment and study course of a subject and to substantiate the integrity of the trial data submitted for review to the regulatory agencies. Source documentation will include, but not be limited to, worksheets, hospital and/or clinic or office records documenting subject visits including study and other treatments or procedures, medical history and physical examination information, laboratory and special assessments results, pharmacy records, device accountability records, and medical consultations (as applicable).

## 6.2. CASE REPORT FORMS

Data for this clinical trial will be collected and documented on the subject Case Report Forms (CRFs) provided, which may be in paper form or in an electronic form. Authorized study site personnel will complete CRFs only. CRFs must be reviewed and signed by the Investigator or his/her designees.

Since there is a potential for errors, inaccuracies, and misinterpretation in transcribing data onto the CRFs, the following documents must be available at all times for inspection and comparison to the CRFs by the study monitor where appropriate:

- data query forms
- originals and photocopies/certified copies of all relevant records and reports
- copies of test results

Sample CRFs to be used with this clinical trial are provided in Appendix 2.

## 6.3. ELECTRONIC DATA ENTRY

All sites will be required to complete and submit case report forms on **Biomet's online database, Joint Assist**, in a timely manner. Forms will be monitored for completeness and accuracy by Biomet Japan.

Further, it is imperative that the investigator answers all questions on the case report forms. All data should be accurate, indelible and legible.

# 7. DATA REPORTING

## 7.1. INTERIM REPORT

An interim report will be provided after each follow-up period.

## 7.2. FINAL REPORT

Final report will be provided after 10 yr follow-up period.

# 8. RISK ANALYSIS

This clinical study is to collect data on the E1 liner and Delta Ceramic and CoCr femoral head hip system which is intended to help the participant gain mobility and decrease pain. Risks associated with this Hip system include general surgical and Hip arthroplasty risks. Due to the investigational nature of the system, there are unknown risks.

**General Surgical Risks**

As with any surgical procedure, there are risks involved with total joint replacement surgery. Potential adverse events include, but are not limited to: early or late infection perhaps necessitating device removal; component dislocation; damage to nerves and blood vessels; fracture of the bone or device; device loosening; allergic reactions to the metallic devices; phlebitis; long-term swelling; pulmonary embolization; and delayed wound healing. Other potential adverse effects include: prolonged illness; hematoma; wound dehiscence and/or drainage; the need for blood transfusions and/or further surgery; or permanent pain; deformity; and inconvenience. Risks associated with the anesthetic are those such as permanent brain damage, pneumonia, blood clots, and heart attack. Rarely some adverse events may be

fatal. These possible adverse events are not unique to the 1 liner and Delta Ceramic and CoCr femoral head hip system and, as stated above, may occur with any total joint replacement surgery.

As with any joint replacement post-operative activity, limitations may be imposed depending upon the participant's age, general health, baseline (pre-operative) activity level and baseline (pre-operative) condition of the Hip and other joints.

**Potential Risks Associated with E1 liner and Delta Ceramic and CoCr femoral head hip system**

As with all hip replacement systems, potential adverse effects include risk of infection, loosening of the components, breakage or bending of the components, or change in position of the components any of which can necessitate removal and/or revision surgery. There have been reports of sensitivity reactions to the components of Hip systems. Other potential adverse effects of Hip replacement surgery include neurovascular damage, dislocation, thromboembolic disease, and other less common adverse effects.

1. Material sensitivity reactions. Implantation of foreign material in tissues can result in histological reactions involving various sizes of macrophages and fibroblasts. The clinical significance of this effect is uncertain, as similar changes may occur as a precursor to or during the healing process. Particulate wear debris and discoloration from metallic and polyethylene components of joint implants may be present in adjacent tissue or fluid. It has been reported that wear debris may initiate a cellular response resulting in osteolysis, or osteolysis may be a result of loosening of the implant.
2. Early or late postoperative infection and allergic reaction.
3. Intraoperative bone perforation or fracture may occur, particularly in the presence of poor bone stock caused by osteoporosis, bone defects from previous surgery, bone resorption, or while inserting the device.
4. Loosening or migration of the implants can occur due to loss of fixation, trauma, malalignment, malposition, bone resorption or excessive, unusual and/or awkward movement and/ or activity.
5. Periarticular calcification or ossification, with or without impediment of joint mobility.
6. Inadequate range of motion due to improper selection or positioning of components.

7. Dislocation and subluxation due to inadequate fixation malalignment, malposition, excessive, unusual and/or awkward movement and/or activity, trauma, weight gain, or obesity. Muscle and fibrous tissue laxity can also contribute to these conditions.
8. Fatigue fracture of component can occur as a result of loss of fixation, strenuous activity, mlalignment, trauma, non-union, or excessive weight.
9. Fretting and crevice corrosion can occur at interfaces between components.
10. Wear and/or deformation of articulating surfaces.
11. Valgus-varus deformity.
12. Patellar tendon rupture and ligamentous laxity.
13. Interoperative or postoperative bone fracture and/or postoperative pain.

**Minimization of Risk**

It is believed that none of the previously mentioned adverse events will occur in significant numbers. This study protocol has reduced the potential risk to the participant through the following methods:

1. By defining a participant population that limits the exposure of the device to participants conforming to the proposed indications, exclusions, and age requirements
2. The surgical technique has been developed to help eliminate potential operative difficulties.

## 9. MONITORING PLAN

Prior to commencing the study Biomet Japan will provide the investigators with the necessary information to enable him/her to carry out his responsibilities. This information includes but not limited to:

- Investigator Brochure i.e. study protocol, investigator responsibilities, device information, etc.
- Ethical Committee Approval Information.
- Case Report Forms.
- Patient Consent Forms
- EDC user manual

The monitor of the evaluation periodically reviews the post-operative follow-up dates on all subjects for each evaluator. A follow-up schedule is then sent to each investigator, which illustrates any follow-up, reports which are due or missing. Every effort is made to assure that follow-up reports are completed in a timely manner, including contacting the evaluator by post, telephone or by personal visit when necessary. Also, during the course of the evaluation, the monitor will conduct periodic discussions with the investigator or staff to ensure that the evaluation is being conducted in accordance with the protocol. The monitor will maintain records of each visit or discussion.

# 10. ETHICAL AND REGULATORY REQUIREMENTS

## 10.1. CODE OF CONDUCT

The Investigator will ensure that the clinical study is conducted in accordance with

1. Protocol
2. Regulatory and IRB/EC requirements
3. ISO 14155, GCP, the Declaration of Helsinki (optional)

## 10.2. INSTITUTIONAL REVIEW BOARDS/ETHICS COMMITTEE

The Investigator must obtain appropriate Independent Ethics Committee (IEC) approval before the study can be initiated. A copy of the written approval from the IEC and a copy of the approved informed consent form should be sent to the Sponsor. A list of the IEC members (including their Institution affiliations, gender makeup, and occupations); or a statement from the IEC specifying that the membership comply with applicable regulations is to be provided to the sponsor.

Any changes to the protocol must be discussed and approved by the Sponsor in writing unless the change is made to assure the safety of the subject. In the non-emergent setting, after agreement on the changes has been reached, an amendment to the protocol will be provided by the Sponsor for submission to the IEC for review and approval prior to initiation of the change. Any change made emergently must be documented in the subject's

medical record and reported to the Sponsor within the time period required by local SOPs and applicable regulations.

The Investigator must immediately forward to the IEC any written safety reports or updates from the Sponsor.

The Investigator must keep the IEC informed of the progress of the study as required by the IEC but at least annually.

## 10.3. INFORMED CONSENT

Subjects (or the subject's legally authorized representative) will be provided with an informed consent and patient information sheet in order to give ample opportunity to review the consent and ask questions. The signed informed consent will be obtained before any study procedures begin. If the subject agrees to participate in the study, the subject/representative must sign the informed consent form. The witness and the Investigator must also sign the informed consent form. A copy of the informed consent form should be given to the subject/representative. All subjects who meet all of the entry criteria will be considered for inclusion in this trial. Any subject meeting any of the exclusion criteria will be excluded from the trial.

The informed consent form must be approved by the institution’s IEC. Subjects will be informed of new information learned during the study, which may affect the subject’s decision to continue participation in the study.

An Informed Consent Log will be completed to document the existence of the signed informed consent form. The log will contain: Subject ID, date informed consent form signed, and the version signed. The monitor will initial and date the log once the executed informed consent form has been reviewed. Signed informed consent forms (or copies) are to be maintained in the study file and must be available for verification by monitors or inspectors.

## 10.4. SUBJECT CONFIDENTIALITY

To ensure study patients’ privacy, all patients will be identified by unique identification numbers. All case report forms will only include patient IDs. It is the responsibility of the investigator to maintain a list of patient identification and Joint Assist.

Further the Joint Assist database is restricted, allowing a doctor to only view and enter data from his own patients. User authentication is required to view research data. The data is transmitted to a centralized database through a secured (SSL) channel on the Internet. Data in transit is in 128-bit encryption. The access to the centralized database is limited to those who are responsible for maintaining the database.

The Sponsor will maintain the confidentiality of the identity of subjects enrolled in the study and the information contained in their study records. The Sponsor will also instruct the study investigators in the importance of maintaining the confidentiality of study records. The records will be made available as required for review by governing regulatory agency such as FDA and a reviewing IEC/IRB, however to the extent possible, the subject's identity will not be disclosed.

## 11. APPENDICES

Appendix 1 Informed Consent and Patient Information Sheets

Appendix 2 Case Report Forms

Appendix 3 Investigator's Brochure / Instructions for Use if applicable

Appendix 4 Declaration of Helsinki if applicable

**APPENDIX 4**

# WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
## Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)

55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)

59th WMA General Assembly, Seoul, October 2008

**A. INTRODUCTION**

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

**B. PRINCIPLES FOR ALL MEDICAL RESEARCH**

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor

and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other

relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are

accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

**ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE**

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

• The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or

• Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient’s decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

**REFERENCES**

1. Data on file at Biomet. Bench test results not necessarily indicative of clinical performance.