Introduction

Over the past few years, there has been considerable interest and much controversy surrounding “minimally invasive” total joint replacement. The advocates say that these methods have a great potential to benefit the patient [1]. Soft-tissue trauma, operative blood loss, post-operative pain, hospitalization time and the need for rehabilitation are theoretically reduced. These reductions may well have a positive economic benefit as well. However, there are surgeons that are concerned that these minimally invasive procedures may introduce new potential problems [1, 2].

In reviewing literature on minimum invasive surgery (MIS) it becomes quickly apparent that there are quite few well-designed studies for hips or knee arthroplasties [3-21]. This is in least in part due to the subjective nature of the clinical variables that MIS is believed to impact. Further, it is quite difficult to conduct a prospective, randomized investigation in this era of the web-educated consumer. Often the surgeon is faced with a self-diagnosed patient who has a stack of pages printed off from various web pages. The content of these web pages are certainly not often subject to peer review, hence the validity of many of the claims is questionable. Hospital Institutional Review Boards now challenged with the added responsibility of the HIPAA (Health Insurance and Portability and Accountability Act – implemented in 2003) patient privacy regulations are careful to assure that patients are highly informed of every aspect of study design and dissemination of information regarding any investigations they are invited to participate in. Although this is clearly the ethical thing to do, such education does inject a potential bias effect that may confound the measured variables. If a patient knows they will get the “standard” incision or a “mini” incision, there is a strong potential that the euphoria from the “mini” or the disappointment from getting the “standard” will bias the subjective variables to be measured. However, other more objective data such as blood loss and operative time may still provide useful information. Certainly, the patient and the evaluators could be blinded in the immediate post-operative phase, but not for the entire 6- to 12-week period in which the benefits of MIS surgery are most likely realized.

A review of the MIS literature reveals a common base of variables being investigated. The common operative variables include blood loss, incision length and complications. The post-operative variables include transfusions, length of stay, discharge disposition, narcotic use, Hip or Knee Society scores, SF12 or 36, complication rate, time to ambulation (use of support, ability to ascend/descend stairs), ability to transfer (bed and/or chair), time to stat rehabilitation (rehab) and number of rehab units required. Readmission, complication rates (such as infections, dislocations, fractures or nerve palsies) and component placement (including any subsequent subsidence) were also generally reported in the post-operative period.

The patient groups and length of follow-up in the literature varied substantially. The majority of studies utilized non-randomized selected and/or non-consecutive series and often the studies would lack an appropriately matched control population. A review of the literature found only one prospective randomized study with a 2-year or greater follow-up [21]. Due to the relative newness of the popularity of the MIS procedures, the follow-up periods in the abstracts and literature vary significantly from 3 months to over 30 years with the vast majority being 2 years or less [19, 20].

Potential benefits of the MIS procedures must be balanced against the associated risks of undertaking a
more technically demanding operation. Nevertheless, no surgeon can deny the potential benefits of the reduced soft-tissue trauma. In order to prove the advantages of these methods without marketing, bias objective data has to be generated and evaluated. Unfortunately, there is a paucity of data in existence to aid the surgeon in deciding the viability of the MIS procedures. The goal of this chapter is to present considerations when designing or evaluating MIS clinical studies.

The Importance of Clinical Trials

While laboratory testing and animal studies may provide strong supporting evidence that one product or intervention will produce a desired effect, well-conducted clinical trials are essential to establish that a specific interventional procedure produces the intended clinical outcome. A recent Journal of Bone and Joint Arthroplasty (JBJS) article evaluated the validity of claims made in orthopedic print advertisements and concluded that approximately half the claims were not supported by enough data to be used in a clinical decision-making process. In the article, a well-supported statement was defined as a statement with enough supporting evidence to be used in clinical practice and a high-quality study was defined as a study that could be published in the peer-reviewed literature [22]. In general, the orthopedic literature reports that more higher quality clinical trials are needed to support evidence-based orthopedic practice, and the application of standardized guidelines for the reporting of clinical trials should improve the quality [23, 24]. National agencies, such as US Food and Drug Administration, European Union Medical Device Directives and the UK National Institute for Clinical Excellence offer guidelines for conduct of clinical studies [25–27]. These guidelines set standards for the design, conduct and performance of clinical studies that ensure the accurate reporting of data and protection of the rights, safety, well-being and privacy of the subjects.

Properly Designed Clinical Trials

Careful monitoring of clinical studies in terms of conformity with rules and specifications of Good Clinical Practice (GCP) therefore should provide a sound basis for study design and protection of study subjects. Adherence to the principles of ethical treatment of clinical research subjects contained in the Declaration of Helsinki, the gold standard for ethical research behavior, insures an appropriate level of conduct [28]. In addition, assurance that specific regional legislation (i.e., US HIPAA patient privacy rules) and local hospital ethical committee regulations are met assures adherence to quality-based principles and methods [29].

Therefore, when designing investigations, they must include approval of the protocol by the hospital ethics committees, such as the Institutional Review Board and, when applicable, governmental agencies. Adherence to GCP guidelines should ensure that strict ethical rules (Declaration of Helsinki and its amendments) in the conduct of clinical trials are observed, that these trials are conducted in accordance with high standards of quality and that authentic, scientifically verifiable and reliable data are the result of such studies.

The first element to consider in the preparation of a sound study protocol is the identification of a clear and concise study objective. This often may be posed as a question. Does my device perform a specific function? Does this surgical intervention offer the specific advantage intended? Answering the question will require the researcher to consider a number of other issues, such as suitable study endpoint or response variable, study design (randomized, cohort, case-control), instruments needed to record study results and acceptable patient population. It is important to select the appropriate
patient population for the study, one that is a subset of the general population that is representative of a group of people targeted for the application of the medical device or intervention. Selection of rigorous and unambiguous inclusion and exclusion criteria for the study will uniquely characterize the study population and relate to the intended use of the device. Determination of sample size by a statistician is essential to assure that the research question posed will be able to be answered. Utilization of validated instruments to collect study results not only increases the quality of the study, but also allows comparison to the literature.

**Minimal Invasive Total Hip Arthroplasty: Considerations in Designing a Protocol**

**Pre-Operative**

There are multiple variations of surgical approaches to the hip joint and their modifications: the lateral, anterolateral, direct anterior, posterior and posterolateral. In addition to the established conventional approaches with reduced incision length, an anterior-modified Smith Peterson approach can be applied. The typical approaches utilized for MIS THA are subdivided into single- or two-incision techniques. Before starting with any type of MIS approach, the surgeons should be aware of their own learning curve. As always, implementation of any new surgical technique into daily clinical practice should be done in a slow, graduated manner, incorporating cadaver trials and training workshops.

The success of THA depends on several factors, including proper patient selection and education, appropriate implant design, correct surgical technique, proper instrumentation, and effective peri-operative care. A number of studies have suggested that alignment errors outside the safe zone defined by Lewinek [30] are associated with more rapid failure and less satisfactory functional results after THA [31]. The accuracy of implantation is therefore an accepted prognostic factor for the long-term survival of THA.

The primary objective of a clinical investigation of the MIS surgical technique should be to assess the safety and efficacy of the procedure with a dedicated and modified instrumentation. The study protocol should clearly define the parameters unique to the MIS procedure and identify the MIS approach to be evaluated with a detailed surgical technique for the investigator to follow. Efficacy of the MIS surgical technique should be assessed by short post-operative and long-term data gained from radiographic, clinical and patient outcome assessments and from complication rates. While various options exist for a potential study design, for new techniques, the authors suggest conducting prospective randomized clinical studies in order to demonstrate clinical results that may be directly compared to the standard of care and to keep study bias as small as possible. Blinding the patients to the approach type may minimize the placebo effect. Dependent on the approach, this might not be achievable due to anatomical location (e.g. comparing modified Smith Peterson to conventional anterolateral). A solution might be to cover all wounds with the same size and identically placed bandages until hospital discharge. By evaluating all patient data by an independent reviewer (blinded when possible), the potential bias can be minimized. Sample-size calculation and primary endpoints of the study need to be defined. Proponents of MIS THA surgery suggest that the procedure has the potential to reduce soft-tissue trauma and thereby reduce operative blood loss, post-operative pain, and hospitalization time, speed the post-operative recovery, and improve the cosmetic appearance of the scar [1]. Therefore, surgical and peri-operative endpoints to evaluate may include intra-operative blood loss (utilizing the method described by Sehat et al. [32]), surgical time, use of pain medication, wound complications, length of hospital stay, day of first ambulation, and walking distance on the day of discharge.

Prior to study initiation, the investigator determines the sample-size calculations and defines the hypothesis and the tests for the statistical calculations. A description of the patient population is identified and incorporated into the inclusion/exclusion criteria. The statistical plan defines tests to be used that will depend on the variability of study results. In case of a non-normal distribution (big differences between median and mean), non-parametric tests have to be used (Wilcoxon rank-sum, Wilcoxon signed-rank test, ANOVA [Kruskal-Wallis test]). With normal distribution, parametric tests will be applied (Student's t test, paired t test, analysis of variance).

Once approval is obtained from the appropriate authorities, the study enrollment may begin. The investigator is responsible for evaluating each patient against inclusion and exclusion criteria and to make sure that the patient meets the study-enrollment requirements. It is not recommended to include patients with character-
istics that could influence the outcome independent from any surgical influence. However, since it is generally agreed that MIS THA surgery is not appropriate for every patient, it is extremely important to carefully select the patient population to be included in the study.

**Clinical Variables**

Patients should be excluded that
- either have or are suspected of having an infection,
- are planning to become pregnant,
- have systemic or metabolic diseases affecting bones,
- are mentally incompetent or non-compliant,
- have significant other joint involvement or other significant co-morbidities, or
- will not sign an informed consent.

Patients should be assessed pre-operatively, intra-operatively and post-operatively according to the study protocol, and appropriate data should be recorded both in their hospital notes and case report forms. Since it is hypothesized that the major benefits of MIS will occur in the short term, a clinical study should be data-intensive in that period in order to assure study end-points associated with early clinical success may be properly evaluated. Follow-up visits may be at 6 and 12 weeks or at 6 and 24 weeks post-operatively. For the first 6 weeks, it may be useful to have the patient answer questions over the phone, via e-mail on a weekly or bi-weekly basis. A patient diary may also be used (see appendix). For the long-term arm of the study, the evaluation should include additional visits at 1, 2, and 5 years after surgery to monitor any effects due to the new surgical technique. As described before, if possible, an independent and blinded examiner should do all follow-up examinations.

The researchers are faced with a plethora of choices of which variables to collect. The challenge is to collect the minimum number of variables necessary to prove the study hypothesis. Initially, the pre-operative variables to be collected must be decided upon, which generally includes basic demographic data (date of visit, patient's study number, patient's initials, date of birth, weight, height, gender, primary diagnosis, affected hip and date of informed consent signature). Since the investigator wants to gain information about a new surgical technique, operative clinical variables associated with the MIS surgical procedure as compared to the standard incision procedure such as instrumentation used, time to perform surgery, length of incision, blood loss and muscle incision as well as type and size of implants, and method of implant fixation should be recorded. Post-operative evaluation of factors which could be significant changed by the new technique need to be measured. For example, as the MIS surgical intervention could have an influence on the adductor muscles, a Trendelenburg test should be recorded [33]. Additionally, clinical scores may be used. Depending on the objective to prove, the investigator must choose tests designed to answer the hypothesis of the investigation. Since major claimed advantages of MIS are faster rehabilitation and less pain, it makes sense to apply validated tests designed to capture these variables. Patient self-administered questionnaires such as the WOMAC, SF-12 or SF-36 would be preferable in order to minimize potential bias. Also the Harris hip score, or its equivalent, would be additional options [34-40]. A common disadvantage of all the scores is that they may not capture the important variables of the MIS technique. Additional questions posed to the patients in the peri-operative time frame may be necessary to capture information relevant to the MIS surgical technique. Careful recording of this information in well-controlled randomized trials may provide useful data-collection instruments for future studies.

**Assessment of Clinical Variables**

**Intra-Operative**

What constitutes MIS should be clearly defined in the study protocol and patients randomized to either group verified by intra-operative variables that confirm that the patient received the appropriate intervention. For example, if the minimally invasive surgical technique is defined as 10 cm to be measured at the time of incision and before closure and the patient's incision is measured as 15 cm at the start of the procedure, then the reason for the deviation from the protocol must be explained and the patient's data analyzed separately. Incision length should be measured with a ruler with the length defined as the widest visible distance from one to the other side of the incision. This should be done at the time of incision and again at the end of the surgical intervention. The minimal desired incision should still be large enough that the surgeon can visualize the circumference of the
acetabular rim. In any case, the minimal possible incision length is determined by the half circumference of the cup. Therefore, the report of incision length should be related to the cup size. We would recommend to use a ratio \( L = \frac{C}{S} \) where \( C \) represents the incision length and \( S \) the half circumference of the cup \( (S = \pi r) \). Even with modified instrumentation, the surgeon should avoid any excessive abrasion against the surrounding skin and soft tissue. In spite of a small incision, it is still possible to induce a large amount of soft-tissue trauma to underlying structures. For example in a two-incision procedure, it may be beneficial to template the cup size pre-operatively to provide a preliminary indication of the skin incision needed to get the implant inserted. Patients requiring an incision larger than the minimal incision size should not be included in a randomized trial. This information should be reflected in the inclusion and exclusion criteria.

The condition of the wound must be carefully monitored in the post-operative period. The authors suggest paying close attention to the wound condition in general (no frazzled edges, no surrounding hematoma) after closing the skin and the following days after surgery. For the assessment of blood loss, it is recommended to compare the estimation of the surgeon and the anesthesiologist. However, these estimates should be correlated to objective values like hemoglobin, hematocrit and the intravenous fluids including the amount of transfusions. For monitoring soft-tissue trauma, the muscle enzymes creatinine kinase, myoglobin concentration could provide useful markers. As stated previously, surgical time, the type and size of implant, fixation techniques and adverse events have to be recorded. A major focus should be put on the narcotic medication and instantaneous pain-management regime. For this reason, the authors recommend to describe the narcotic usage by equi-analgesic equivalency to morphine (mg EEM) [41]. Patients with spinal anesthetics should be excluded because the EEM cannot be calculated for the intra-operative analysis.

Prior to Discharge

While the patients are in hospital, specific clinical parameters should be measured on a daily basis. Due to budget reasons in European hospitals, most patients will not be discharged before the 5th post-operative day. As opposed to the hospital length of stay, a better variable to measure would be the required medical stay. Therefore, in a multi-center study it is important to carefully review the clinical parameters to be measured with all the study sites and obtain consensus that the parameters are in fact measurable. This will reduce the introduction of bias due to site-specific restrictions. Specific variables to record at the identified intervals may include the post-operative day the patient is able to perform each of the following functions: walk a defined distance (100 meters) on a flat surface, ascend and descend stairs (10 steps), independent transfers to a chair or bed. Independent, daily improvement of walking distance in meters, number of stair steps will also be recorded. Lastly, it is important for the researchers to agree on specific "discharge" criteria that once met would denote that the patient was at the end of their required "medical stay" regardless or not they stayed at the hospital due to some other non-medical reason.

Since the post-operative physical rehabilitation protocol can have an important impact on the outcome, the physical rehabilitation program should be standardized. An example of a typical physical therapy regime is as follows:

- 1st post-operative day: rising from bed, standing, walking on flat surface with two crutches, isometric exercises, active and passive motion, no flexion, adduction and internal rotation; no extension, adduction and external rotation;
- 2nd to 6th post-operative day: continuing of the training of first post-operative day, stair climbing;
- post-operative course: continuing of the training of the first post-operative days.

However, it is understood that these guidelines would be altered in the scenario when the study protocol is such that the patient decides when they are ready to proceed to the next rehabilitation platform.

The wound should be assessed for redness, swelling (measured as the circumference of the fully extended lower limb at 25, 35, 50 cm distances distally to the ASIS) or effusion, and observations documented and recorded as adverse events if necessary. Any operative site-related adverse event should be recorded including but not limited to any signs of neurological disorders, such as nerve palsy or foot drop, dislocation and/or subluxation of components, excessive hip pain with or without the need for medication, hip instability, and limb length discrepancy. If the patient is suspected of having sus-
tained damage of a nerve due to the surgery, an examination by the neurologist should be performed. Systemic medical events, such as urinary retention, and cardiovascular events should be recorded regardless of whether the investigator feels the events are related to the MIS surgery.

Since most conventional tests are too long for frequent administering to the patients, daily diaries while in hospital and weekly thereafter for the first 6 weeks post-operatively could be used. A sample version can be found in the appendix. Careful instruction must be provided to the patient on how to complete the diary. The diary can provide valuable information regarding the dynamics of rehabilitation. Since this is an action to be done by the patients, the bias will be minimized, but compliance is important.

**Post-Operative at 6, 12 Weeks and 1, 2 and 5 Years**

Variables include a conventional clinical examination with measurement of range of motion, Trendelenburg test, leg length discrepancy, WOMAC, and SF-36 score evaluation [39, 40, 41]. Complications need to be recorded. In order to limit the surgeons’ bias, patients should be asked for satisfaction (VAS from very dissatisfied to highly satisfied), self assessment of scar (VAS from very dissatisfied to highly satisfied) and measurement of length of scar. The independent reviewer should check whether the scar is dry without any effusions or signs of necrosis. The patient should be asked about the presence of any pain on weight-bearing. If pain exists, the reviewer should ask about the location.

**Radiological Analysis**

Attainment and maintenance of optimum component placement is essential to long-term success of an implant. Therefore, radiological analysis of anteroposterior and lateral films obtained post-operatively before discharge and at scheduled postoperative office visits should be performed by an independent radiologist, blinded to the surgical technique. The Hip Society recommends a standard method of review for total hip arthroplasty and may provide ease of reference to the literature [42].

**Conclusions**

It is well known that total hip arthroplasty is considered a very successful procedure that offers patients pain relief and return to function. Minimally invasive surgery for total hip arthroplasty has the potential to offer patients increased satisfaction with shorter recovery time and cosmetic advantage of a smaller scar. However, as with any new procedure, the benefits must be demonstrated clinically. To date, there has been little data to demonstrate unequivocal advantage. We recommend the use of prospective, randomized clinical studies with clearly defined study hypotheses, surgical techniques, and clinical endpoints that will provide surgeons and patients with the information they need to make the appropriate choice.

**Appendix: Suggested Clinical Data Collection for MIS Study**

<table>
<thead>
<tr>
<th>Standardized data collection forms (x = complete form)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evaluation</strong></td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td>Demographics</td>
</tr>
<tr>
<td>Surgical details</td>
</tr>
<tr>
<td>Clinical (i.e., Harris hip score)</td>
</tr>
<tr>
<td>Radiographic A-P and lateral</td>
</tr>
<tr>
<td>Patient outcomes, WOMAC And SF-36</td>
</tr>
</tbody>
</table>

\(^a\) Prior to discharge additional information.
Pre-discharge patient activity/medical assessments

<table>
<thead>
<tr>
<th>Activity</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day goal achieved</th>
<th>Day of discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfer bed to chair</td>
<td>Record</td>
<td>Record</td>
<td>Record</td>
<td>NA</td>
</tr>
<tr>
<td>Walk on flat surface</td>
<td>Record</td>
<td>Record</td>
<td>Record</td>
<td>NA</td>
</tr>
<tr>
<td>Ascend and descend stairs</td>
<td>NA</td>
<td>NA</td>
<td>Record</td>
<td>NA</td>
</tr>
<tr>
<td>Ambulatory status (crutches, walker, cane, other)</td>
<td>NA</td>
<td>NA</td>
<td>Record</td>
<td>NA</td>
</tr>
<tr>
<td>Discharge disposition (home, rehab, other)</td>
<td>NA</td>
<td>NA</td>
<td>Record</td>
<td>NA</td>
</tr>
<tr>
<td>WOMAC Pain sub score (daily patient diary) a</td>
<td>NA</td>
<td>NA</td>
<td>Record</td>
<td>NA</td>
</tr>
<tr>
<td>Medical</td>
<td>NA</td>
<td>NA</td>
<td>Record</td>
<td>NA</td>
</tr>
<tr>
<td>Pain Meds (EEM) b</td>
<td>NA</td>
<td>NA</td>
<td>Record</td>
<td>NA</td>
</tr>
</tbody>
</table>

a Patient diary to be completed daily in hospital, then weekly until 12 week evaluation. Diary questions utilizing the modified WOMAC [38] should be answered with the same scaling (0 to 10) as the original WOMAC score for the following parameters: ascending stairs, rising from sitting, walking on flat surface, getting in/out of car, putting on socks, rising from bed, sitting.
b Equi-analgesic equivalency to morphine.

References

Part V: Evaluation of MITJA


