**Clinical Study Protocol**

**STUDY TITLE**

**A Prospective, Observational, Cross- sectional study to assess the risk of fracture(s) in patients undergoing elective orthopedic and spinal procedures.**

1. TITLE PAGE

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| --- | --- |
| Protocol Title: | A Prospective, Observational, Cross- sectional study to assess the risk of fracture(s) in patients undergoing elective orthopedic and spinal procedures. |
| Protocol version: | Version 01 |
| **Sponsor:** | Cadila Healthcare Ltd |
| **Sites:** | Multi-centric |
| **Indication:** | Osteoporosis, Osteopenia  |
| **Compliance statement:** | This study will be performed in compliance with ICH E6 R1 ‟Guidance on Good Clinical Practice”, Indian Good Clinical Practices Guideline, ICMR guidelines and Declaration of Helsinki. |
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 **2.0 INVESTIGATOR’S DECLARATION**

  **Title:** A Prospective, Observational, Cross- sectional study to assess the risk of fracture(s) in patients undergoing elective orthopedic and spinal procedures.

I, the undersigned have read and understood this protocol and hereby agree to conduct the study in accordance with this protocol and to comply with all requirements regarding the obligations of investigators and all other pertinent requirements of the ICH E6 R1, Guidance on Good Clinical Practice, Indian Good Clinical Practices Guidelines and Schedule Y, ICMR guidelines on ethical principles of Biomedical Research, Declaration of Helsinki amended latest by WMA General Assembly, Seoul, Oct. 2008.. I further agree to ensure that all associates assisting in the conduct of this study are informed regarding their obligations.

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 **Investigator’s Name Investigator’s Signature**

 **Date-** ------/------/--------

 **3.0 LIST OF INVESTIGATORS**

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1. **LIST OF ABBREVIATIONS**

|  |  |
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| **Abbreviation** | **Definition** |
| BMD | Bone Mass Density |
| FRAX  | Fracture Risk Assessment Tool |
| DEXA | Dual-Energy X-ray Absorptiometry |

 **6.0 PROTOCOL SYNOPSIS**

|  |  |
| --- | --- |
| **Disease Area:** | Osteoporosis/ Osteopenia |
| **Title of Study:**A Prospective, Cross- sectional study to assess the risk of fracture(s) in patients undergoing elective orthopedic and spinal procedures. |
| **Study Objective:****Primary objective:*** To evaluate the preoperative prevalence of Osteoporosis and/or Osteopenia and overall bone quality in prospective Elective Joint Replacement / Spinal Procedural patients which may affect the postoperative outcome after prosthetic insertion into the bone.

**Secondary objective:*** To evaluate the levels of Homocysteine in the study Patients and correlation with Osteoporosis/ Osteopenia.
 |
| **Sponsor Medical Expert: Dr Manish Mahajan** **Investigators:**  Dr. Amrithlal Mascerhans (Bangalore)**Dr. Dilip Shah (Mumbai)**Dr. Dipak Dave (Ahmedabad)Dr. Gurinder Bedi (Delhi)Dr. Harish Bhende (Mumbai)Dr. P C Dey (Bhubaneshwar)Dr. Rajiv Raj Choudhry (Surat)Dr. Ranjith Unnikrishnan (Trivandrum)Dr. S. Arumugam (Chennai)**Dr. Sandeep Garg (Lucknow)**Dr. Satishchandra Gore (Pune)Dr. Sujoy Kumar Bhattacharjee (Faridabad)Dr. Vikas Mehra (Chandigarh)Dr. Vinod Aggarwal (Mumbai) |
| **Study Centers: Lucknow, Mumbai, Chandigarh, Faridabad, Bangalore, Chennai, Ahmedabad, Surat, Pune, Trivandrum, Bhubaneshwar** |
| Number of Evaluable Patients (Planned):A total of One hundred and forty (n=140) patients will be enrolled and analyzed. |
| **Inclusion criteria**1. Patients giving informed consent to participate in the study
2. Male or female
3. Age - Male ≥ 60 years or Female ≥ 55 Year
4. Patients who are undergoing elective orthopedic and spinal surgical procedures.

**Exclusion criteria**1. Not willing or not able to sign informed consent
2. Patients who underwent spine surgery in recent 2 years
3. Patients on concomitant chemotherapy drugs
 |
| Duration of Screening Period: Four Weeks |
| **Methodology:****Screening Visit:** After obtaining Informed consent, Patients will be checked for inclusion and exclusion criteria. Demographic data and detailed medical history will be recorded. For BMD, DEXA scan will be done to obtain T score and following this, FRAX tool which utilizes the T Score will be used to obtain the FRAX score. Laboratory assessments of the Patients will be carried out for the evaluation of serum homocysteine level. |
| **Statistical Analysis:** | Statistical analysis will be performed according to results obtained from parameters. The tests will be performed at a 5% significance level (P <0.05). The qualitative characteristics will be described using absolute and relative frequencies and the quantitative measures will be described in summary measures (mean, standard deviation). |
| **Expected date of start of study:** | Within one month after the Ethics committee permission. |
| **Expected duration of study:** | **Screening** : 4 weeks**Compilation of data**  **:** 8 weeks**Statistical analysis** **:** 4 weeks**Report writing** **:** 4 weeks |
| **Expected date of Draft report:** | After 5 months of initiation of the study. |

**7.0 BACKGROUND and Introduction**

**Osteoporosis: A global public health problem**

Osteoporosis is a major global public health problem associated with significant morbidity, mortality, and socioeconomic burden. Worldwide, it is estimated that 1 in 3 women and 1 in 5 men above the age of 50 will experience osteoporotic fractures. 1

India is the second most populated country in the world with approximately 10% of population over 50 years of age.In 2013, sources estimate that 50 million people in India are either osteoporotic or have low bone mass.2

Studies indicate that osteoporosis and osteopenia or low bone mass may occur at a relatively younger age in Indian population.3

Arthroplasty and spine surgery patients are at a higher risk for osteoporosis pre-surgery, due to age and sex, as well as post -surgery, due to the resulting bone resorption and remodeling.

**Complications of osteoporosis in patients undergoing replacement surgery and spine surgery:**

With increase in life expectancy, the aging process also has led to an increasing number of patients with osteoporosis who need hip or knee replacement to treat osteoarthritis or an acute femoral neck fracture.4

Osteoporosis and abnormal bone metabolism may prove to be significant factors influencing the outcome of arthroplasty surgery, predisposing to complications of aseptic loosening and peri-prosthetic fracture.5

Osteoporosis is a relatively common finding in patients undergoing spine surgery also. Osteoporosis increases the risk for complications secondary to implant or bone union failure, including proximal junctional failure and pseudo-arthrosis. 6

**Prevalence of osteoporosis in patients undergoing replacement surgery and rationale for preoperative BMD Scan:**

A prospective observational study published in ***Phys Sportsme, 2013* found high prevalence of previously undiagnosed low bone mass in study patient population > 40 years of age with minimal trauma fractures** (prevalence of previously undiagnosed osteoporosis was 19%, undiagnosed osteopenia 50%).7

In patients with severe hip and knee osteoarthritis needing arthroplasty, the overall rate of osteoporosis at was 23% and a further 43% of patients were classified as osteopenic.8

Hence, a significant proportion of patients undergoing arthroplasty have osteoporosis but this diagnosis may be missed unless bone mineral density (BMD) measurements are performed.

**Dual X-Ray Absorptiometry (DEXA)**

For diagnosis and assessment of fracture risk standard measure is to evaluate BMD of the patient with the help of dual x-ray absorptiometry (DEXA) which is expressed in terms of Gram of Mineral per square centimetre scanned (g/cm2).

A reference value for young healthy normal adults of the same sex can be related with the BMD of patient by using the T-score. The T-score is reported as the number of standard deviations that a patient’s bone mineral density value is above or below the reference value for a healthy thirty-year-old adult. Osteopenia and Osteoporosis is defined by the standard deviation rather than by an absolute value of BMD. So, patient with T Score between -1 and -2.5 gives us the diagnosis of Osteopenia and patient with T Score ≤ -2.5 gives us the diagnosis of Osteoporosis. But measurement of BMD with DEXA also have some limitations. DEXA provides a 2D projection of a 3D structure and thus it cannot capture three dimensional geometry of bone and so it does not truly symbolizes the volumetric BMD but rather a projected areal BMD. Also, several clinical factors are of great value when assessing fracture risk than BMD alone. For example, age of the patient is an influential risk factor in Osteoporosis and Osteopenia.9

**Fracture Risk Assessment Tool (FRAX)**

So to resolve the limits of DEXA, the Fracture Risk Assessment Tool (FRAX) was developed and the aim of FRAX was to deliver an assessment tool for the prediction of fractures in either sex with the use of several clinical risk factors with or without BMD.

These clinical risk factors comprise of age, sex, race, height, weight, body mass index, a history of fragility fracture, a parental history of hip fracture, use of oral glucocorticoids, rheumatoid arthritis and other secondary causes of osteoporosis, current and past smoking or chewing Tobacco History, and alcohol intake of 3 or more units daily. FRAX computes the 10 year probability of a major osteoporotic fracture and of a hip fracture calibrated to the fracture and death hazards. Also in adding to the clinical risk factors, the geographical area of the subject where he or she be inherent in, is considered.9



FRAX Score TOOL (<https://www.sheffield.ac.uk/FRAX/tool.aspx?country=51>)

**8.0 STUDY END POINTS**

1. Proportion of Patients undergoing elective orthopedic and spinal having Osteopenia (T Score between -1 and -2.5) and Osteoporosis (≤ -2.5)
2. Proportion of Patients with, > 3% 10 year estimated risk of hip fracture of more > 20% 10 year estimated risk of major fracture.
3. **STUDY OBJECTIVES**

**Primary objective:**

* To evaluate the preoperative prevalence of Osteoporosis and/or Osteopenia and overall bone quality in prospective Elective Joint Replacement / Spinal Procedural Patients.

**Secondary objective:**

* To evaluate the levels of Homocysteine in the study subject and correlation with the prevalence of Osteoporosis/ Osteopenia.

**10.0 STUDY Design**

**Overview of the Study Design**

A Prospective, Cross- sectional, open label, Multi-centric study to assess the risk of fracture(s) in patients undergoing elective orthopedic and spinal procedures.

Methodology:

This is a prospective, Cross- sectional, Multicentre, observational study to assess the risk of fracture(s) in Patients undergoing elective orthopedic and spinal procedures.

* Ethics Committee approval will be taken.
* The data will be collected from eligible Patients, undergoing elective orthopedic and spinal procedures.
* All the Subjects will be evaluated as per the Inclusion & Exclusion Criteria and will undergo a thorough medical history and appropriate laboratory investigations.
* Bone mineral density will be measured by dual-energy x-ray absorptiometry at the femoral neck and Lumbar spine.
* The FRAX tool will be utilized to evaluate fracture risk of Patients. It is based on individual patient models that integrate the risks associated with clinical risk factors as well as bone mineral density (BMD) at the femoral neck.
* Blood samples will be placed on ice immediately, processed within 120 minutes, and kept frozen until homocysteine levels are measured.

**Study Schedule**

|  |  |
| --- | --- |
| **ACTIVITY** | **Screening** |
| Age or Date of Birth | x |
| Sex | x |
| Weight (kg) | x |
| Height (cm) | x |
| H/ o Previous Fracture | x |
| Family H/o of hip Fracture | x |
| Smoking/tobacco use Status | x |
| H/o Glucocorticosteriod | x |
| k/c/o Rheumatoid arthritis | x |
| Alcohol 3 or more units/day | x |
| Femoral neck BMD (g/cm2) | x |
| Secondary Osteoporosis | x |
| BMD- DEXA Scan | x |
| FRAX Score | x |
| Homocysteine levels  | x  |

 **11.0 STUDY POPULATION**

A total of 140 Patients undergoing Elective Joint Replacement / Spinal Procedural will be enrolled. Both men and women shall participate in the trial if they fulfill inclusion and exclusion criteria.

**Sample size:**

A total of one hundred and forty patients will be enrolled and analyzed.

Considering the assumed prevalence of 20% for 3 parameters; BMD (T score of ≤ 2.5 based on DEXA), FRAX (patients who would require treatment based on 10-year risk of hip fracture / major osteoporotic fracture) and Homocysteinemia; the sample size of 246 and 62 Patients would be required at precision level of 5% and 10% respectively.

**WITHDRAWAL CRITERIA**

1. On request of Subject.
2. At the discretion of investigator.
3. On protocol violation and non-compliance with its specification.

**12.0 PATIENTS ELIGIBILITY**

 **Inclusion criteria**

1. Patients willing to provide informed consent to participate in the study
2. Male or female
3. Age - Male ≥ 60 years and Female ≥ 55 Year
4. Patients who are undergoing elective orthopedic and spinal surgical procedures.

**Exclusion criteria**

1. Not willing or not able to sign informed consent
2. Patients who underwent spine surgery within 2 years
3. Patients on concomitant chemotherapy drugs

 **13.0 ETHICAL consideration**

1. **Ethics Committee review & Communications:** The study will be initiated after the EC permission.
2. **Informed Consent process:** The Patients will be screened for the Study after the Patients have given their consent and are willing to come for regular visits.
3. **Statement of Subject Confidentiality:** The patient’s confidentiality will be maintained. Only initials of the Patients, will be available in any published reports or the CRF.

 **14.0 STUDY monitoring procedure**

Study shall be monitored to check that the CRF is appropriately filled by the investigators. Any discrepancies shall be brought to the notice of Ethical committee.

**Quality Control**

1. Prior to the enrollment of any subject at a site, the Investigator will Review protocol and all study related procedures.
* Procedures for the informed consent
* Procedures for completing the CRFs
1. Personal patient data will be kept confidential. CRF’s or any other documents will identify a patient by initials and numbers only.

**Data handling & management**

1. All the study data will be recorded directly on the CRFs.
2. Only the investigator are authorized to make entries on the CRF.
3. The CRFs to be completed in English
4. Any corrections to be made by drawing a single line through the original entry, entering the new value and placing initials and date next to the new entry.
5. After the completion of CRFs, Investigators will review all CRFs for completeness and accuracy.
6. Statistical analysis after all enquiry and entry done and data is locked.

 15.0 DECLARATION of Helsinki (October 2008)

* 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 fulfillment 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.
1. **BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH**
	1. 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.
	2. 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.
	3. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
	4. 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, and 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.
	5. 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.
	6. 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.
	7. 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.
	8. 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.
	9. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
	10. 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.
	11. 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.
	12. 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.
	13. 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.
	14. 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.
	15. 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.
	16. 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.
	17. 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.
	18. 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.
	19. 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.
	20. 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.
2. **ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE**
	1. 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.
	2. 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.
	1. At the conclusion of the study, Subjects 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.
	2. 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.
	3. 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 judgment 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.

**16.0 DATA ANALYSIS**

A total of 140 completed cases will be analyzed. Statistical analysis will be performed according to results obtained from parameters. The tests will be performed at a 5% significance level (P <0.05). The qualitative characteristics will be described using absolute and relative frequencies and the quantitative measures will be described in summary measures (mean, standard deviation).

**17.0 REFERENCES**

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