SITE / SPONSOR Collaborations: Solutions to KEY Issues

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SITE'S PERSPECTIVE

- Controversial Issues
- Investigational Drugs, Biologicals, and Devices
- Barrier's to New Medications
- Drug Development Pathway
- Consulting Opportunities in Clinical Research
- Conflicts of Interest
- Educational Requirements
- Research Opportunities / Networks / Sites
- Solutions to Key Issues: My experiences

My Background

Orthopedic Pharmaceuticals

- DVT Prophylaxis
- Peri-operative Pain Management
- Arthritic Pain Management
- Orthobiologics
- Rheumatology Trials
- Pain Trials
- Spine Trials
- Knee Lubricants
- Diabetic and Hypertension Trials

Drug Development Pathways

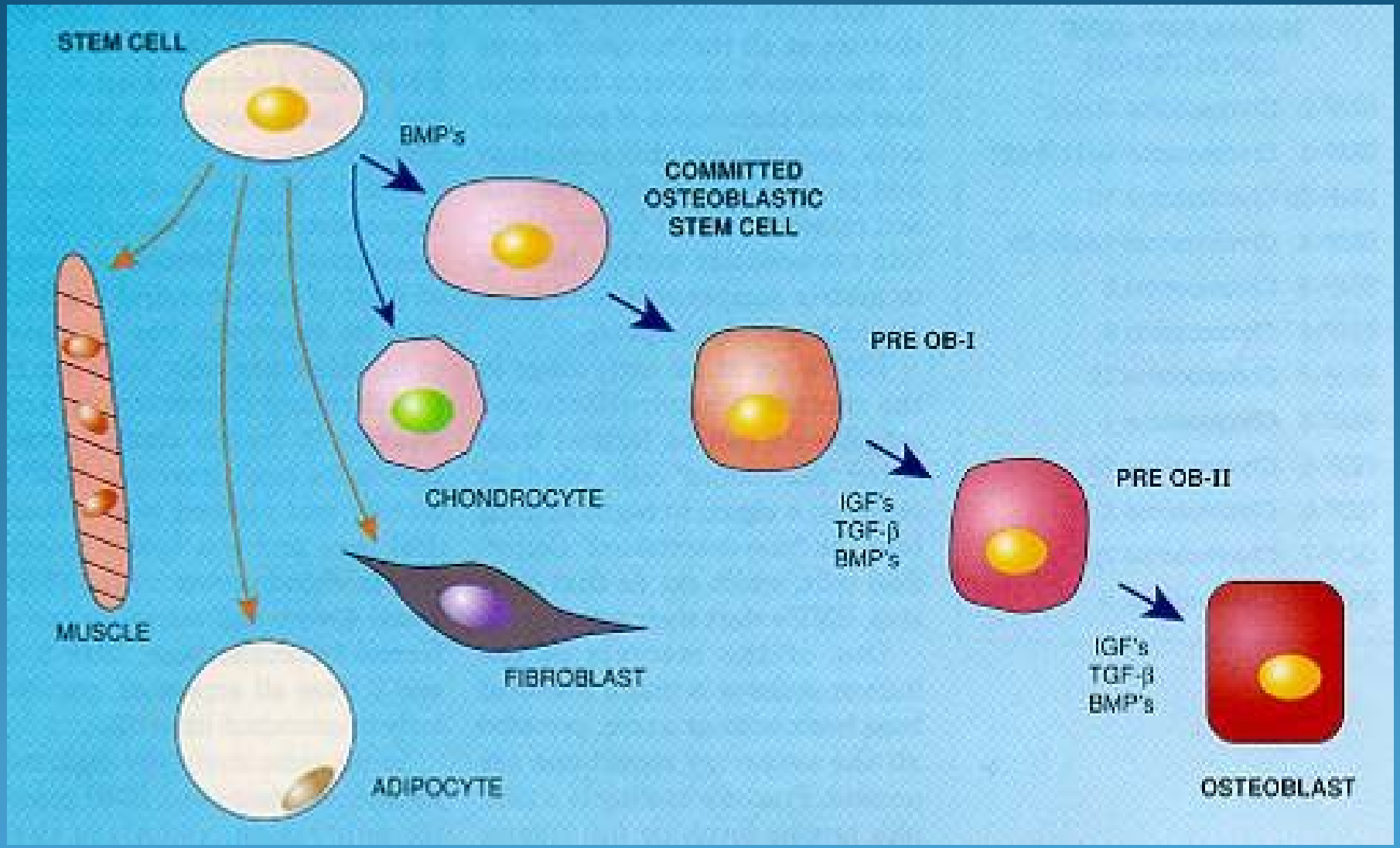
Osteoconduction

Scaffold upon which bone can grow

OsteoInduction-

Chemotactic stimulation of cells to induce production of Bone

Mechanism of Action (Cascade)



- Formulations to Enhance the Healing of Bone

Bone Graft Extenders

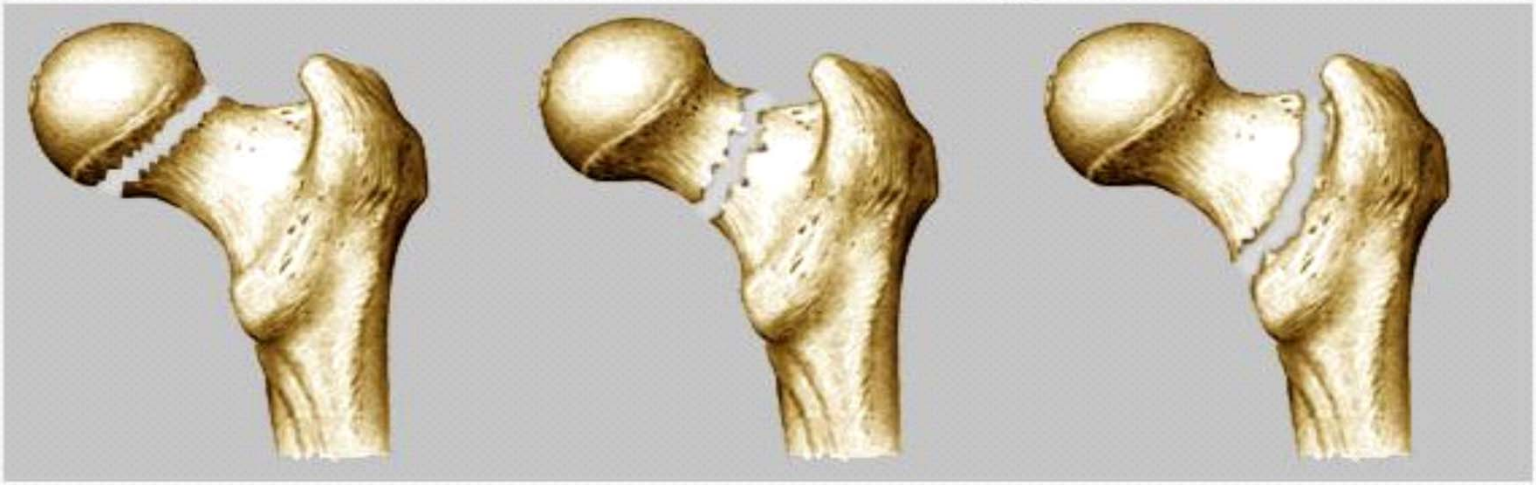
Bone Graft Enhancers

Bone Graft Substitutes

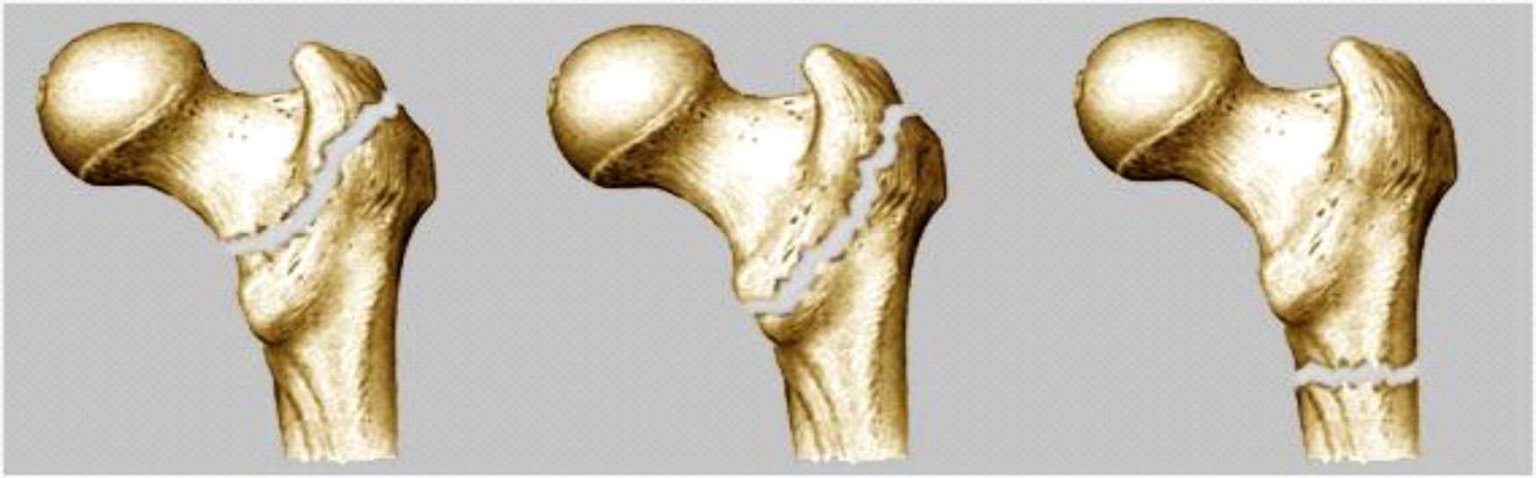
Devices

- Hip Fracture Care

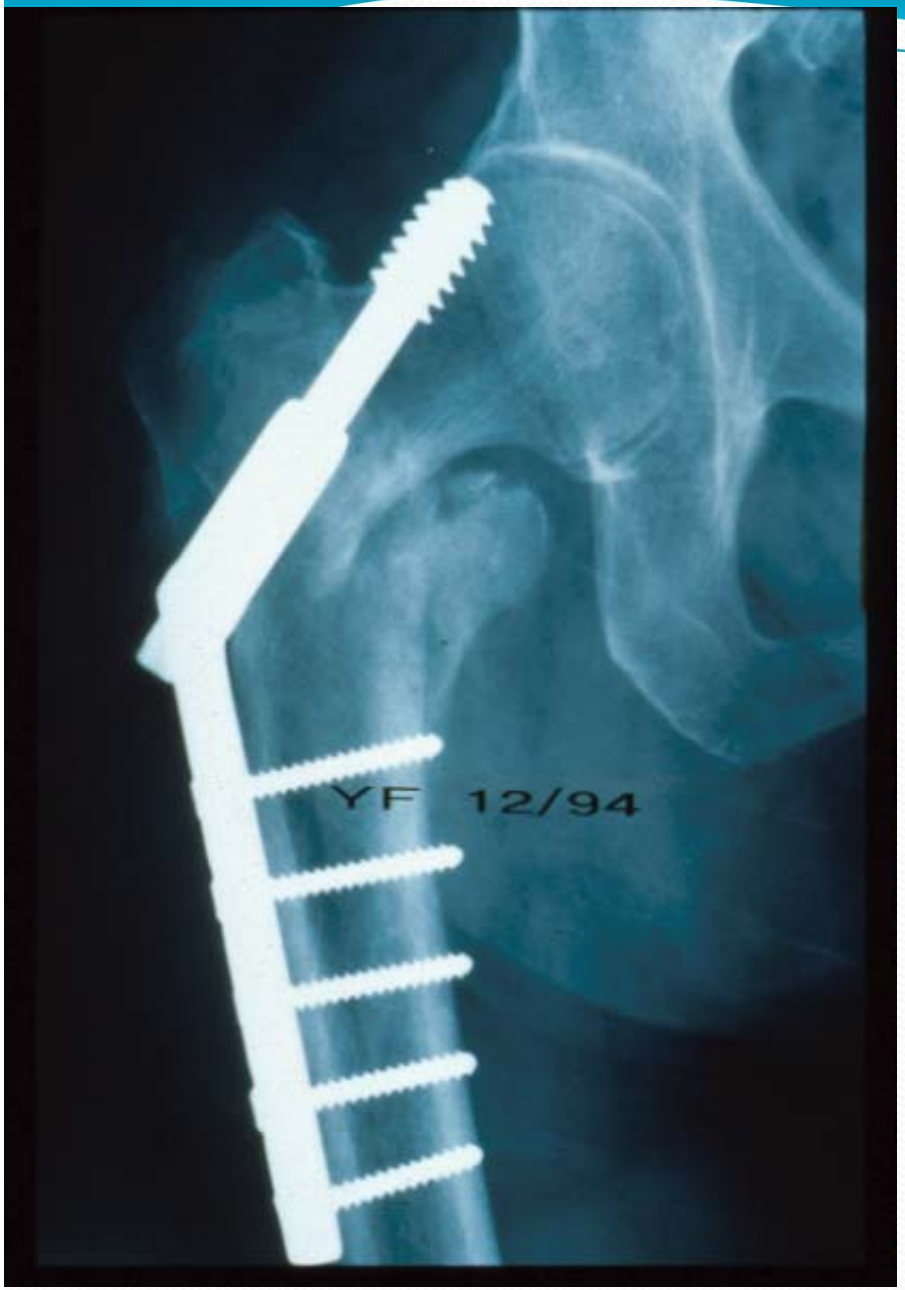
Fractures of the Hip



Subcapital | Transcervical | Base Neck



Intertrochanteric | Peritrochanteric | Subtrochanteric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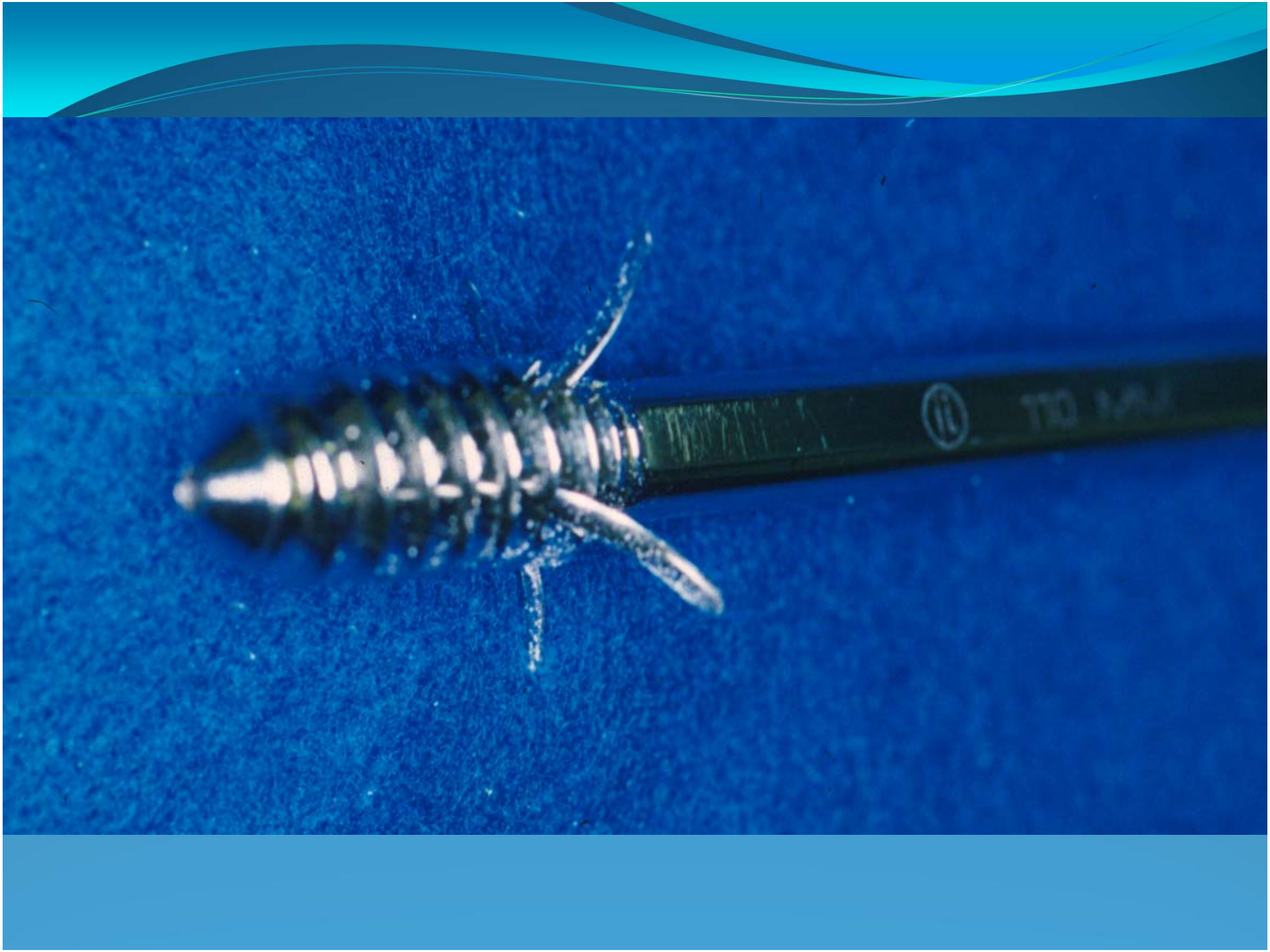
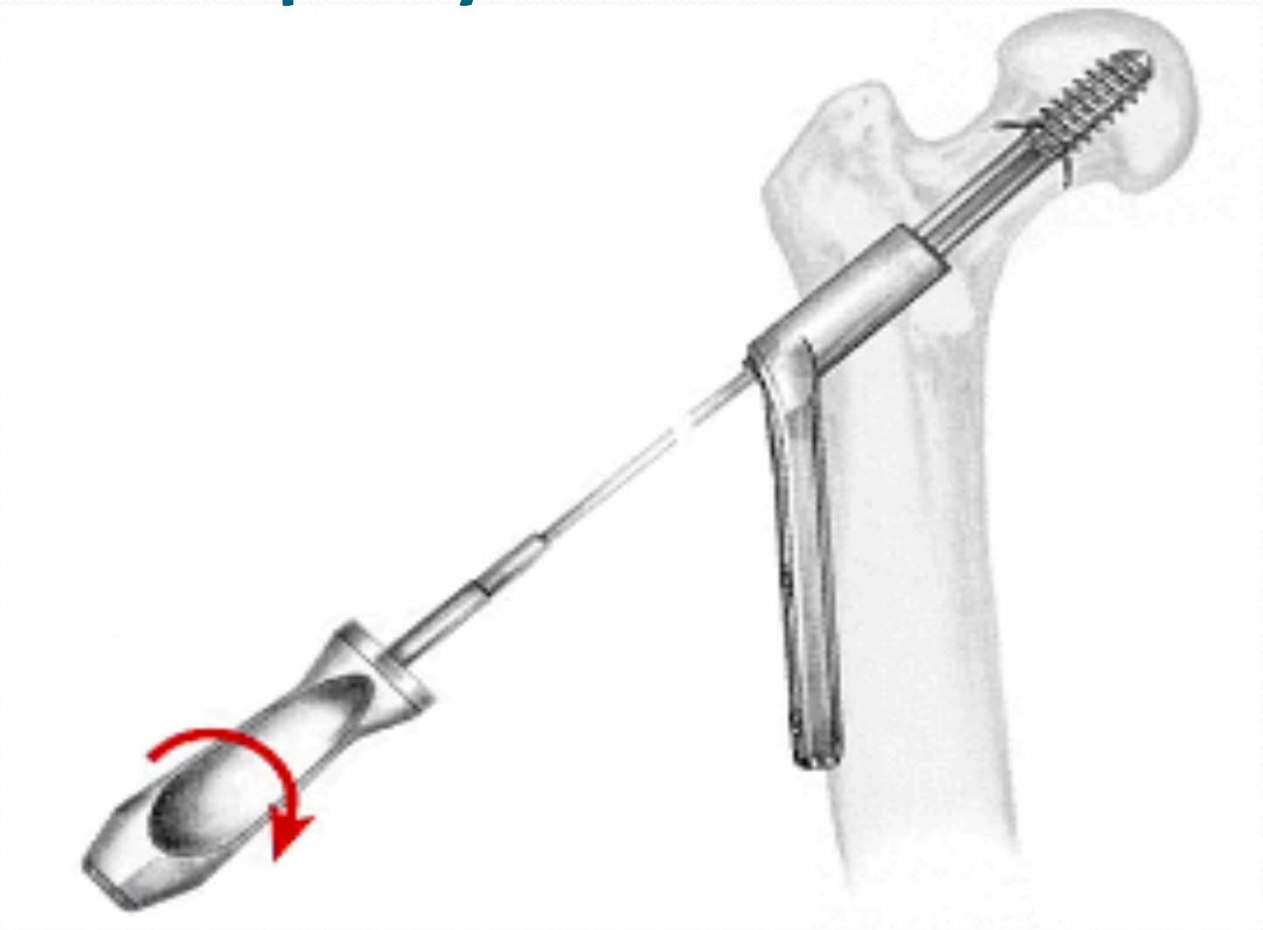
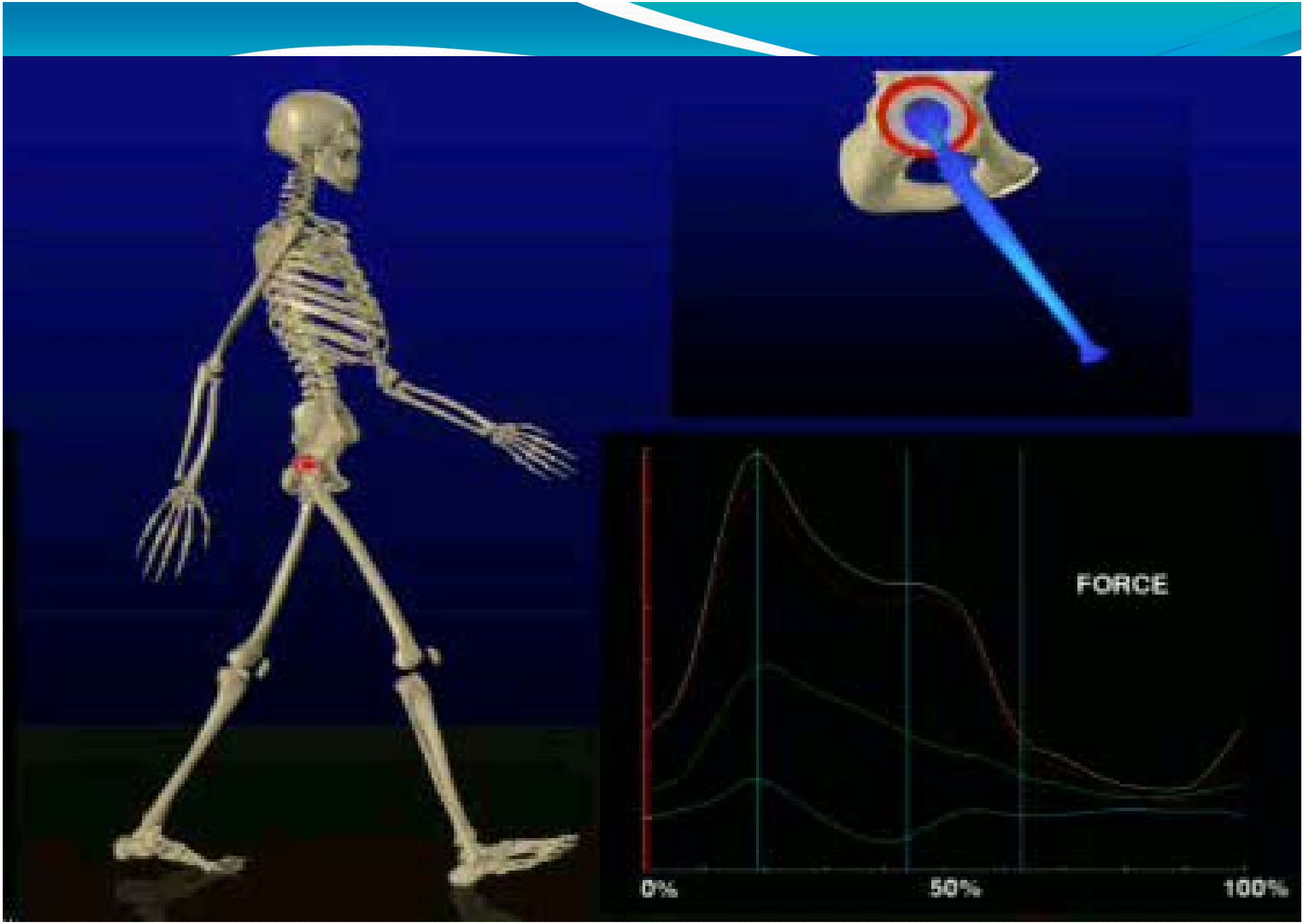


Talons Deployed

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Controversioal Issues

- Solution:
- Good Documentation
- Good SOP's
- Good Management
- Solutions to Common Mistakes
- Regulatory Inspections

Drug Development Pathway

Barriers to New Drugs

Avoiding Problems at you Site

- Lessons Learned from 22 years of Clinical Research Studies in both a Group and an Independent Site's Perspective
- Good Documentation
- Good SOP's
- Good Management of your Site
- Good Ethics

Creating Source Documents

- QUALITY CONTROL

Most **Common** Inspection and Audit **Findings**

- **Lack of** reliable, accurate and adequate source documentation

- Ensures that the study results are **credible and valid**
- Supports the fundamental principle of **protecting Subject's rights, safety and well-being**
- We are protecting our **Investigator**

What is the **PURPOSE**?

- To **reconstruct** the trial as it happened.
- To enable an independent observer to **reconfirm** the data.
- To **provide audit trail** to permit investigation if and when required.

What **IS IT**?

- **Medical record** of the subject before, during and after the trial.
- Tool that **confirms the eligibility** criteria of the subject.
- **Documents the progress** of the subject from consenting till completion.
- **Records the accountability** of the investigational product dispensed, consumed and returned by the subject.
- Serves as the **complete medical record** of the subject as the reference to the treating physician at any point of time.
- **Foundation for the data** that gets transcribed into a CRF which ultimately gets translated into a clinical study report.

- **"If it is not documented, it never happened"**
- **"Document what is done, as well as what is not done"**

ICH E6 1.51: **Source Data**

- "All information in ***original*** **records** and *certified copies* of original records of clinical findings, observations, or other activities in a clinical trial **necessary for the reconstruction and evaluation of the trial**. Source data are contained in source documents (original records or certified copies)."

ICH: International Conference of Harmonization: ensures that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner

ICH E6 1.52: **Source documents**

- "Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial)."

ICH E6 4.9: **Records and Reports**

- Investigator should ensure:
  - **Accuracy**
  - **Completeness**
  - **Legibility**
  - **Timeliess** of Data
  - **Consistency** (with the SDs)
  - Records are **retained** (at least 2 years after marketing approval or discontinuation of the trial)
  - Records are **accessible**
- **Any change** should be:
  - Dated, initialed and explained
  - Should not obscure the original entry

Advent **Management**

- Different Models for Clinical Research

Causes for Deficiencies

- It involves a **variety of documents from various sources**
- It is often completed by **several people**
- Research happens over a **long period**
- There are additional **unmonitored medical records** (Diaries of coordinator, Inpatient records of the hospital, Electronic records, etc.)
- Source Documents **do not reflect accurately** the protocol and CRF
- There are not any additional notes, comments or **supporting documents**
- Sponsors/CROs have **different level of expectations**

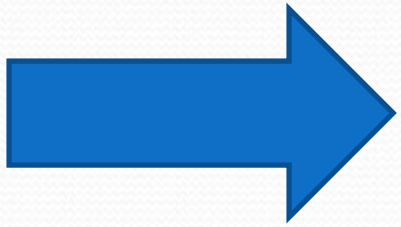
ATRIBUTES OF GOOD DOCUMENTATION

- **A**ttributable: Who documented the data.
- **L**egible: Readable and signatures identifiable.
- **C**ontemporaneous: Information documented in the correct time frame.
- **O**riginal: is the first record made. If not it should be exact copy.
- **A**ccurate: consistent and real representation of facts.

- **Enduring:** Long-lasting and durable.
- **Available and accessible:** Easily available for review.
- **Complete:** Until that point in time.
- **Consistent:** Demonstrate the required attributes consistently.
- **Credible:** Based on real and reliable facts.
- **Corroborated:** The data should be backed up by evidence.
- **Condition:** the state of the source documents, in terms of filing, storing and readability.

If we have….

- Consistency
- Credibility
- Corroboration



we have….

- **Integrity**
- **Quality**

Regulatory Expectations During Inspections

WHAT THEY **DON'T WANT TO SEE…**

- Discrepancies in data
- Conflicting information
- Missing pages
- Numerous unexplained corrections
- Unreported events
- Delay in transcribing data in CRFs
- Discrepancies between source and the CRF
- Incorrect/incomplete documentation
- Checkboxes not checked
- Lab reports not marked for significance for out of range value

WHY?

Doesn't assure data quality and safety of the Subject

Data may be deemed unfit for use

Efforts and time spent by the team will be for nothing

Regulatory Expectations During Inspections

WHAT THEY **WANT TO SEE**…

- **Adequate and accurate** case histories
- **Availability** of source documents
- Ability to **confirm** eligibility criteria

For Data **Integrity and Quality…**

- Get adequate **training** in protocol and GCP before trial participation
- **ALCOA**
- Ensure **supervision** throughout the entire duration of the study
- Keep open communication with **Investigator** for:
  - **Review** of documentation
  - **Timely resolution** of medical, ethical or GCP issues.
  - To validate **medical data**
- Keep open communication with **Sponsor/CRO**
- Ensure that **original documents**/certified copies are in charts
- Source document should speak for itself as it happened

- Quality Control and Assurance (**P.T.**)

References

- Annual report of the GCP Inspectors working Group 2009. Available from: http://wwwemeaeuropaeu/docs/en_GB/document_library/Annual_report/2010/04/WC500089199pdf.
- Guidance for Industry: Computerized Systems Used in Clinical Investigations US FDA 2007
- Handbook for good clinical research practice -WHO guidance for implementation ISBN 92 4 159392 X (NLM classification: W 20.5)
- Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials. EMA/INS/GCP/454280/2010
- Guidance On Clinical Trial Inspection -CDSCO Govt. of India Nov. 2010
- Available from: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2010/default.htm
- http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3121265/

BUSINESS OPPORTUNITIES

- Individual Sites
- Work for Sponsors: CRO or Pharmaceutical Industry
- Group Practice & Clinical Research
- Physician Networks
- Conflicts of Interest
- dbramlet@adventcrc.com

Education Requirements in Clinical Research

- CPI
- Attend Meetings
- ACRP
- DIA
- MAGI

AT THE END OF THE STUDY

- SPONSOR / SITE COLLABORATIONS:
- TIME OF MY LIFE
- A SITE IS ONLY AS GOOD AS IT'S LAST TRIAL
- YOUR REPUTATION and YOUR INTEGRITY is KEY TO YOUR SUCCESS IN CLINICAL RESEARCH

THANK YOU

Questions