# Foundation for NIH (FNIH) Bone Quality Biomarker Project: Design, Goals, Progress

## FDA Osteoporosis Workshop
## 11/4/15

**Dennis Black, Ph.D.**
**University of California, San Francisco**
**For the FNIH BQ Project Team**

# Disclosures

- **Consulting: Radius, Amgen**
- **DSMB membership: Eli Lilly**
- **Research grant: Alexion**

# Foundation for NIH (FNIH) Bone Quality Biomarker Project

## Overall Goal

**Use the existing, large evidence base from randomized trials in osteoporosis to examine the extent to which biomarkers can increase efficiency for future drug development**

# FNIH Bone Quality Biomarker Project

## Ultimate goal

**Develop a surrogate biomarker that can be used as endpoint for fracture in clinical trials**

## Immediate goals

1) **Advance qualification of biomarkers for drug development and patient management in osteoporosis**
2) **Develop repository & database of clinical trial data**

# Project organization

- **Project Team (Steering Committee)**
  - Chair: Gayle Lester, NIAMS
  - Academic investigators (UCSF, Harvard, U. Sheffield)
  - Stakeholders (eg. FDA, NIH, ASBMR, etc) and funders
- **Coordinating Center UCSF**
  - Overall PI: Dennis Black
  - Co-PI's: Doug Bauer (UCSF), Mary Bouxsein (Harvard)
- **FNIH**
  - Sanya Fanous-Whitticker (Project Manager)
- **Other study units**
  - ON Diagnostics (Contractor for finite element analysis)
  - Prof. Richard Eastell (U. Sheffield), consultant
  - Charles McCulloch (UCSF), Biostatistician

# FNIH BQ Project: Organization and Funding

- All funding through FNIH ("neutral convenor")
- FNIH organized and performed fundraising from industry and other sources
- Funders

| | | |
|---|---|---|
| Agnovos | ASBMR | Amgen |
| Daiichi-Sankyo | Dairy Research Institute | Eli Lilly |
| Merck & Co | Roche Diagnostics | |

# Biomarkers in FNIH BQ Project

**Evaluate 3 biomarkers to qualify them for use in drug development and patient management**

**1 & 2) Imaging-based biomarkers of bone strength**

- **Bone mineral density (BMD) from DXA**
- **Estimated bone strength from QCT-based finite element analysis**

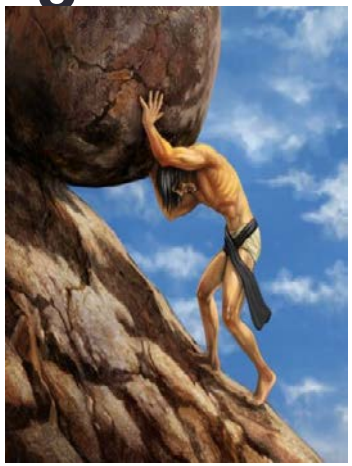
**3) Bone turnover markers (BTM's)(serum, urine)**

# Study Fracture Endpoints

- **Evaluate each of the 3 types of biomarkers with respect to 4 fracture endpoints:**
  1. **Vertebral Fracture**
  2. **Non-Vertebral Fracture**
  3. **Hip Fracture**
  4. **Major Osteoporotic Fracture**

# FNIH BQ Project: Database

**Collect, assemble and combine individual data from <u>all existing trials</u> of osteoporosis agents**



**>150,000 participants**

**> 50 trials**

**14 drugs, including approved and not approved**

- **Hope to later add drugs currently under development**

- ***Resource for future use to address many further questions***

# Data Assembly Process

- Contact each sponsor (or investigator)
- FNIH: establishes data sharing agreements with sponsor
- UCSF: provides specifications and oversees data transfer; creates common data set for pooling and analyses

  - Begun in 2013.
  - Data agreements and transfers ~ 50% complete.
  - Goal for completion of data transfers: Spring, 2016

# Ambitious Data Assembly Goals: Working in our favor

- **Public and governmental pressure to make clinical trial results more transparent**
  - **Institute of Medicine, NEJM, Other groups**

NEJM Perspective

JANUARY 15, 2015

## Sharing Individual Patient Data from Clinical Trials

Jeffrey M. Drazen, M.D.

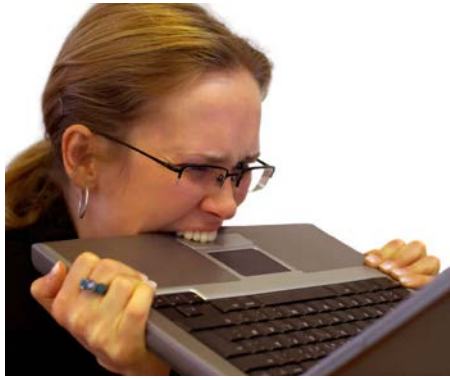
Two years ago, you finished a trial that took 5 years of your life. You'd had an idea for a new indication for a marketed drug. After cajoling the drug maker and pleading with your colleagues around

the report with our readers, editors, and editorial board; we anticipate that the International Committee of Medical Journal Editors will also formulate policy

# Challenges of Data Assembly and Harmonization

- **Legal contracts with sponsors**
- **Life in the real world**
  - Company mergers
  - Loss of patent
  - Loss of staff with specific knowledge
  - Data ownership
  - HIPAA issues

- **Variability in data and documentation**
  - Fracture definitions
  - Adjustment of DXA measurements



- **Sponsors (funders as well as data providers) incredibly supportive**

# Status of Data Collection (for Approved Agents)

| Drug | Type | Company | N trials | N patients | Received at UCSF? |
|---|---|---|---|---|---|
| Alendronate | Bisphosphonate | Merck | 10 | 20,500 | Yes |
| Risedronate | Bisphosphonate | PG…Actavis | 6 | 16,900 | Yes |
| Ibandronate | Bisphosphonate | Roche/ Genentech | 5 | 8,900 | Yes |
| Zoledronic Acid | Bisphosphonate (IV) | Novartis | 8 | 12,000 | Pending final FNIH contract |
| Denosumab | RL inhibitor | Amgen | 1 | 7,800 | Yes |
| Raloxifene | SERM | Lilly | 1 | 7,700 | Yes |
| PTH (1-34) | Anabolic | Lilly | 4 | 2,400 | Yes |
| Estrogen | HT | WHI/ NHLBI | 2 | 27,500 | Approved |

# Status of Data Collection (for Not Approved Agents)

| Drug | Type | Company | N trials | N patients | Received UCSF? |
|---|---|---|---|---|---|
| Lasofoxifene | SERM | Sermonix | 2 | 12,000 | Pending |
| Arzoxifene | SERM | Lilly | 1 | 9,350 | Initial request |
| Basedoxifene | SERM | Pfizer | 3 | 12,000 | Approved |
| Clodronate | BP | McCloskey | 2 | 5,700 | Initial request |
| PTH (1-84) | Anabolic | NPS/ Shire | 3 | 3,000 | Not likely |
| Tiludronate | BP | Sanofi/Actavis | 1 | 2,300 | Not likely |

**Expect to have total of 45 trials with >142,000 patients**

**Hope to augment in future with drugs in development**

# Likely Number of Patients with Each Biomarker

Total N > 142,000
- For primary analyses, limit to placebo-controlled trials

| | |
|---|---|
| Patients with clinical data: | ~ 125,000 |
| DXA BMD: | 100,000-110,000 |
| BTMs: | 18,000 – 25,000 |
| QCT/FEA scans: | 400 – 800 |
| Hip Fractures: | 1200-1400 |

# Summary of Data Analysis

- Individual, patient-level meta-analysis
- Main outcome: % of treatment effect explained
- Proportional hazards model
- Power
  - > 98% for PTE > 20%

# Possible Outcomes from FNIH Study

**1) <u>DXA-based aBMD</u>: >100,000 patients from RCTs**

- **Assess value of BMD changes as biomarker and potential surrogate**

**Examples of other BMD-related issues that can be addressed**

- **Larger fx reduction in those with low BMD (T-score < -2.5) or in those with high FRAX risk**
- **Identify a BMD threshold for "treat to target"**

# Possible outcomes from FNIH study

## 2) Bone turnover markers: >20,000 measurements

- Assess BTM changes as (drug) class-specific biomarker
- Confirm usefulness for drug development
- Confirm utility in clinical care

## 3) QCT-based finite element analysis for bone strength

- Association of change in FEA-strength with reduction in fracture risk
- Design of future trials to expand evidence base for FEA as biomarker

# Biomarker Types

- **Diagnostic Biomarkers**
  - Identify patients with a particular disease or a disease subset
- **Prognostic biomarkers**
  - Indicate future clinical course with respect to a specified clinical outcome, in the absence of therapeutic intervention
- **Predictive biomarkers**
  - Identify patients likely to respond (favorably or unfavorably) to a specific treatment
- **Response biomarkers**
  - Indicate that biological response has occurred in a patient after having received a therapeutic intervention
    - *Pharmacodynamic biomarkers* - Indicators of intended activity of the therapeutic, not necessarily strong predictors of efficacy
    - *Efficacy-response biomarkers* - Predict specific disease-related clinical outcome, could serve as primary clinical endpoints or surrogates for a clinical end point
    - *Safety-related response biomarkers*- Indicators of potential adverse drug reactions - Likely to be specific for a type of drug toxicity, usually organ specific



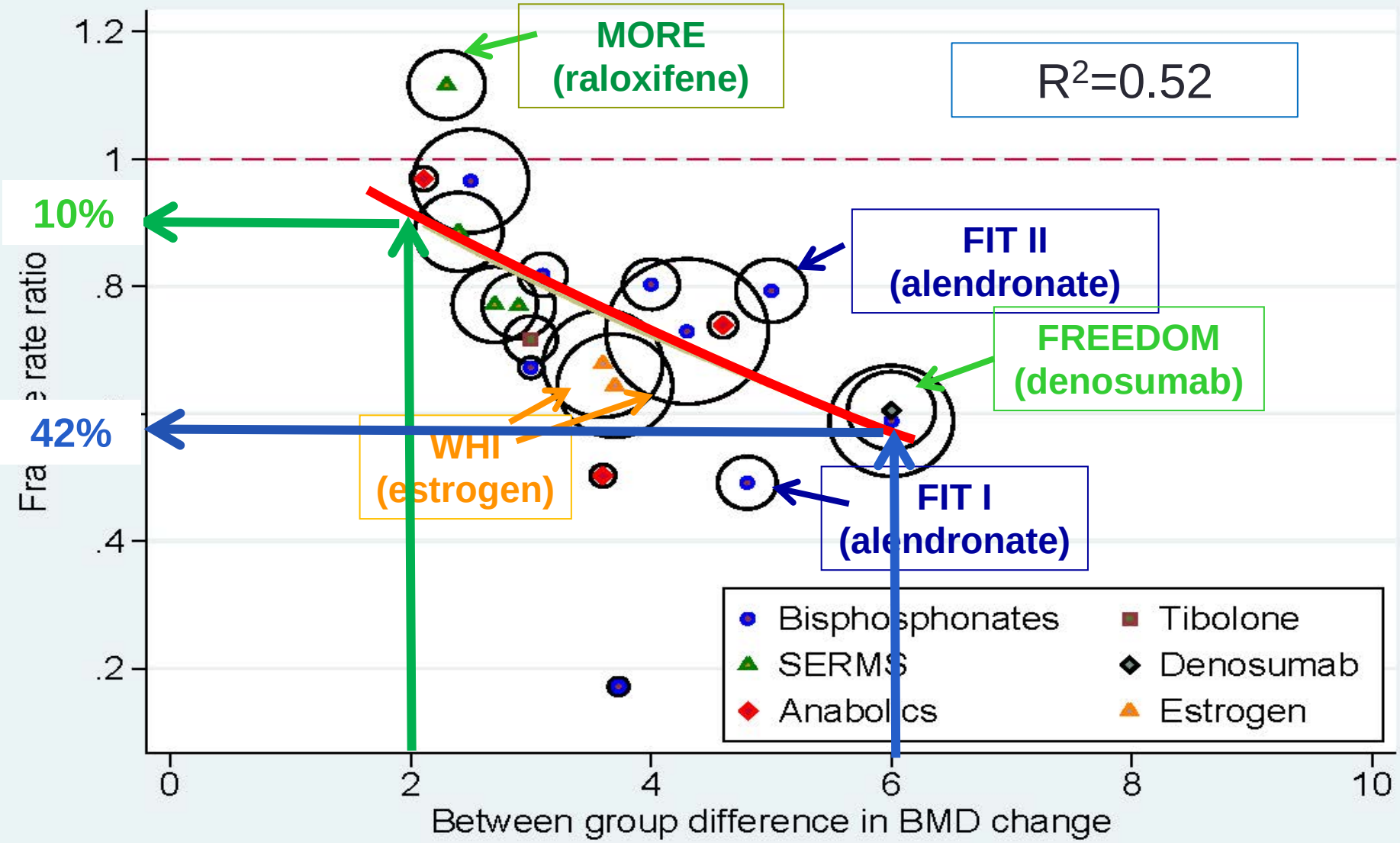
Amur, et al Clin Phar & Ther, 2015

# Meta-analysis of Change in Hip BMD and Hip Fracture Reductions*

- Part of qualification for "clinical surrogate"
- Study-level meta-analysis of published data
  - 18 trials; 104,000 patients; 1100 hip fractures
- Compare changes in hip BMD to hip fx reduction
- Preview of potential once we can analyze individual data on >125,000 patients

*Black et al ASBMR 2015

# Change in Total Hip BMD vs Reduction in Hip Fracture*




*Bubble size ~ to n fractures in study*

# Examples of Other Research Questions

- **Can combining biomarkers increase their utility?**
  - **Imaging biomarker + bone turnover marker**
  - **Morphometric vert fx + imaging biomarker + bone turnover marker**
- **Do osteoporosis meds reduce fractures in subgroups?**
  - **For example, among diabetics or in the elderly**

# Future Analyses of FNIH database: How?

- **Tremendous value in this unique database which can be used as a resource**
  - **Future analysis plans submitted to FNIH Project Team**
  - **Evaluated and prioritized by Project Team**
  - **Separate funding**
  - **Analysis at UCSF**

# Summary: FNIH Bone Quality Study

- **Assemble large collection of individual patient data from RCTs for pooled analyses of biomarkers**
  - **Can perform analyses across treatment types**
  - **Apply consistent statistical and imaging-analysis methods across all studies**
  - **Large numbers ➔ high statistical power**
- **Will be able to perform analyses to assess qualification for biomarkers**
- **Create resource for future studies and research questions**

# Thanks

# Thanks to Foundation for NIH and Project Team

**Chair**: Gayle Lester, NIAMS

**PI**: Dennis Black, UCSF

**Co-PI**: Doug Bauer, UCSF

**Co-PI**: Mary Bouxsein, Harvard Medical School

**Consultant:** Richard Eastell, U. Sheffield

**Statistician**: Charles McCulloch, UCSF

**CRO**: ON Diagnostics (Tony Keaveny)

**Scientific Program Manager**: Sanya Fanous-Whitaker, FNIH

# Thanks to Foundation for NIH and Project Team (including funders)

**FNIH Project Team Members (Government):**
Douglas Fester – American Society for Bone and Mineral Research; Theresa Kehoe, Bruce Schneider – FDA; Lyndon Joseph, Gayle Lester – NIH

**FNIH PT Members/Funders (Corporate):**
Dominique Favell – AgNovos Healthcare; Andreas Grauer – Amgen Inc.; Victor Dishy – Daiichi Sankyo, Inc.; Jeffrey Zachwieja – Dairy Research Institute®; Bruce Mitlak – Eli Lilly and Company; Anne de Papp – Merck Sharp & Dohme Corp.; Jim Harris, Ursula Klause – Roche Diagnostics Corporation

# Finite Element Modeling: Likely Sources of QCT/FE for main analyses

| Data Source Name / Study Name | Data Sponsor | Ppts with BL/FU scans | Status | Purpose |
|---|---|---|---|---|
| **FREEDOM** | Amgen | 73 | BioClinica de-identifying | FE for denosumab |
| **HORIZON PFT 2301** | Novartis | 203 | De-identified at UCSF | FE for ZOL |
| **FACT** | Eli Lilly | 53 | At OND | FE for alendronate and TPTD |
| **PaTH** | NIAMS | 178 | At UCSF | FE for alendronate (also PTH(1-84)) |
| **Ibandronate Quality (IQ)** | GSK | 71 | At OND (awaiting CDA/ data) | FE for ibandronate |