



The American Society for  
Bone and Mineral Research

# **Osteoporosis Trials: Ethical Considerations in Study Design**

This conference was supported by unrestricted educational grants from the following companies:

Alliance for Better Bone Health (Procter & Gamble  
Pharmaceuticals and Aventis Pharma)

Amgen, Inc.

Eli Lilly and Company, Inc.

F. Hoffmann-La Roche, Ltd.

Merck & Co., Inc.

Pfizer, Inc.

Wyeth Pharmaceuticals

## Information for Attendees

### **Osteoporosis Trials: Ethical Considerations in Study Design June 14-15, 2002**

#### Friday, June 14

Natcher Conference Center – Building 45  
National Institutes of Health  
45 Center Drive  
Bethesda, Maryland 20892

#### Saturday, June 15

Hyatt Regency Bethesda  
7400 Wisconsin Avenue  
Bethesda, Maryland 20814

---

## **HOTEL**

Hyatt Regency Bethesda  
7400 Wisconsin Avenue  
Bethesda, MD 20814  
Tel: (301) 657-1234  
Fax: (301) 657-6453

---

## **AIRPORT**

Hyatt Regency Taxi to  
Reagan National Airport:  
\$28-\$35

Hyatt Regency Taxi to  
Dulles International Airport:  
\$37-\$45

Hyatt Regency Taxi to  
Baltimore/Washington  
International Airport  
\$45-\$55

*\*The Hyatt is located less than 30 minutes from the Reagan National and Dulles International airports.*

**Bethesda to Reagan National Airport by METRO:** From Bethesda to Reagan National Airport (only) you may use the METRO system. From Bethesda, take the Red Line in the direction of Glenmont to the Chinatown-Gallery Place stop. From there, transfer to the Yellow Line in the direction of Huntington.

**NOTE:** Use the **Bethesda stop** for the Hyatt Regency. Use the **Medical Center stop** for the Natcher Center/NIH campus.

---

## **CONFERENCE MEALS**

Your registration for the conference includes continental breakfast on Friday, June 14. Lunch on Friday is available for purchase in the Natcher Building First Floor Dining Center. On Saturday, breakfast will be available for purchase at the Hyatt Regency.

**TABLE OF CONTENTS**  
**The American Society for Bone and Mineral Research Presents:**

**Osteoporosis Trials:  
Ethical Considerations in Study Design**

**Day 1**  
June 14, 2002  
Bethesda, Maryland

*7:30 - 8:05 a.m.*

**Registration/Continental Breakfast**

*8:05 - 8:10 a.m.*

**Welcome**

Robert R. Recker, M.D., ASBMR President

**SESSION 1: Moderator: Robert R. Recker, M.D., ASBMR President**

*8:10 - 8:40 a.m.*

**Introduction: The Terms of the Problem .....1**

Robert Heaney, M.D., Creighton University, Omaha, Nebraska

*8:40 - 9:10 a.m.*

**Revised Declaration of Helsinki and Human Subjects Research.....4**

Nancy Dickey, M.D., Texas A&M University, College Station, Texas

*9:10 - 9:40 a.m.*

**International Regulatory Perspective on Placebo and Active Control Trials.....6**

Susan S. Ellenberg, Ph.D., U.S. Food and Drug Administration, Rockville, Maryland

*9:40 - 10:10 a.m.*

**FDA's Guidance Document for Developing Drugs Used to Treat Postmenopausal**

**Osteoporosis.....7**

Eric Colman, M.D., U.S. Food and Drug Administration, Rockville, Maryland

*10:10 - 10:30 a.m.*

**Break**

**SESSION 2: Moderator: Joan McGowan, Ph.D., National Institutes of Health**

*10:30 - 11:00 a.m.*

**Potential Study Designs Applicable Specifically to Osteoporosis for Anti-Fracture Clinical  
Trials.....9**

Robert Temple, M.D., U.S. Food and Drug Administration, Rockville, Maryland

*11:00 - 11:30 a.m.*

**Human Subject Protections, HHS Regulations – 45 CFR 46.....11**

Judith Brooks, Office for Human Research Protections, Rockville, Maryland

*11:30 - 12:00 p.m.*

**European Ethical Guidelines.....13**  
John Kanis, M.D., University of Sheffield, Sheffield, United Kingdom

*12:00 - 1:00 p.m.*

**Lunch**

**SESSION 3: Moderator: Bess Dawson-Hughes, M.D., Tufts University**

*1:00 - 1:30 p.m.*

**Adverse Outcomes of Osteoporotic Fractures in the General Population.....15**  
L. Joseph Melton III, M.D., Mayo Clinic and Foundation, Rochester, Minnesota

*1:30 - 2:00 p.m.*

**Risk of Death and Disability in Placebo-Controlled Osteoporosis Trials.....17**  
Steven R. Cummings, M.D., University of California, San Francisco,  
San Francisco, California

*2:00 - 2:30 p.m.*

**Industry Viewpoints/Perspectives (Videotaped Presentation).....19**  
Michael Rosenblatt, M.D., Harvard Medical School, Boston, Massachusetts

*2:30 - 3:00 p.m.*

**Surrogates for Fracture Endpoints in Osteoporosis Clinical Trials.....21**  
Sundeep Khosla, M.D., Mayo Clinic and Foundation, Rochester, Minnesota

*3:00 - 3:30 p.m.*

**Break**

**SESSION 4: Moderator: Richard O'Brien, M.D., Creighton University**

*3:30 - 4:00 p.m.*

**Clinical Equipoise and Study Design.....23**  
Charles Weijer, M.D., Ph.D., Dalhousie University, Halifax, Canada

*4:00 - 4:30 p.m.*

**Ethicist Reaction.....25**  
David Wendler, Ph.D., National Institutes of Health, Bethesda Maryland

*4:30 - 5:00 p.m.*

**Ethics of Clinical Trials of New Treatments for Osteoporosis.....26**  
Robert Levine, M.D., Yale University, New Haven, Connecticut

*5:00 - 5:30 p.m.*

**Assessment of Various Study Designs, Ethical and Scientific: Audience Participation.....27**  
Robert R. Recker, M.D., ASBMR President

*5:30 p.m.*

**Adjourn**

**The American Society for Bone and Mineral Research Presents:**

**Osteoporosis Trials:  
Ethical Considerations in Study Design  
Day 2  
June 15, 2002  
Bethesda, Maryland**

**8:00 a.m.**

**Presentation of Summary Statement and Discussion.....28**

**Panel:** Lawrence G. Raisz, M.D., *Panel Chair*  
University of Connecticut Health Science Center, Farmington, Connecticut

Ethel Siris, M.D., Columbia University, New York City, New York

Susan S. Swift, D.P.A., Susan S. Swift, Ltd., New York City, New York

Alexander Morgan Capron, L.L.B., University of Southern California,  
Los Angeles, California

Sue K. Donaldson, Ph.D., The Johns Hopkins University,  
Baltimore, Maryland

**12:00 p.m.**

**Adjourn**

### ***ORGANIZING COMMITTEE***

Robert R. Recker, M.D., *Chair, ASBMR President*  
Eric Colman, M.D., *U.S. Food & Drug Administration*  
Bess Dawson-Hughes, M.D., *NOF President-Elect*  
Richard Eastell, M.D., *ASBMR Councilor*  
Robert Lindsay, M.D., *NOF Immediate Past-President*  
Robert Marcus, M.D., *ASBMR Past-President*  
Joan McGowan, Ph.D., *National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH*  
Richard L. O'Brien, M.D., *Creighton University Center for Health Policy and Ethics*  
Clifford J. Rosen, M.D., *ASBMR President-Elect*  
Nelson B. Watts, M.D., *Chair, ASBMR Professional Practice Committee*

### ***CO-SPONSORS***

The National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH  
Office of Research on Women's Health, NIH  
Agency for Healthcare Research and Quality

American Academy of Orthopaedic Surgeons  
American Association of Clinical Endocrinologists  
American College of Rheumatology  
The Endocrine Society  
The International Bone and Mineral Society  
The International Society for Clinical Densitometry  
The National Osteoporosis Foundation  
Orthopaedic Research Society

### ***SUPPORTERS***

**This conference was supported by unrestricted educational grants from the following companies:**

Alliance for Better Bone Health (Procter & Gamble Pharmaceuticals and Aventis Pharma)  
Amgen, Inc.  
Eli Lilly and Company, Inc.  
F. Hoffmann-La Roche, Ltd.  
Merck & Co., Inc.  
Pfizer, Inc.  
Wyeth Pharmaceuticals

### ***COPYRIGHT***

Copyright © 2002 by the American Society for Bone and Mineral Research. Reproduction, distribution or transmission of this abstract program or the works contained herein in whole or in part, or other intended use, is prohibited without express written permission from the American Society for Bone and Mineral Research.

### ***DISCLAIMER***

All authored abstracts, findings, conclusions, or recommendations contained herein are those of the author(s) and do not necessarily reflect the views of the American Society for Bone and Mineral Research or herein imply any endorsement. No responsibility is assumed, and responsibility is hereby disclaimed, by the American Society for Bone and Mineral Research for any injury and/or damage to persons or property as a matter of products' liability, negligence or otherwise, or from any use or operation of methods, products, instructions, or ideas presented in the material herein (2002 Osteoporosis Trials: Ethical Considerations in Study Design On-site Program). Discussions, views and recommendations as to medical procedures, choice of drugs and drug dosages are the responsibility of the authors.

# Osteoporosis Trials: Ethical Considerations in Study Design PROGRAM

**June 14, 2002**

National Institutes of Health  
Natcher Conference Center  
Bethesda, Maryland, USA

<b>June 14</b>	<b>Topic</b>	<b>Speaker</b>
<b>Session 1</b>	<b>Moderator: Robert R. Recker</b>	
8:05 a.m.	Welcome	Robert R. Recker
8:10 a.m.	Introduction: The Terms of the Problem	Robert Heaney
8:40 a.m.	Revised Declaration of Helsinki and Human Subjects Research	Nancy Dickey
9:10 a.m.	International Regulatory Perspective on Placebo and Active Control Trials	Susan Ellenberg
9:40 a.m.	FDA's Guidance Document for Developing Drugs Used to Treat Postmenopausal Osteoporosis	Eric Colman
<b>10:10 a.m.</b>	<b>BREAK</b>	
<b>Session 2</b>	<b>Moderator: Joan McGowan</b>	
10:30 a.m.	Potential Study Designs Applicable Specifically to Osteoporosis for Anti-Fracture Clinical Trials	Robert Temple
11:00 a.m.	Human Subject Protections, HHS Regulation - 45 CFR 46	Judith Brooks
11:30 a.m.	European Ethical Guidelines	John Kanis
<b>12:00 p.m.</b>	<b>LUNCH</b>	
<b>Session 3</b>	<b>Moderator: Bess Dawson-Hughes</b>	
1:00 p.m.	Adverse Outcomes of Osteoporotic Fractures in the General Population	L. Joseph Melton
1:30 p.m.	Risk of Death and Disability in Placebo-Controlled Osteoporosis Trials	Steven Cummings
2:00 p.m.	Industry Viewpoints/Perspectives	Michael Rosenblatt (videotaped presentation)
2:30 p.m.	Surrogates for Fracture Endpoints in Osteoporosis Clinical Trials	Sundeep Khosla
<b>3:00 p.m.</b>	<b>Break</b>	
<b>Session 4</b>	<b>Moderator: Richard O'Brien</b>	
3:30 p.m.	Clinical Equipoise and Study Design	Charles Weijer
4:00 p.m.	Ethicist Reaction	David Wendler
4:30 p.m.	Ethics of Clinical Trials of New Treatments for Osteoporosis	Robert Levine
5:00 p.m.	Assessment of Various Study Designs, Ethical and Scientific: Audience Participation	Robert R. Recker
<b>5:30 p.m.</b>	<b>Meeting Adjourned</b>	

# Osteoporosis Trials: Ethical Considerations in Study Design PROGRAM

June 15, 2002

Hyatt Regency  
Bethesda, Maryland, USA

<b>June 15</b>	<b>Topic</b>	<b>Panel</b>
<b>Session 5</b>	<b>Moderator: Nelson Watts</b>	
8:00 a.m.	Presentation and discussion of summary statement by panel	Lawrence G. Raisz, Chair A.M. Capron Ethel S. Siris Susan S. Swift Sue K. Donaldson
<b>12:00 p.m.</b>	<b>Meeting Adjourned</b>	

## Disclosure/Conflict of Interest

The ASBMR is committed to ensuring the balance, independence, objectivity and scientific rigor of all its educational activities. ASBMR desires for audiences at its educational programs to be informed of a presenter's academic and professional affiliations and the existence of any significant financial interest or other relationship a presenter has with the manufacturer(s) of any commercial product(s) discussed in an educational presentation. This policy allows the listener/attendee to be fully informed in evaluating the information being presented.

The following key was used to identify the potential conflicts which are listed at the end of the biographical information of each speaker.

1. stock options or bond holdings in a for-profit corporation or self-directed pension plan
2. research grants
3. employment (full\* or part-time)
4. ownership or partnership
5. consulting fees or other remuneration (payment)
6. non-remunerative positions of influence such as officer, board member, trustee, or public spokesperson
7. receipt of royalties
8. speakers bureau

\* For full-time employees of industry or government, the affiliation listed in the biographical information will constitute full disclosure.



June 14, 2002

Dear Meeting Attendee,

On behalf of the American Society for Bone and Mineral Research, I am pleased to welcome you to “Osteoporosis Trials: Ethical Considerations in Study Design.” The impetus for this conference arose in late 2000 when ethical concerns began to arise concerning placebo-controlled antifracture efficacy trials in osteoporosis. This came about due to our success in developing agents that are truly effective in preventing fractures due to osteoporosis. The continued development of new osteoporosis agents resulted in considerable ethical confusion and uncertainty in the field, as judged by the discussion that has taken place.

This ASBMR initiative began with a meeting, held at the Creighton University Center for Health Policy and Ethics, in June, 2001. That meeting introduced the problem to ethicists, solicited their response, and tried to formulate the proper questions to be raised at this larger conference later. The purpose of this 2002 conference is to provide a forum to present a comprehensive discussion of the ethical aspects of placebo-controlled trials of new drugs in osteoporosis.

We hope this will provide background material to guide investigators, pharmaceutical industry, government agencies and institutional review boards in assessing the ethics of various study designs for testing new agents in osteoporosis. We emphasize that this meeting will provide a forum for full discussion. We do not intend to produce a consensus at this meeting since it is doubtful that a consensus exists, nor will it likely arise immediately out of this conference. We expect the proceeds of this conference to be published in the near future.

Sincerely,

A handwritten signature in black ink that reads "Robert R. Recker". The signature is written in a cursive style with a large, stylized initial "R".

Robert R. Recker, M.D.,M.A.C.P., F.A.C.E.  
ASBMR President

---

## **Introduction: The Terms of the Problem**

**Speaker: *Robert Heaney***

**8:10 a.m. – 8:40 a.m.**

---

Robert P. Heaney, M.D.  
John A. Creighton University Professor and Professor of Medicine  
Creighton University

Evidence of efficacy is now required for new drug indications in most jurisdictions. In osteoporosis, efficacy generally means reduction in risk of fragility fracture, relative to no treatment (i.e., placebo).

At least four bisphosphonate agents, three natural hormonal agents, and one SERM, as well as protective garments, have demonstrated such efficacy for prevention and/or treatment of osteoporosis. Additionally, at least four trials have shown anti-fracture efficacy (as well as bone mass benefits) for supplemental calcium and/or vitamin D alone, relative to placebo. (These supplemented intakes have generally been higher than those used as co-therapy or as the "placebo" arm in the trials of pharmacological and hormonal agents.). Fracture risk reductions of current generation pharmacotherapeutic agents are substantial (on the order of 40-70%), relative to modest calcium supplementation. With recent agents reduction in risk of multiple or more severe fractures is even greater. Finally, at least one of the hip protectors currently being used has shown 90+% reduction in hip fracture risk while the patient is wearing the garment.

Given the efficacy of these agencies, it follows that individuals in the placebo-treated arm of any future clinical trial will incur a risk of fracture higher than could be achieved with currently approved treatments. Fractures are relatively uncommon events and large numbers of participants must be enrolled in clinical trials to ensure sufficient numbers of fractures for statistical assessment. Further, trials with fracture end-points must usually last 2-4 years. Small differences in efficacy, as would be sought in a superiority trial, require very large sample sizes, with correspondingly high exposure of participants to risk, as well as high cost. In addition to cost and functional impairment, many osteoporotic fractures are associated with an excess risk of death and serious adverse events.

For these reasons concerns have been raised about the ethicality of designing future efficacy trials incorporating a placebo arm.

Use of active agent control arms in such trials avoids the ethical problem but presents significant inferential difficulties. While such trials can be designed to establish either equivalency or superiority of a new agent relative to an approved treatment, absolute efficacy will remain uncertain. This is because absolute efficacy of the approved agent in the population being tested

is itself unknowable from such a design and often cannot safely be extrapolated from prior studies.

The use of surrogate markers could in theory reduce both cost and risk, perhaps substantially, and might reduce ethical concern about use of placebo-treated contrast groups. But there is no prevailing consensus regarding such surrogates.

Despite the efficacy of existing agents, there is still room for improvement in therapy, and many promising agents are now in development. Stopping this development would deny substantial benefit to many present and future individuals with this disorder.

*Robert P. Heaney, M.D., F.A.C.P., F.A.I.N., is John A. Creighton University Professor and Professor of Medicine, Creighton University, Omaha, Nebraska. Dr. Heaney completed his undergraduate and medical degrees at Creighton. He took internship and residency training in Internal Medicine at St. Louis City Hospital in St. Louis, Missouri, and served Research Fellowships at the Oklahoma Medical Research Foundation in Oklahoma City, Oklahoma, and at the National Institutes of Health in Bethesda, Maryland. He has held faculty appointments at the University of Oklahoma, at George Washington University, and at Creighton, where for nine years he served as Chairman of the Department of Internal Medicine from 1961-1969. Dr. Heaney was Creighton's first Vice-President for Health Sciences, a position he held from 1971-1984, and since 1984 has held the all-university chair named in honor of the University's founder.*

*Dr. Heaney serves or has served on the editorial boards of all the major scientific publications in the field of bone biology and chaired the Scientific Advisory Panel on Osteoporosis of the Office of Technology Assessment (U.S. Congress). He is a past member of the Board of Directors of Loyola University of Chicago and of the Association of Academic Health Centers, and currently is a member of the Board of Trustees of the National Osteoporosis Foundation. He served as a member of the panel on Calcium and Related Nutrients of the Food and Nutrition Board (NAS) in the recent setting of the DRIs for bone-related nutrients.*

*Dr. Heaney has worked for over 45 years in the study of osteoporosis and human calcium physiology. He has received numerous honors and awards, including the Kappa Delta Award of the American Academy of Orthopaedic Surgeons and the Alumni Achievement Citation of his alma mater. In 1990 he was awarded honorary membership in The American Dietetic Association, and in 1993 he was elected Fellow of the American Institute of Nutrition, both in recognition of his work in delineating human calcium absorptive performance and in defining human calcium requirements. In 1994 he received the Frederic C. Bartter Award of the American Society for Bone and Mineral Research in recognition of his career in clinical research.*

Moderator: Robert Recker, M.D.

**Session 1, Friday, June 14, 2002**

---

Disclosures: Bayer, 5; Eli Lilly & Co., 2, 8; General Mills, 2, 5; GlaxoSmithKline, 2, 5; Lane Laboratories, 2; Mead Johnson, 2; National Dairy Council 2, 8; Procter & Gamble Pharmaceuticals, 2; Rhodia, Roots Inc., 2

---

---

## Revised Declaration of Helsinki and Human Subjects Research

Speaker: *Nancy Dickey*

8:40 a.m. – 9:10 a.m.

---

Nancy W. Dickey, M.D.  
President of the Health Science Center  
Vice Chancellor for Health Affairs - The Texas A&M University System  
Chair of DOH Workgroup on the Modification of the Declaration of Helsinki - 1999-2000

The *Declaration of Helsinki* (DOH) was created by the World Medical Association (WMA) following World War II and the atrocities committed in the name of medical research. The declaration is a set of principles largely addressing the rights and protection of human subjects in medical research. Over the course of the last 40 years, a number of modifications to the declaration have occurred. Most recently, between 1997 and 2001, the WMA undertook a comprehensive evaluation of the declaration. Two work groups, multiple international symposia, and extensive online consultation preceded the modifications that were voted at the WMA Congress in the fall of 2000. Several of the changes which were adopted by the WMA in 2000 have been the subject of widespread discussion and criticism. The areas of greatest concern are the use of a placebo, the adequacy of informed consent, and the obligation at the conclusion of the study to populations involved in the study. The purpose of today's discussion will be to discuss the most recent changes to the *Declaration of Helsinki* and its application to research in general and to osteoporosis research in particular.

*Dr. Nancy Wilson Dickey, past president of the American Medical Association, founding program director of the Family Practice Residency of the Brazos Valley, and Professor of Family and Community Medicine at The Texas A&M University System Health Science Center College of Medicine, is President of the A&M System Health Science Center and Vice Chancellor for Health Affairs. Prior to her appointment as president, Dr. Dickey served first as acting, then as interim, dean of the College of Medicine from June 2000 until December 31, 2001. She took office as HSC president on January 1, 2002. In addition to serving as president of the AMA in 1998-1999, Dr. Dickey has participated in numerous other professional organizations, from the American Academy of Family Physicians and Texas Academy of Family Physicians to the Texas Medical Association. Among Dr. Dickey's many honors are recognitions by the Texas Society of Pathologists, the University of Texas Medical School at Houston, and Who's Who in American Colleges and Universities. Dr. Dickey earned her undergraduate degree from Stephen F. Austin State University in Nacogdoches, Texas, followed by her M.D. in 1976 from the University of Texas Medical School at Houston, where she was a recipient of the Distinguished Alumni Award. From 1987 to 1990, she was on the National Institutes of Health's Advisory Council on Allergy and Infectious Diseases. Dr. Dickey has also been an active editorial advisor and reviewer for a number of professional publications and has contributed to general-interest periodicals as well. Currently, she serves as editor in chief of Medem, an Internet-based patient education company. Medem is a partnership of the AMA and nearly a dozen medical specialty societies and several state associations. She has served as a reviewer for the Journal of the American Medical Association and on the editorial advisory boards of Patient Care, Medical World News and Medical Ethics Advisor. She currently serves on the editorial board of Archives of Family Medicine. She also is a frequent speaker at professional and civic organizations around the country. Dr. Dickey and her husband, Franklin (Champ), have three grown children, Danielle, Wilson and Elizabeth.*

Disclosures: World Medical Association, 2

---

---

## International Regulatory Perspective on Placebo and Active Control Trials

**Speaker:** *Susan Ellenberg*

**9:10 a.m. – 9:40 a.m.**

---

Susan S. Ellenberg, Ph.D.

Director, Office of Biostatistics and Epidemiology

Center for Biologics Evaluation and Research, U.S. Food and Drug Administration

The ethics of placebo-controlled trials are sometimes questioned, and the interpretive difficulties of active control trials are often not well understood. To address these and other problems in selecting control groups, an international consortium of scientists representing regulatory authorities as well as the pharmaceutical industry the *International Conference on Harmonization* developed a guidance document entitled, “Choice of Control Group in Clinical Trials.” This document has been adopted as regulatory guidance by the European Union, the United States and Japan. Key points are as follows: active control trials when intended to demonstrate equivalence/noninferiority to a known active agent are interpretable only when one can be sure that the active control will produce some definable effect in any given trial; in many disease areas, effects of known active agents are too variable for such an effect to be predicted in any given trial; placebo controls are ethical even if known effective treatments are available as long as no permanent harm to participants assigned to placebo for the duration of the trial would be expected. International statements of ethical principles, including the most recent clarification of the *Declaration of Helsinki*, have taken positions consistent with this guidance document.

*Dr. Susan Ellenberg is Director, Office of Biostatistics and Epidemiology, in the Center for Biologics Evaluation and Research at the U.S. Food and Drug Administration. Dr. Ellenberg has published extensively in both statistical and medical journals on topics including surrogate endpoints, data monitoring committees, clinical trial designs, adverse event monitoring, and special issues in cancer and AIDS trials. She has also played a leading role in the development of international standards for clinical trials performed by the pharmaceutical industry. She is a Fellow of the American Statistical Association and the American Association for the Advancement of Science, and is an elected member of the International Statistical Institute.*

Disclosures: None

---

---

## FDA's Guidance Document for Developing Drugs Used to Treat Postmenopausal Osteoporosis

Speaker: *Eric Colman*

9:40 a.m. – 10:10 a.m.

---

Eric Colman, M.D.  
Medical Team Leader  
Division of Metabolic and Endocrine Drug Products  
U.S. Food and Drug Administration

In 1994, the Food and Drug Administration's (FDA) Division of Metabolic and Endocrine Drug Products issued a Draft Guidance entitled, *Guidelines for preclinical and clinical evaluation of agents used in the prevention and treatment of postmenopausal osteoporosis*. The Guidance was developed to assist industry in the design of preclinical and clinical studies that, if successfully completed, would support approval of drugs used to prevent and treat postmenopausal osteoporosis.

To support clinical trial data, it is recommended that preclinical studies examining bone quality (i.e., architecture, strength) be conducted in two animal species. One study should be conducted in the ovariectomized rat model, and the second in a non-rodent model.

The current version of the Guidance document focuses on what is required to gain approval for the treatment and prevention of postmenopausal osteoporosis. Because a treatment-related increase in bone mineral density does not necessarily translate into a reduction in risk for osteoporotic fracture, sponsors are encouraged to demonstrate that their drug favorably affects bone mineral density and the risk for fracture in a population of postmenopausal osteoporotic women. In recent years, to gain approval for the treatment of postmenopausal osteoporosis, sponsors have conducted 3-year, randomized, double-blind, placebo-controlled trials with the incidence of morphometric vertebral fractures as the primary efficacy endpoint. Once a drug has been shown to reduce the risk for fracture, sponsors may then rely on favorable increases in bone mineral density in postmenopausal osteopenic women to support approval of an indication for the prevention of postmenopausal osteoporosis.



*Eric Colman received a Bachelor of Science degree from Cornell University in 1983. After graduate training at Columbia University, Dr. Colman attended Temple University School of Medicine, graduating with an M.D. in 1990. He then took his internship and residency training in Internal Medicine at the University of Maryland Medical System, completing this work in 1993. Following two years of fellowship training in the Division of Gerontology at the University of Maryland, Dr. Colman joined the Division of Metabolic and Endocrine Drug Products at the FDA. Dr. Colman is currently Medical Team Leader for the medical group that oversees regulation of drugs used to treat osteoporosis.*

Disclosures: None

---

## Potential Study Designs Applicable Specifically to Osteoporosis for Anti-Fracture Clinical Trials

Speaker: *Robert Temple*

10:30 a.m. – 11:00 a.m.

---

Robert J. Temple, M.D.  
Associate Director for Medical Policy  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration

Osteoporosis outcome trials to date have used placebo-control designs. These are easy to interpret and highly informative. If it became difficult to continue such trials, there are several possible alternatives that could be considered, including non-inferiority studies, add-on studies and dose-response studies. These designs and their advantages and limitations will be considered.

*Dr. Robert Temple is Associate Director of the Office of Medical Policy of FDA's Center for Drug Evaluation and Research and is also Acting Director of the Office of Drug Evaluation I (ODE-I). ODE-I is responsible for the regulation of cardio-renal, oncologic and neuropharmacologic/psychopharmacologic drug products. The Office of Medical Policy is responsible for regulation of promotion through the Division of Drug Marketing, Advertising, and Communication, and for assessing quality of clinical trials through the Division of Scientific Investigations.*

*Dr. Temple was born in New York City, July 18, 1941. He received a B.A. Magna cum Laude from Harvard College in 1963 and received the M.D. degree from New York University School of Medicine in 1967. At NYU he was elected to Alpha Omega Alpha. He completed an internship and residency in internal medicine at the Columbia Presbyterian Medical Center in 1969. He is board-certified in internal medicine and clinical pharmacology.*

*Dr. Temple was a Clinical Associate and then Chief Clinical Associate in the Clinical Endocrinology Branch of the National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, from 1969-1972, investigating the effects of lithium on the thyroid and examining the effects of agents that disrupt microtubules on steroid secretion. He became a reviewing Medical Officer in the Division of Metabolic and Endocrine Drug Products in 1972, and moved to become Assistant to the Director of the Bureau of Drugs in 1974. In 1976, he became the Director of the Division of Cardio-Renal Drug Products, serving in that role until 1982. From 1982 to 1988 he was Acting Director and then Director of the Office of Drug Research and Review. The responsibilities of that office have been divided in various ways, most recently (since 1995) among five Offices of Drug Evaluation (ODE's 1-5).*

*Among other awards that he has received are FDA's Award of Merit on six occasions, three Commissioner's Special Citations, the Public Health Service Superior Service Award, the DHHS Distinguished Service Award, the Secretary's Special Citation, and the Drug Information Association Outstanding Service Award. He received the American Society for Clinical Pharmacology and Therapeutics' Rawls-Palmer Progress in Medicine Lecture and Award in 2001. He also received the National Organization for Rare Disorders Public Health Leadership Award in 2001.*

*Dr. Temple is on the editorial board of Clinical Pharmacology and Therapeutics. He was on the Board of Directors of the Society for Clinical Trials from 1983-1987 and was President of the Society in 1987. He is an honorary Fellow of the American College of Clinical Pharmacology.*

Disclosures: None

---

---

## Human Subject Protections, HHS Regulation – 45 CFR 46

**Speaker: *Judith Brooks***

**11:00 a.m. - 11:30 a.m.**

---

Judith Brooks  
Health Policy Analyst  
Education Division  
Office for Human Research Protections  
U.S. Department of Health and Human Services

When conducting clinical trials it is ethical principles that drive the federal regulations for protecting human subjects. Ethical principles such as those set forth in the *Belmont Report*: Respect for persons, Beneficence, and Justice. Of course, the only way we have to ensure ethical research is being conducted is by being in compliance with the federal regulations. In osteoporosis research, there are at least two groups of individuals that need special considerations if they are to participate in clinical trials. They are children and the elderly. Each represent opposite ends of the spectrum for decision-making capabilities.

In Subpart D of the 45 CFR 46 Protection of Human Subjects, children are defined as persons who have not attained legal age, as defined by each state. They require parental permission to participate in clinical trials and for medical treatment. Under 45 CFR 46, Institutional Review Boards have additional duties for protecting children involved as subjects in research.

The elderly, while not specifically singled out in the regulations, fall into the criteria for IRB approval of research, (46.111.b), which states “When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards shall be included into the study to protect the rights and welfare of these subjects.”

*Judith Brooks earned her Baccalaureate degree in Nursing from Fitchburg State College in Fitchburg, Massachusetts, in 1978. She spent the next ten years working in ICU and in emergency nursing before earning a Master of Science degree in Health Service Administration from Central Michigan University and assuming the position of Clinical Nurse Manager at Walter Reed Army Medical Center in Washington, D.C.*

*Ms. Brooks transferred to the Department of Clinical Investigations at Walter Reed in 1992, where she served as a Clinical Research Associate, a member of the IRB, and spent five years in IRB administration. In 1997, she joined the NIH, in the National Institute of Allergy and Infectious Diseases, Division of AIDS, as a Program Official for both domestic and international, multicenter clinical trials.*

*Most recently, she accepted a position as a Health Policy Analyst in the Education Division of the Office for Human Research Protections. In this capacity, she conducts presentations on various aspects of human research protection, serves as a member of the OHRP Interdivisional Policy Coordination Committee, the National Human Research Protections Advisory Committee and the Federal Interagency Human Subjects Research Subcommittee.*

Disclosures: None

---

## European Ethical Guidelines

**Speaker: John Kanis**

**11:30 a.m. - 12:00 p.m.**

---

John Kanis, M.D.  
Director  
WHO Collaborating Centre for Metabolic Bone Diseases  
University of Sheffield Medical School

The advent of effective agents for the treatment of osteoporosis has led to the view that placebo-controlled trials to test new agents for efficacy are no longer appropriate. Rather, studies of superiority, equivalence or non-inferiority should be undertaken. Such studies require very large sample sizes and the burden of osteoporotic fracture in a trial setting is substantially increased. Studies of equivalence cannot be unambiguously interpreted since the variance in effect of active comparator agents is too large. If fracture studies are required by regulatory agents, there is still a requirement for placebo-controlled studies, though perhaps of shorter duration than demanded at present.

*Professor Kanis is Director of the WHO Collaborating Centre for Metabolic Bone Diseases at Sheffield. His interest in bone disease covers basic and clinical research, health technology assessment, epidemiology and health economics. He is an author of more than 500 scientific publications and a Royal Society of Medicine Award Winner for his Textbook on Osteoporosis. He is an Editor of Bone and sits on the Editorial Board of several peer review journals. He is a long-standing advisor for Government Departments and non-Governmental organizations in several countries. He founded the International Osteoporosis Foundation in 1988 and was Chairman of its Scientific Advisory Board until 1998. He coordinates and participates in many international research collaborations and has served on the project management team of several EC-funded research awards (e.g., EVOS, EPOS).*

Disclosures: Abiogen, Italy, 5; Aventis, France, 5; Bayer, Germany, 5; Besins Iscovesco, France, 2; Biosintetica, Brazil, 5; Boehringer Ingelheim, UK, 5; Boehringer Mannheim, Germany, 2; British Biotech, UK, 1; Catalyst, UK, 5; Celtrix, USA, 1, 5; Eli Lilly, USA, 5; Gador, Argentina, 5; Glaxo, UK, 1, 5; Health Technology Assessment, UK, 2; Hoechst Marion Roussel, France, 5; Hologic, Belgium, 2, 5; Hologic, USA, 5; IGEA, Italy, 2, 5; International Osteoporosis Foundation, Switzerland, 2; Kissei, Japan, 5; Lehman Brothers, UK, 5; Leiras, Finland, 2, 5; Leo Pharma, Denmark, 2; Lilly, UK, 2, 5; Lilly, USA, 1; Medical Research Council, UK, 2; Merck Research Labs, USA, 5; Merck Research, USA, 1, 2; Merlin Ventures, UK, 5; MRL, China, 5; Novartis, Switzerland, 2, 5; Novo Nordisk, Denmark, 1, 5; Novo Nordisk, UK, 2;

Nycomed, Norway, 5; Organon, Holland, 5; OsteoMeter, Denmark, 5; Parke-Davis, USA, 5; Pfizer, USA, 5; Proctor and Gamble, USA, 1, 5; Roche, Germany, 5; Roche, Switzerland, 2, 5; Rhone-Poulenc Rorer, France, 2, 5; Rotta Research, Italy, 5; Schering, Berlin, 5; Shire, UK, 1, 5; Strakan.UK, 1, 2, 5; Strathmann, Germany, 5; Teijin, Japan, 5; Teva, Israel, 5; Theramex, Monaco, 5; Trent Health, UK, 2; Unigene, USA, 1, 5; Warburg-Pincus, UK, 5; Warner-Lambert, USA, 5; WHO, Geneva, 2, 5

---

## Adverse Outcomes of Osteoporotic Fractures in the General Population

Speaker: *L. Joseph Melton*

1:00 p.m. - 1:30 p.m.

---

L. Joseph Melton III, M.D.  
Michael M. Eisenberg Professor  
Mayo Clinic and Foundation

Fractures related to osteoporosis exact a terrible toll on the population with respect to morbidity and cost, and to a lesser extent mortality, that will increase dramatically with the growing elderly population. Attention has focused on the 10-20% excess deaths following hip fracture, but most are due to underlying medical conditions unrelated to osteoporosis. More important is fracture-related morbidity. An estimated 10% of patients are disabled by hip fracture and 19% require institutionalization, accounting for 140,000 nursing home admissions annually in this country. Distal forearm and vertebral fractures less commonly result in nursing home placement, but about 10% of women with vertebral deformities experience chronic pain and a substantial minority have poor function following forearm fracture. All of these fractures interfere greatly with the activities of daily living and can have a substantial negative impact on quality of life. Annual expenditures for osteoporotic fractures in the United States (\$17.5 billion in 2002 dollars) are dominated by hip fracture treatment, but vertebral fractures, distal forearm fractures and, importantly, the other fractures related to osteoporosis contribute one-third of the total. Although all are at increased risk of future fractures, few of these patients are currently treated for osteoporosis, and only a subset (i.e., vertebral fractures) are considered candidates for many trials. Eligibility criteria should be expanded and fracture endpoints generalized (e.g., hip fracture "equivalents") to acknowledge the overall burden of osteoporotic fractures.

*Dr. Melton received his undergraduate and medical training at Louisiana State University and his training in epidemiology (M.P.H.) at the University of Michigan School of Public Health. He has been on the staff of Mayo Clinic since 1977 as a consultant in the Division of Epidemiology. Dr. Melton is also the Michael M. Eisenberg Professor at Mayo Medical School. He is a fellow of a number of professional societies, including the Association of American Physicians, the American Epidemiological Society and the Royal Society of Medicine and recently received the Frederick C. Bartter Award for clinical investigation from the American Society for Bone and Mineral Research. He is a member of four editorial boards and currently serves as Associate Editor of the Journal of Bone and Mineral Research. Dr. Melton has been a Trustee of the*



*National Osteoporosis Foundation and a consultant to the Radiologic Devices Panel of the Food and Drug Administration, as well as a member of several national and international expert panels evaluating the utility of bone densitometry for osteoporosis screening. He has published over 500 original papers and reviews on a variety of subjects, mainly dealing with the epidemiology of osteoporosis and fractures.*

Disclosures: None

---

---

## **Risk of Death and Disability in Placebo-Controlled Osteoporosis Trials**

**Speaker: *Steven R. Cummings***

**1:30 p.m. - 2:00 p.m.**

---

Steven R. Cummings, M.D., F.A.C.P.  
Professor of Medicine and Epidemiology & Biostatistics  
University of California, San Francisco Coordinating Center

Several treatments reduce rates of fractures but it is not clear how much they reduce mortality or quality of life. Participants in the Fracture Intervention Trial (FIT) kept track of days of disability (difficulty performing usual activities) following fractures. Over the course of the trial, the alendronate group experienced significantly ( $P < .05$ ) fewer days of disability than did the placebo group (mean difference = 2.9 days / year in those with vertebral fracture and 2.0 days / year in those without but with femoral neck  $T \leq -2.5$ ).

There have been no significant differences in all-cause mortality in large published randomized trials in which the treatment significantly reduced the risk of fractures. For example, the risk of death in FIT I (women with vertebral fractures) was 2.1 in the placebo and 2.3% in the alendronate group ( $P > .05$ ).

Among the 6459 women in the FIT trial, we observed no difference in change in physical health, pain, or overall quality of life measured by the SF-12 between the placebo and alendronate-treated participants with vertebral fractures, with osteoporosis or with "osteopenia." Moreover, among the 300 to 1400 osteoporotic women who had various quality of life measurements in the MORE trial, there were no significant differences in change in any of 36 dimension of overall quality of life (Nottingham Health Profile) or "osteoporosis-specific" quality of life (by OPAQ or EFO) between the placebo- or raloxifene-treated participants with osteoporosis.

Therefore, compared with osteoporotic women assigned to effective anti-resorptive treatments, those assigned to placebo have a greater risk of fracture that cause a few extra days of limited activities, but no increased risk of death, and no significant decrement in quality of life.

*Dr. Steven R. Cummings is Professor of Medicine and Epidemiology & Biostatistics at the University of California, San Francisco. He directs the UCSF Coordinating Center, which conducts studies on osteoporotic fractures and women's health. He is also the Director of the Clinical Research Program. He completed his M.D., Residency in Internal Medicine, and Fellowship in Clinical Epidemiology at UCSF and served as Chief of General Internal Medicine, Associate Chair of Medicine for Clinical Research, and now is Assistant Dean for Clinical Research in the School of Medicine. He co-founded the Postgraduate Clinical Research Training Program at UCSF 20 years ago and is co-author of the textbook Designing Clinical Research. He is a member of the Board of Directors of the National Osteoporosis Foundation; and a past member of the Council of the American Society for Bone and Mineral Research. Dr. Cummings leads the NIH-funded Study of Osteoporotic Fractures and several other NIH-funded studies. He led the Fracture Intervention Trial, which was the first study to show that raloxifene, a "designer estrogen," reduced risk of fractures and breast cancer.*

Disclosures: Merck, 5; Novartis, 2; Organon, 2; Pfizer, 2

---

## **Risk of Death and Disability in Placebo-Controlled Osteoporosis Trials**

**Speaker: *Michael Rosenblatt***

**2:00 p.m. - 2:30 p.m.**

---

Michael Rosenblatt, M.D.  
Minot Professor of Medicine  
Harvard Medical School

In order to represent industry on the topic of this conference, position papers were obtained from six pharmaceutical and biotechnology companies. Despite a wide range of positions in the market with regard to prevention and treatment of osteoporosis, all companies were unanimous in their concerns about the ability to conduct randomized placebo-controlled clinical trials (PCTs) in the future. The clinical research environment contains conflicting directives. Regulatory agencies strongly prefer (even insist upon) PCTs as a requirement for drug approval, while many physicians, human studies institutional review boards and informed patients believe that it is now not ethical to place patients on placebo because effective therapies for osteoporosis are available. PCTs offer the best means of calibrating the absolute efficacy of a new agent and identifying its side-effects on a "neutral" background.

Are comparison clinical trials (CCTs) using an approved drug the answer? No. Examples will be given which illustrate that such trials require very large numbers of patients (approximately 15,000-20,000) in order to demonstrate "non-inferiority" or (approx. 30,000) to demonstrate "superiority" compared to an existing therapy. Such studies are not only impractical, but also result in greater numbers of fractures during the course of clinical research in both the new treatment and control (active comparator) groups than would occur in PCTs. Total adverse experiences and exposure of patients to investigational agents is considerably greater when CCTs rather than PCTs are performed.

Based on this analysis, industry recommends as the basis of regulatory approval of new agents for osteoporosis: 1) conduct of PCTs in patients at low risk for fracture (e.g., T-score <-2.5 and no previous osteoporotic fracture); 2) use of BMD as an endpoint for the indication "to preserve or improve bone mass;" 3) a 2-year, rather than 3-year, trial period; 4) demonstration of no adverse effect on bone quality preclinically; 5) extrapolation of these results to higher risk patients; 6) an option for the sponsor to perform additional fracture endpoint studies post-approval in order to obtain an indication for "treatment to reduce the risk of fractures specifically in the spine (or hip) (or both); 7) the option to file for a "prevention" claim prior to a "treatment" claim.

*Dr. Rosenblatt is the George R. Minot Professor of Medicine at Harvard Medical School. He served as the President of Beth Israel Deaconess Medical Center from 1999-2001. Previously, he was the Harvard Faculty Dean and Senior Vice President for Academic Programs at CareGroup and Beth Israel Deaconess Medical Center. Prior to that, he served as Director of the Harvard-MIT Division of Health Sciences and Technology, during which time he led a joint venture for M.D., Ph.D., and M.D.-Ph.D. training. Earlier, he was Senior Vice President for Research at Merck Sharp & Dohme Research Laboratories where he co-chaired the worldwide development team for alendronate (FOSAMAX), Merck's bisphosphonate for osteoporosis and bone disorders. In addition, he directed drug discovery efforts in several other therapeutic areas for laboratories located in the United States, Japan, and Italy. He is the recipient of the Fuller Albright Award of the American Society for Bone and Mineral Research for his work on parathyroid hormone, the Vincent du Vigneaud Award in peptide chemistry and biology, and the Chairman's Award from Merck. His research is in the field of hormone-receptor interactions, hormonal regulation of calcium metabolism, osteoporosis and cancer metastasis to bone.*

*He has chaired the Gordon Conference on Chemistry and Biology of Peptides, and served on the NIH Board of Scientific Counselors of the National Institute of Diabetes and Digestive and Kidney Diseases of the NIH. He has been elected to the American Society of Clinical Investigation, the Association of American Physicians, to Fellowship in the American Association for the Advancement of Science, the presidency of the American Society for Bone and Mineral Research, and the presidency of the Interurban Clinical Club. He testified before a U.S. Senate Hearing on U.S. biomedical research priorities in 1997. From 1981 to 1984, he served as Chief of the Endocrine Unit, Massachusetts General Hospital. He received his undergraduate degree from Columbia and his M.D. from Harvard.*

Disclosures: None

---

## Surrogates for Fracture Endpoints in Osteoporosis Clinical Trials

Speaker: *Sundeep Khosla*

2:30 p.m. - 3:00 p.m.

---

Sundeep Khosla, M.D.  
Professor of Medicine  
Mayo Medical School  
Consultant in Endocrinology, Metabolism and Nutrition  
Mayo Clinic and Foundation

Currently, clinical trials of new drugs for osteoporosis typically use vertebral fractures as the primary endpoint. These trials must include large numbers of subjects and confirm vertebral fractures by radiological analyses. In addition to the massive costs involved, it is becoming difficult to find sufficient subjects to carry out these studies. Use of a surrogate marker (i.e. BMD) would reduce the sample sizes needed for such studies by perhaps an order of magnitude. There is now overwhelming observational data demonstrating that BMD is an excellent marker for fracture risk in the population. The main problem with BMD as a surrogate marker in clinical trials came from studies of sodium fluoride, in which marked increases in spine BMD were not associated with significant decreases in fracture risk. This was likely due to effects of fluoride on the formation of abnormal bone with impaired biomechanical competence. However, assuming that animal studies demonstrate that the bone formed in the presence of a drug is of normal quality (histologically and biomechanically), a case can be made for accepting BMD as a valid surrogate for fracture risk. The major caveat with this, however, is that for anti-resorptive drugs, it is becoming clear that changes in BMD provide a very conservative estimate of the reduction in fracture risk. In general, the magnitude of the observed fracture risk reduction with these agents may be twice as large or more than would be expected from the changes in BMD. Current evidence suggests that this discrepancy is likely due to the added effects of these drugs on reducing bone turnover, thus preventing (or reversing) microarchitectural damage to bone. Thus, for these agents, models combining changes in BMD with changes in bone turnover may provide more robust surrogates for fracture endpoints, and this approach should be evaluated with data from recent trials. For formation stimulating agents, BMD may well be a valid surrogate for fracture, provided again that the bone formed by these agents is of normal quality.

*Sundeep Khosla's current research explores male and female osteoporosis and sex steroid regulation of bone cells. He is Professor of Medicine at the Mayo Medical School as well as Consultant in Endocrinology, Metabolism, and Nutrition at the Mayo Clinic and Foundation in Rochester, Minnesota, USA. Dr. Khosla is a fellow at the American College of Physicians and a member of the Association of Osteobiology. In 2000, he received an ASBMR Award for Outstanding Research in the Pathophysiology of Osteoporosis. Dr. Khosla has served in numerous editorial and peer review positions, including associate editor of the ASBMR Primer on Metabolic Bone Diseases & Disorders of Mineral Metabolism; editorial board of the Journal of Clinical Endocrinology & Metabolism; editorial board of Endocrinology; as a member of the Scientific Advisory Board of the National Osteoporosis Foundation; member of the Committee of Scientific Advisors, International Osteoporosis Foundation; and member of the Scientific Advisory Board, International Society of Men's Health.*

*Born on July 7, 1957, in Bombay, India, Dr. Khosla graduated Phi Beta Kappa with a B.A. in Chemistry from Harvard College in 1978. In 1982, he received his M.D. cum laude in 1982 from Harvard Medical School/Harvard-MIT Program in Health Sciences and Technology. Dr. Khosla has been a professor of Medicine, at the Mayo Medical School from 1988 to the present. He has been the director of the fellowship program, and vice-chair for education, division of endocrinology, since 1999.*

Disclosures: None

---

## Clinical Equipoise and Study Design

**Speaker:** *Charles Weijer*

**3:30 p.m. - 4:00 p.m.**

---

Charles Weijer, M.D., Ph.D.  
Associate Professor of Medicine, Department of Bioethics  
Dalhousie University

The proper role for placebo controls in clinical trials testing the efficacy of novel drugs continues to vex scientists, regulators, and ethicists alike. International regulations are of little help. The *Declaration of Helsinki*, despite a recent and confusing clarification, continues to prohibit placebo controls when a “current...therapeutic method” exists. ICH E-10 allows placebo controls unless “an available treatment is known to prevent serious harm, such as death or irreversible morbidity in the study population.” The origin of this curious ethical standard is not disclosed; nor is the requirement of ICH E-6 discussed, which requires that “Clinical trials should be conducted in accordance with...the *Declaration of Helsinki*.” Obviously, we must seek clarity elsewhere.

The fundamental ethical question of the randomized controlled trial is: “When may the physician offer legitimately trial enrollment to her patient?” The most widely accepted answer is offered by clinical equipoise. Accordingly, a physician may offer trial enrollment to her patient when there exists at the start of the trial a state of honest, professional disagreement in the community of expert practitioners as to the preferred treatment. Furthermore, clinical equipoise requires that the trial be designed in such a way as to, if successful, eliminate disagreement as to the preferred treatment. Placebo controls are inappropriate when there is standard treatment and ‘no treatment’ is not an acceptable option in the standard of care. Proponents of alternative ethical standards that are permissive with regard to placebos fail to address the fundamental duty owed by the physician to the patient. These alternatives, therefore, permit placebo controls at the expense of the ability to do clinical trials at all.



*Professor Weijer (pronounced VAY-er) is associate professor of medicine in the Department of Bioethics in the Dalhousie University School of Medicine in Halifax, Canada. Prior to assuming his position at Dalhousie University, he was assistant professor of medicine at the University of Toronto and clinical bioethicist at Mount Sinai Hospital, Toronto. Professor Weijer was a member of the World Medical Association's Working Group revising the Declaration of Helsinki (1998 – 1999). He was twice consultant for the U.S. National Bioethics Advisory Commission. Professor Weijer's work advocating a component analysis approach to research risk was adopted by NBAC in its final report, Ethical and Policy Issues in Research Involving Human Participants (2001). He is currently a member of the Council for International Organizations of Medical Sciences (CIOMS) Steering Committee revising the CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects. Professor Weijer is also currently Scientific Officer for the Canadian Institutes of Health Research Health Ethics, Law, and Humanities Grants Panel. Professor Weijer received his bachelor's degree and his medical degree from the University of Alberta. He received his honors bachelor's degree in philosophy, master's degree in bioethics, and doctoral degree in experimental medicine and philosophy from McGill University.*

Disclosures: NIL, 2

---

---

## Ethicist Reaction

**Speaker: *David Wendler***

**4:00 p.m. - 4:30 p.m.**

---

**No abstract was submitted for this presentation.**

*Dr. David S. Wendler is head of the unit on vulnerable populations section on human subjects research at the National Institute of Health (NIH). His research interests include: evaluating pediatric assent in a study of hypertrophic cardiomyopathy, a survey of individuals at risk for Alzheimer's Disease, and a survey of organ procurement organizations. He was a post-doctoral fellow in the bio-ethics program at the NIH from 1993-1996. Dr. Wendler received the NIH Clinical Center Special Service Award in 1998 as well as an NIH award for research in ethics in 1996. His clinical service roles include membership at the Clinical Center Bioethics Consult Service since 1994. He has also been a coordinator at the Clinical Center Advance Directives Program from 1994 as well as a bioethics representative at the Infectious Disease Rounds since 1998. Beginning in 1995, Dr. Wendler has been executive secretary of the Clinical Center Ethics Committee. He is also a member of the National Institute on Drug Abuse IRB. Dr. Wendler received his Ph.D. in Philosophy and Biology from the University of Wisconsin, Madison, in 1993.*

Disclosures: Merck, 5

---

---

## Ethics of Clinical Trials of New Treatments for Osteoporosis

Speaker: *Robert Levine*

4:30 p.m. - 5:00 p.m.

---

**Abstract for this presentation can be found in the pocket at the back of this program booklet.**

*Dr. Robert J. Levine is Professor of Medicine and Lecturer in Pharmacology at Yale University School of Medicine, Co-Director of the Law, Policy and Ethics Core of Yale University's Center for Interdisciplinary Research on AIDS, and Co-Chair of the Executive Committee of Yale University's Interdisciplinary Bioethics Project. He is a Fellow of The Hastings Center, the American College of Physicians and the American Association for the Advancement of Science; a member of the American Society for Clinical Investigation and American Society for Pharmacology and Experimental Therapeutics, Past-President of the American Society of Law, Medicine & Ethics, past-Chairman of the Connecticut Humanities Council, and a Director of PRIM&R (Public Responsibility in Medicine and Research). In the past he was also Chair of the Institutional Review Board at Yale-New Haven Medical Center (1969 - 2000) and Chief of the Section of Clinical Pharmacology at Yale, Associate Editor of Biochemical Pharmacology and Editor of Clinical Research. Dr. Levine is the founding editor of IRB: A Review of Human Subjects Research (Editor 1979 - 2000 and currently Chair of the Editorial Board) and has served as consultant to several federal and international agencies involved in the development of policy for the protection of human subjects\*. He is the author of numerous publications and is currently preparing the third edition of his book, Ethics and Regulation of Clinical Research. In the last 25 years, most of Dr. Levine's research, teaching and publications have been in the field of medical ethics, with particular concentration on the ethics of research involving human subjects.*

\*Recent activities include:

- Council of International Organizations of Medical Sciences, Steering Committee for Revision of *International Ethical Guidelines for Biomedical Research*, Chairperson
- World Medical Association; Working Group for Revision of the *Declaration of Helsinki*, Chair
- Joint United Nations Programme on HIV/AIDS (UNAIDS), Project on Ethics in HIV Vaccine Trials, Consultant with the assignment of developing their *Guidance Document* for trials of preventive HIV vaccines
- CDC, External Review Group for Human Subjects Protection, Chairperson. (Group is charged to assess CDC's human subjects protection activities and make recommendations for their improvement)
- National Institutes of Health, Office of AIDS Research, Prevention Science Working Group
- National Institute of Mental Health, Human Subjects Research Council Workgroup
- Pan American Health Organization: International Bioethics Advisory Board

Disclosures: None

---

---

## Assessment of Various Study Designs, Ethical and Scientific: Audience Participation

Speaker: *Robert R. Recker*

5:00 p.m. - 5:30 p.m.

---

Robert R. Recker, M.D.

Clinical Professor of Periodontics, Creighton University School of Dentistry  
Director, Creighton University Osteoporosis Research Center  
Chief of the Section of Endocrinology, Creighton University Medical School  
President, ASBMR

In this segment of the program the attendees will be given a list of study designs and will be asked to indicate whether they judge each to be ethical and scientifically valid. The study designs will be prepared and listed in the handout to be distributed at the meeting. Each entry on the handout will be judged as ethical (yes/no), and scientifically valid (yes/no). Ten study designs will be presented. The basic design will be given along with entry criteria and primary outcome variables. Each attendee will be asked to fill out the form and to indicate at the bottom their professional category. The results of the survey will be collected and collated for distribution the following morning.

*Dr. Robert R. Recker is clinical professor of periodontics at the Creighton University School of Dentistry, director of the Creighton University Osteoporosis Research Center, and chief of the section of endocrinology at Creighton University Medical School. He has received several honors over his career, including Alpha Omega Alpha, Distinguished Research Career Award, and the Laureate Award from the Nebraska Chapter of the American College of Physicians. Dr. Recker is a fellow at the American College of Endocrinology and a master at the American College of Physicians. He has been a member of, and served in leadership roles for, numerous professional organizations: member and 2002 president, American Society for Bone and Mineral Research; member, advisory committee to the director of the National Institutes of Health; chair, research grants subcommittee, National Osteoporosis Foundation; member, editorial board, Osteoporosis International; Member, Procter & Gamble/Hoechst Marion Roussel Alliance Osteoporosis Board; and member, advisory board, Eli Lilly and Company, Inc. Dr. Recker completed his medical education at the United States Air Force Hospital at the Lackland Air Force Base in Texas and at the Creighton University School of Medicine.*

Disclosures: Alliance for Better Bone Health (Procter & Gamble Pharmaceuticals and Aventis Pharma), 2, 5; Merck, 2, 5; Roche, 2, 5; Eli Lilly and Company, Inc., 2, 5

---

---

## Presentation and Discussion of Summary Statement by Panel

**Panelists:** *Larry Raisz, Chair*

*A.M. Capron*

*Susan Swift*

*Ethel Siris*

*Sue Donaldson*

8:00 a.m. - 12:00 p.m.

---

*Dr. Lawrence G. Raisz has been Professor of Medicine at the University of Connecticut Health Center since 1974. Prior to that he was Professor of Medicine and Pharmacology at the University of Rochester. He established the Division of Endocrinology and Metabolism at UCHC and helped to develop a large program of research on osteoporosis and bone metabolism. In 1993 he became Program Director of the Lowell P. Weicker, Jr., General Clinical Research Center at UCHC. He will step down as Program Director this spring but continue to be active as Director of the UConn Center for Osteoporosis and as the principle investigator of his laboratory research which is funded both by the NIH and the pharmaceutical industry. He is Chairman of the Scientific Advisory Board and a member of the Board of Trustees of the National Osteoporosis Foundation, and internationally recognized for his work in osteoporosis and bone metabolism.*

Disclosures: Procter & Gamble Pharmaceuticals, 2; Pfizer, 2

*A. M. Capron is University Professor, Henry W. Bruce Professor of Equity, and Professor of Medicine at the University of Southern California, where he also heads the Pacific Center for Health Policy and Ethics. Before joining the USC faculty, he taught at Georgetown University, the University of Pennsylvania, and Yale University, and served as Executive Director of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (December 1979-March 1983). Professor Capron is a Trustee of The Century Foundation, a Commissioner of the Joint Commission on Accreditation of Healthcare Organizations, and a Director of the International Association of Bioethics, for which he served as President of the III World Congress on Bioethics in 1996. He is a member of the Institute of Medicine (National Academy of Sciences) on whose Council he served for two terms; a Founding Fellow of the Hastings Center, where he was also a long-time Board member; and a Fellow of the American Association for the Advancement of Science and of the American College of Legal Medicine. Professor Capron has served as President of the American Society of Law, Medicine and Ethics, as Vice President of the Council for International Organizations of Medical Sciences, and as chairman of the Board of Advisors for the American Board of Internal Medicine, and of the Biomedical Ethics Advisory Committee of the U.S. Congress (1987-90), and as a member of the National Bioethics Advisory Commission (1996-2001), and of the*

*Recombinant DNA Advisory Committee at the National Institutes of Health (1984-92). In 1991 he convened the California Consortium on Patient Self-Determination, which mounted the country's most comprehensive statewide response to the federal Patient Self-Determination Act. Professor Capron received his B.A. with High Honors from Swarthmore College and his LL.B. from Yale University, where he was an officer of the Yale Law Journal, chaired the Law Students Civil Rights Research Council, and graduated with the Order of the Coif. Professor Capron has written and edited eight books, including Law, Science and Medicine and the Treatise on Health Care Law.*

Disclosures: None

***Ethel S. Siris, M.D.**, is the Madeline C. Stabile Professor of Clinical Medicine in the Department of Medicine, College of Physicians and Surgeons of Columbia University, and the Director of the Toni Stabile Osteoporosis Center of the Columbia-Presbyterian Medical Center, both in New York, New York. She is a graduate of Radcliffe College, Harvard University, and received her medical degree from the College of Physicians and Surgeons of Columbia University. An endocrinologist, she has worked as a clinician, clinical investigator and medical educator in the area of metabolic bone diseases, including osteoporosis, Paget's disease of bone, and the skeletal complications of cancer. In particular, she has worked extensively with the class of bisphosphonate compounds in these disorders as well as with selective estrogen receptor modulators (SERMS) in osteoporosis. Dr. Siris is a member of the Board of Trustees of the National Osteoporosis Foundation, and the Medical and Scientific Advisory Board of the Bone Measurement Institute, and is Vice Chair of the Paget Foundation for Paget's Disease of Bone and Related Disorders; she has previously served as a member of the Council of the American Society for Bone and Mineral Research and the Endocrinologic and Metabolic Drugs Advisory Committee of the U.S. Food and Drug Administration. She is co-editor of the book, The Bone and Mineral Manual, and is a member of the editorial boards of the Journal of Bone and Mineral Research, Osteoporosis International, and the Journal of Clinical Densitometry. Dr. Siris is also the Medical Director of N.O.R.A., the National Osteoporosis Risk Assessment, a public health initiative and longitudinal study of osteoporosis that includes over 200,000 postmenopausal women in the U.S.*

Disclosures: Alliance for Better Bone Health (Procter & Gamble Pharmaceuticals and Aventis Pharma), 5, 8; Eli Lilly and Company, Inc., 2, 5, 8; Merck, 5, 8; Wyeth Pharmaceuticals, 8

***Susan S. Swift** founded her consulting firm, Susan S. Swift, Ltd., in 1989 after leading significant change efforts as a top-level administrator for an academic health center, a large teaching hospital system and the largest public developmental disabilities program in the world. Her firm helps complex organizations (hospitals, health systems, medical schools, universities and community service organizations) and their leaders understand and shape their environments and determine what they must do to ensure long-term, future success. Her work includes strategic planning, organizational development, executive coaching and consultation about management, governance, and board-related issues. Dr. Swift earned her doctorate in*

*health policy and management at the Wagner School of Public Service at New York University (NYU), where her dissertation focused on the change processes used by four public teaching hospitals to become private. Dr. Swift has served on numerous boards and task forces, including Planned Parenthood of Maryland, which she chaired for two years; the National Osteoporosis Foundation for which she is Chair of the Education Committee; and Pathfinder International, where she currently serves as Finance Chair & Treasurer. Baltimore's Warfield BusinessRecord named her one of Maryland's Top 100 women in 1996. She resides in New York City now where she was recently elected a Fellow of The New York Academy of Medicine. In addition to her consulting, she teaches strategic management at the Wagner School of NYU.*

Disclosures: None

**Dr. Sue K. Donaldson** is Professor of Nursing, School of Nursing and Professor of Physiology, School of Medicine, at the Johns Hopkins University, Baltimore, Maryland (1994-present). She also currently holds a joint appointment in Oncology, School of Medicine and The Johns Hopkins Hospital. From 1994 to 2001 she was Dean of the School of Nursing, Johns Hopkins University. Dr. Donaldson received BSN (1965) and MSN (1966) degrees from Wayne State University, Detroit, Michigan and the Ph.D. in Physiology and Biophysics (1973) from University of Washington, Seattle, Washington. Previously, she was a faculty member at the University of Washington, Seattle, Washington (1973 – 1978), and Rush University, Chicago, Illinois (1978- 1984). Dr. Donaldson also was Professor of Physiology, School of Medicine and Professor of Nursing, School of Nursing, at the University of Minnesota, Minneapolis, Minnesota (1984 -1994). While at the University of Minnesota she was the Cora Meidl Siehl Chair for Nursing Research and the founding Director of the Center for Long-Term Care of the Elderly. She serves as a consultant to the National Institutes of Health (NIH), USPHS and to other research organizations and academic institutions. Dr. Donaldson is a pioneer in nursing research and internationally known for her basic science research in cellular skeletal and cardiac muscle physiology. She has held leadership positions in the Biophysical Society and the American Heart Association. In 1992, Dr. Donaldson was inducted as a Fellow in the American Academy of Nursing (FAAN). Dr. Donaldson was elected to the Institute of Medicine, National Academy of Sciences, in 1993. She currently serves as a member of the Special Medical Advisory Group (SMAG), U.S. Department of Veteran's Affairs, and as a member of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Advisory Council, NIH. Dr. Donaldson is currently the American Academy of Nursing (AAN) representative to the National Coalition for Health Professional Education in Genetics (NCHPEG) and chairs the AAN Expert Panel on Genetics.

Disclosures: None