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SAFETY FIRST:

The Role of the IRB, HIPAA, & DSMB for Ensuring Patient Safety and Trial Interpretation

presented by:

Jonathan N. Tobin, Ph.D.

Clinical Directors Network, Inc. (CDN)

www.CDNetwork.org

New York NY

presented at:

NIH Third Annual Summer Institute on
Design and Conduct of Randomized Clinical Trials
Involving Behavioral and Social Interventions

July 28, 2003

Airlie VA

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Learning Objectives

1. Understand the Ethical Obligations incumbent on Researchers
2. Understand the structures and functions of strategies developed to ensure patient safety:
 - Institutional Review Boards
 - HIPAA – Privacy Rule
 - Patient Safety Boards
 - Data Safety and Monitoring Boards
3. Recognize the statistical issues that are part of trial monitoring and possible early termination:
 - For Benefit
 - For Harm
 - For Recruitment Failure



Session Outline

1. Background on CDN

2. Background on Research Ethics

- IRB/Belmont Report
- HIPAA/Privacy Boards/Protected Health Info
- DSMB/Interim Analyses/Early Stopping Rules

3. Trial Monitoring: Statistical Issues

- Power (1-beta)
- Sample Size (alpha)
- Effect Size (ES) & Clinical Significance
- Variability/Heterogeneity (VAR)

4. DSMB: Establishment of a priori Early Stopping Rules: Policies & Procedures

- Stopping for Harm
- Stopping for Benefit

5. Examples of Early Trial Terminations

- B-HAT
- ALLHAT
- WHI



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CDN:

Past, Present & Future

- An informal network of clinical leaders who practice as primary care providers in low-income and minority communities
- A research and educational organization
- A means to translate clinical research into clinical practice

CDN's Strategic Objectives

- **A means to translate clinical research into clinical practice**
- **Diffuse knowledge through Collaboration**
- **Ensure adequate representation of neglected subgroups (providers and patients)**
- **Include relevant stake-holders in design, conduct, analysis, implementation and sustainability**

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- [Adolescent Nutrition - 09/25/2002 12:19](#)
- [Assessing Adult Immunization Rates in Your Practice: Online ACASA Demonstration - 12/05/2002 11:58](#)
- [Breast Cancer Screening and Early Detection - 12/10/2002 12:09](#)
- [Bubonic Plague: History and Clinical Update - 11/13/2002 12:10](#)

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| DrJNTobin | |

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Who are the Underserved?

Patients and Visits, National and Region II, 2001

Patients:

Medical Users

Reg II:
1,378,066

National:
9,153,138

Dental Users

Reg II:
197,433

National:
1,412,207

Encounters:

Medical

Reg II: 6,947,569
Nat : 40,318,640

Dental

Reg II: 499,426
Nat: 3,230,529

Mental Health

Reg II: 153,646
Nat: 949,523

Substance Abuse

Reg II: 106,502
Nat: 745,855

Other Professional

Reg II: 223,878
Nat: 867,832

Enabling Services

Reg II: 464,254
Nat: 3,320,779

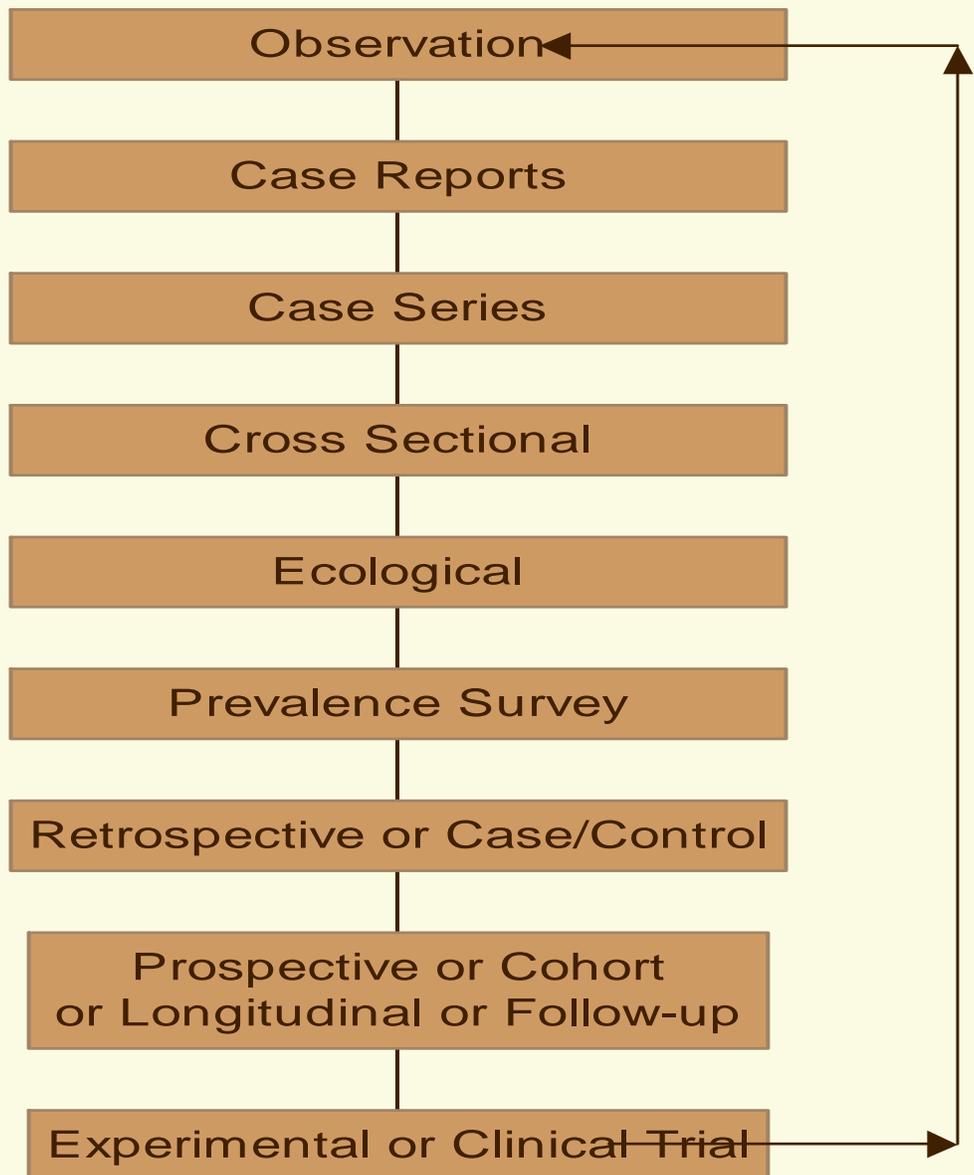
Patients and Encounters by Diagnosis, 2001

| <u>Selected Diagnoses</u> | <u>National</u> | <u>Region II</u> |
|---------------------------------|-------------------|------------------|
| Hypertension | 2,168,686 | 301,260 |
| Diabetes Mellitus | 1,736,317 | 232,341 |
| Other Severe Mental Disorders | 1,652,061 | 218,345 |
| Immunizations | 1,599,683 | 322,336 |
| Pap Smear | 1,105,053 | 170,079 |
| Contraception | 1,013,766 | 142,976 |
| Otitis Media/Eustac Disord | 794,243 | 92,618 |
| Asthma | 624,801 | 144,878 |
| Heart Disease | 442,574 | 55,327 |
| Bronchitis/Emphysema | 398,209 | 46,220 |
| HIV Tests | 311,297 | 69,677 |
| Dermatitis/Other Eczema | 308,024 | 66,849 |
| Symptomatic/Asymptomatic HIV | 242,441 | 65,063 |
| Mammogram | 169,126 | 39,514 |
| Abnormal Cervical findings | 104,007 | 19,200 |
| Sexually Transmitted Diseases | 70,714 | 17,249 |
| Abnormal Breast findings/female | 22,853 | 4,197 |
| Total # Grantees | 748 | 79 |
| Total # Users | 10,280,747 | 1,500,832 |
| Total # Encounters | 40,318,640 | 6,947,569 |

CDN'S RESEARCH PORTFOLIO

| | |
|--------------------------------------|--|
| HIV/AIDS | NIAID, NIMH, HRSA, AmFAR, BMS, DMP, Roche |
| Cancer Control | NCI AHCPR |
| Depression | NIDA, SAMHSA, NIMH |
| Stress Management | NIMH |
| Hypertension | NHLBI |
| Diabetes | HRSA |
| Immunizations | CDC, HRSA, Pharma |
| Migraine/Headache | Merck |
| Anemia | Ortho Biotech |
| Asthma | EPA, DEP, HRSA |
| Genetics | March of Dimes |
| Nutrition/ Phys. Activity | RWJ, NYS Attorney General |

Natural History of Research Design



NATURAL HISTORY OF CLINICAL PRACTICE CHANGE

Clinical Research

Phase I

Phase II

Phase III (Efficacy)

Phase IV (Effectiveness)



Evidence-Based
Clinical Practice Guidelines



Quality Improvement (QI)



TRIST

Translation

Implementation

Sustainability



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Institutional Review Board (IRB)

1. Reviews Study Design, Timeline,
2. Informed Consent
 - Language & Literacy Levels Appropriate
 - Disclosures of Risks and Benefits
3. Monitors Study Progress & Events
 - Patient Recruitment
 - Patient Follow-ups/Drop-outs
 - Adverse Events
 - Deaths

Sources:

- NIH OPRR
- 21 CFR 312, 314, 812, 814
- www.NIH.gov
- www.FDA.gov



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Belmont Report

Basic Ethical Principles

1. **Autonomy**

-Respect for Persons

2. **Beneficence**

- Do No Harm

- Maximize Possible Benefits

- Minimize Possible Harms

3. **Justice**

-Fairness in Distribution

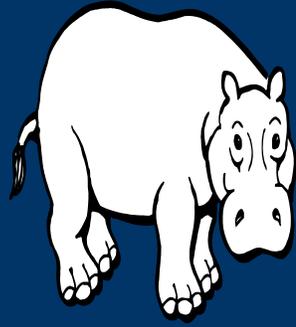
Sources:

- www.nih.gov/grants/oprr/humansubjects/guidance/belmont.htm

HIPAA & Privacy Boards

1. Health Insurance Portability and Accountability Act (HIPAA)
2. Right to Privacy
3. Defines Protected Health Information (PHI)
4. Disclosure and Privacy Policy
5. Establishment of Requirements for a Privacy Board

HIPAA

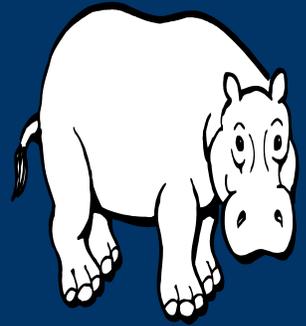


Health Insurance Portability & Accountability Act of 1996

- Public Law 104-191
- Amends 1986 IRS Code
- Kennedy-Kassebaum Act
- First Federal comprehensive health privacy protections
- Establish "National Floor of Legal Protections" rather than "Best Practices" --No preemption of more protective State laws

HIPAA For Dummies

I. Administrative Simplification



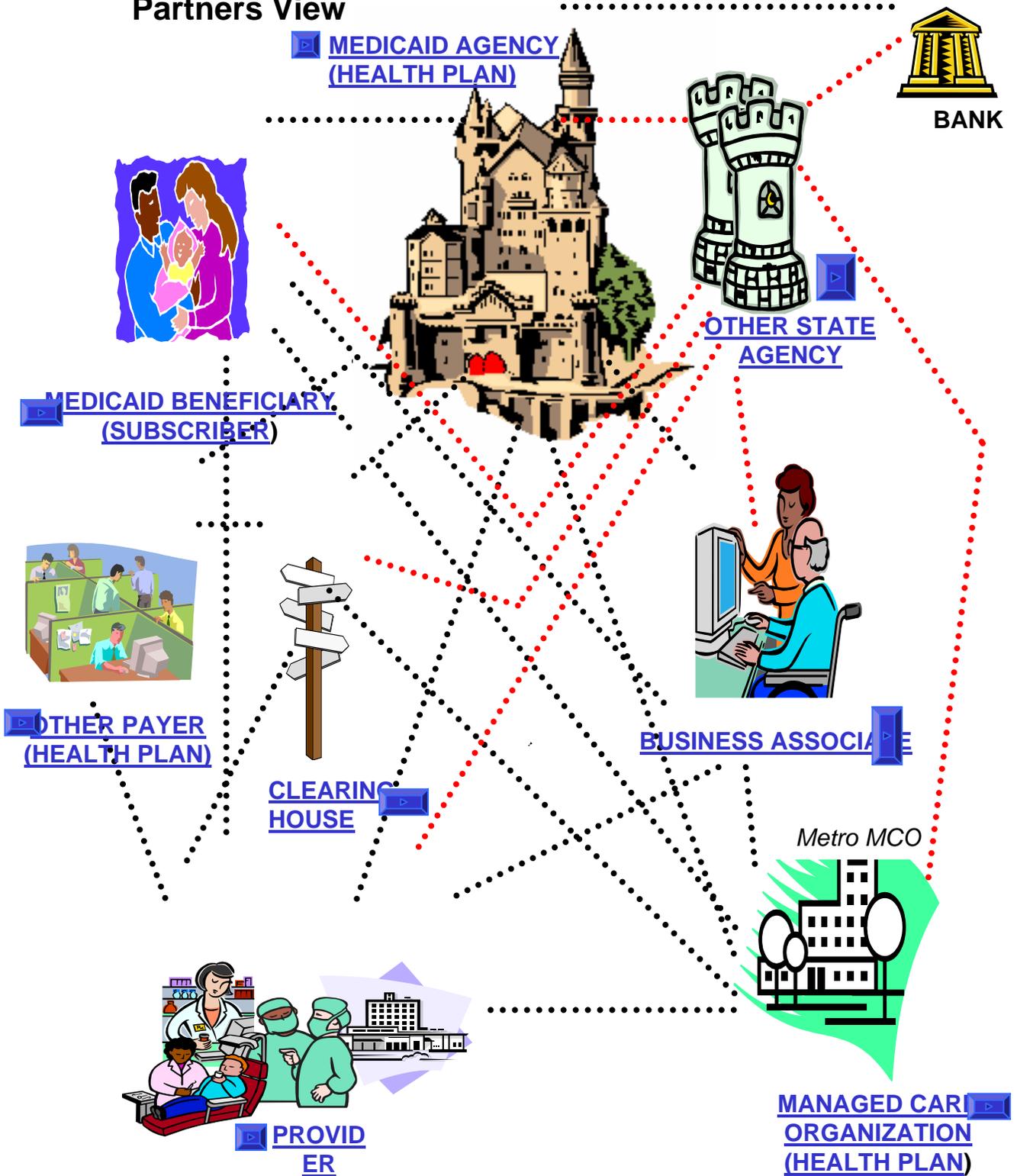
II. National Uniform Standards for Electronic Data Interchange (EDI)

III. Enhancing the Protection of Health Information



Administrative Simplification?

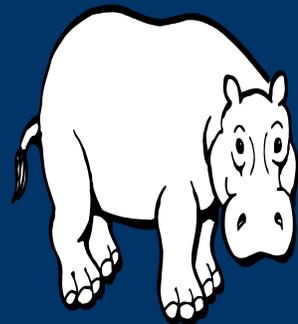
Medicaid Enterprise Data Exchange Partners View



From CMS: Jason Goldwater, MA, MPA May 7, 2002

HIPAA Implications

- National Uniform Standards for Electronic Data Interchange (EDI)
- HHS to **adopt** national standards for electronic administrative and financial health care transactions
- Adopt standards developed by ANSI accredited standards setting organizations where reasonable
- Employer Identification Number (EIN) (Tax ID proposed)
- Health Care Provider Identifier (NPI) (8 position alphanumeric ID proposed)
- Health Plan Identifier (Similar to provider ID)
- Claim Attachments--Joint development by HL7 and X12



From: Jason Goldwater, MA, June 2002

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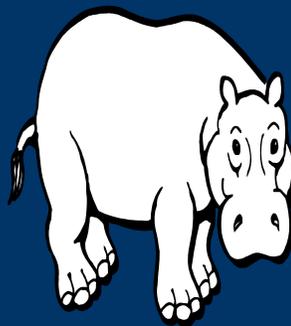
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Primer of HIPAA Key Terms

- Privacy Rule (PR)
- Common Rule (CR)
- Protected Health Information (PHI)
- Covered Entity (CE)
- Business Associates (BA)

- Institutional Review Board (IRB)
- Privacy Board (PB)

- Disclosure of PHI
- Individual Authorization for Disclosure of PHI
- Waiver of Individual Authorization for Disclosure of PHI
- De-identified data



Privacy Rule (PR)

- Regulates content/conditions of documentation that Covered Entities (CE) must obtain before using or Disclosing Protected Health Information (PHI) for Research Purposes
- Gives patients more control over access to their health information
- Sets boundaries on use and release of health information
- Establishes safeguards required of providers
- Specifies accountabilities and penalties for violations
- Tries to balance public health and public responsibility

For Patients:

- Find out how information is used and disclosed
- Limits release of information to minimum reasonably needed for disclosure
- Rights to examine, obtain copies and request corrections

The Common Rule (CR)

Protection of Human Subjects:
45 CFR 46

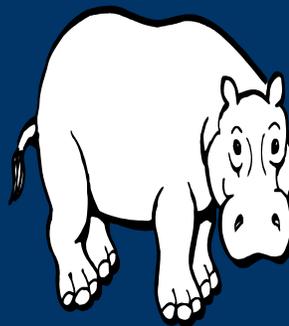
Subpart A - Basic HHS Policy for
Protection of Human Research
Subjects

Subpart B - Additional
protections Pertaining to
Research & Development

45 CFR 46:

<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm>

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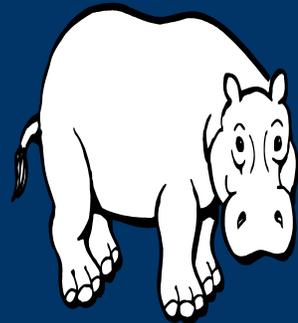
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De-Identification: Stripping Patient Identifiers

Information may be released that relates to individual patients **if all of the following are removed:**

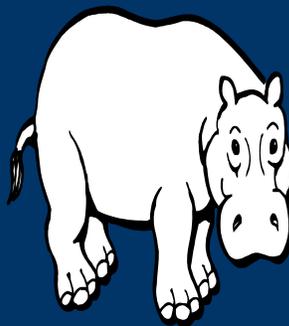
1. Name
2. Geographic subdivisions smaller than a state
3. Dates (except year) of:
Birth Admission Discharge
Death
4. Telephone number
5. Fax number
6. E-mail address
7. Social Security number
8. Medical Records numbers
9. Health Plan beneficiary numbers
10. Account numbers



De-Identification: Stripping Patient Identifiers

Information may be released that relates to individual patients **if all of the following are removed:**

11. License and Certificate numbers
12. Vehicle identifiers (such as license plate number)
13. Device identifiers (such as serial numbers)
14. URLs (Web Universal Resource Locator)
15. Internet Protocol (IP) address
16. Biometric identifiers (such as finger and voice prints)
17. Full face photographic images (and any comparable images)
18. Other unique identifiers



Data Safety and Monitoring Board (DSMB)

Monitors Study Progress

- Patient Recruitment
- Patient Follow-up/Drop-out
- Adverse Events
- Evidence of Main Effects

Sample Size & Statistical Power Considerations

1. Ability to Sample to Detect a Clinically Meaningful Difference
2. Effect Size
 - Size of Difference
 - Effect Size (ES)
 - Variability/Heterogeneity (VAR)
 - Power (1-beta)
 - Sample Size (N)
 - Confidence (1-alpha)
 - 1 vs 2 tails, significance level
3. Establishment of a priori Early Stopping Rules: Policies & Procedures
 - Harm
 - Benefit
 - Recruitment Failure



Sample Size & Statistical Power Considerations

Nominal Significance Level Required for Repeated two-sided significance test by overall alpha (0.05 and 0.01) and N (maximum number of tests performed)

| <u>N</u> | <u>alpha=</u> | |
|----------|---------------|-------------|
| | <u>0.05</u> | <u>0.01</u> |
| 2 | 0.029 | 0.0056 |
| 3 | 0.022 | 0.0041 |
| 4 | 0.018 | 0.0033 |
| 5 | 0.016 | 0.0028 |
| 10 | 0.0106 | 0.0018 |
| 15 | 0.0086 | 0.0015 |
| 20 | 0.0075 | 0.0013 |

(Source: Pocock, 1983, Table 10.2)

Why/When to Perform an Interim Analyses?

- Stop early for a safety problem
- Stop early because drug doesn't work
- Stop early because drug works
- Timed by fraction of:
 - patients enrolled
 - fraction of events observed

Source: Peter A. Lachenbruch, PhD
Division of Biostatistics, FDA CBER (March 24-26, 2003)

Interim Analyses

- Plan analyses
- State number (usually ≤ 5)
- Ensure blindness is maintained
- DSMB usually needed
- Adjust significance levels (O'Brien-Fleming, Haybittle-Peto, Pocock, Bonferroni)

Source: Peter A. Lachenbruch, PhD
Division of Biostatistics, FDA CBER (March 24-26, 2003)



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Interim Analyses

Break blinding if patient has AE?

- Yes - should do for patient's safety, especially if a serious AE has occurred
- Patient is usually removed from the study and treated as a failure
- Because blind is broken in these cases, it's important that treatments be indistinguishable - should look alike, smell alike, etc.

Source: Peter A. Lachenbruch, PhD
Division of Biostatistics, FDA CBER (March 24-26, 2003)

RCTs Terminated

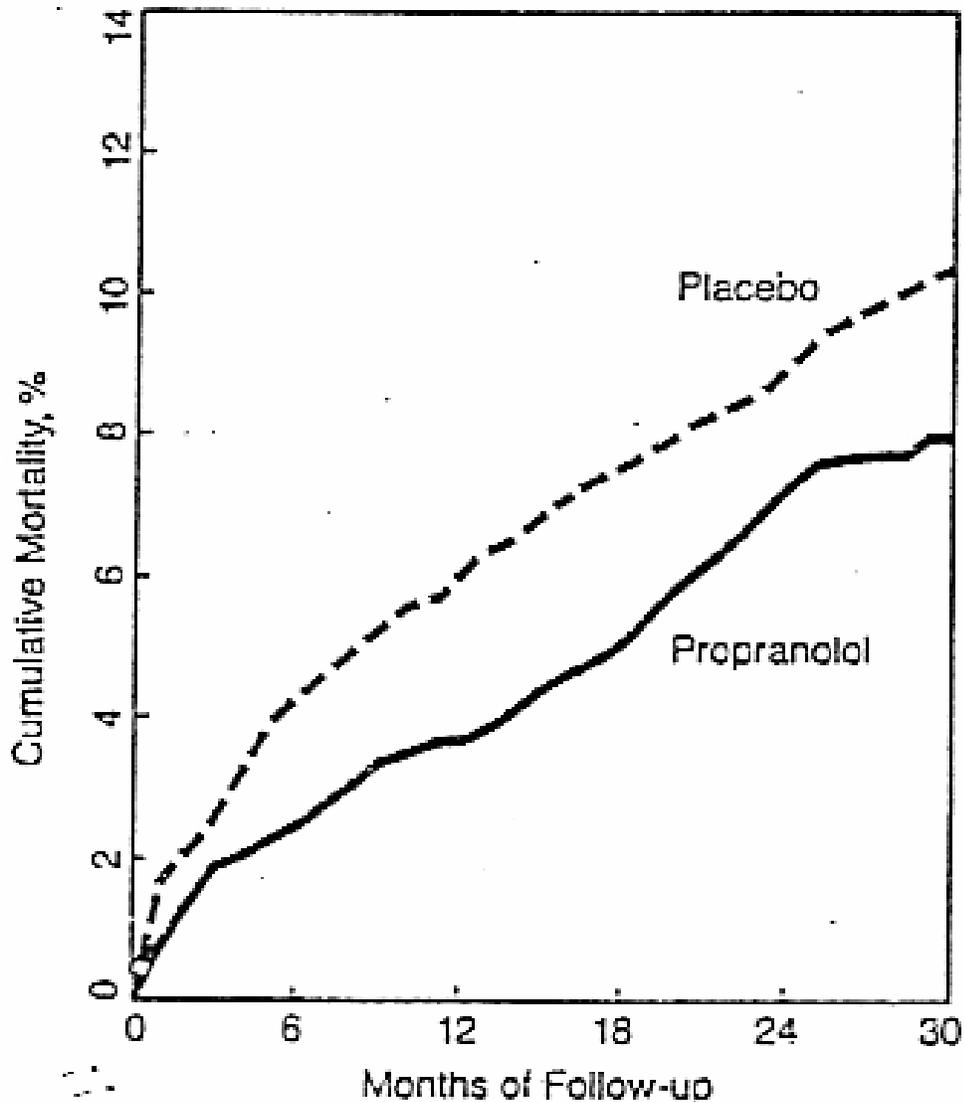
Early

- B-HAT (BENEFIT) Beta Blocker Heart Attack Trial (1981)
- ALLHAT (HARM) Anti-hypertensive and Lipid Lowering To Prevent Heart Attack Trial (2000)
- WHI (HARM) Women's Health Initiative (2002)

Beta Blocker Heart Attack Trial (B-HAT)

JAMA 1981; 246 (18): 2073-2074

Life-table cumulative mortality curves for propranolol hydrochloride and placebo groups. N denotes total number of patients followed up through each time point.



N = 3837 3696 3553 2850 2108 1202

Cooperative Trial. 2073

Beta Blocker Heart Attack Trial (B-HAT)

JAMA 1981; 246 (18): 2073-2074

“The BHAT results ...

Mortality Rates:

Placebo = 9.5%

Propranolol=7.0%

Reduction = 26%

Z=2.82 p=0.005

“... strengthen and extend the conclusions of previous studies of B-blockers in survivors of acute myocardial infarction...”

“...indicate that the beneficial effects of propranolol appear to occur primarily in the first year ...”



U.S. Department
of
Health and
Human Services



National
Institutes
of Health



National Heart,
Lung, and Blood
Institute

ALLHAT

Major Outcomes in High Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic

The Antihypertensive and Lipid- Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

The ALLHAT Collaborative Research Group
JAMA. 2002;288:2981-2997

Sponsored by NHLBI

Presented by

Michael Alderman, MD

Albert Einstein College of Medicine

CDN Webcast 2003 - www.CDNetwork.org



Randomized Design of ALLHAT

High-risk
hypertensive
patients



Consent /
Randomize
(42,418)

- Amlodipine
- Chlorthalidone
- Doxazosin
- Lisinopril

Eligible for
lipid-lowering

Not eligible
for lipid-
lowering

Consent / Randomize
(10,355)

Pravastatin
care

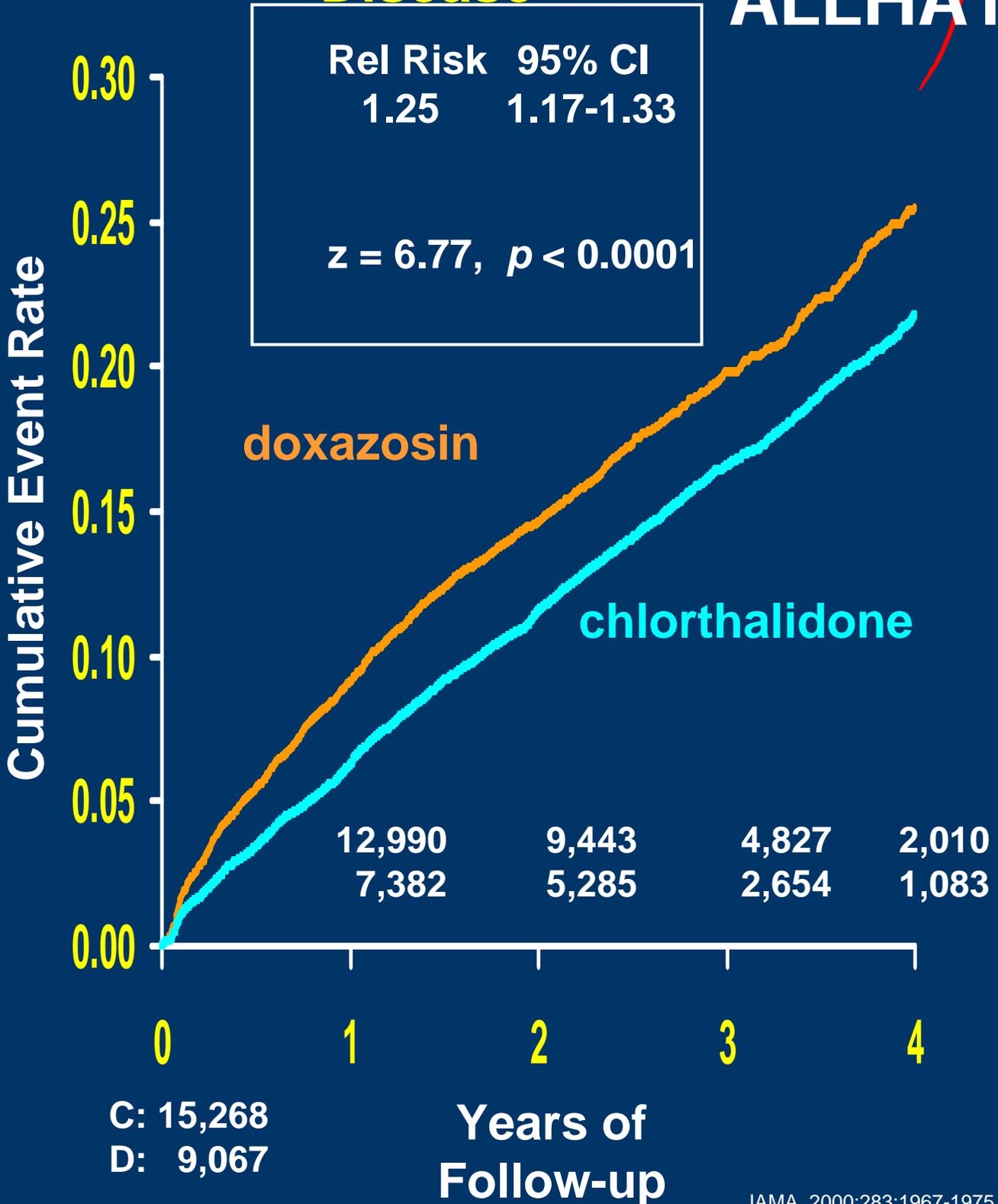
Usual
care



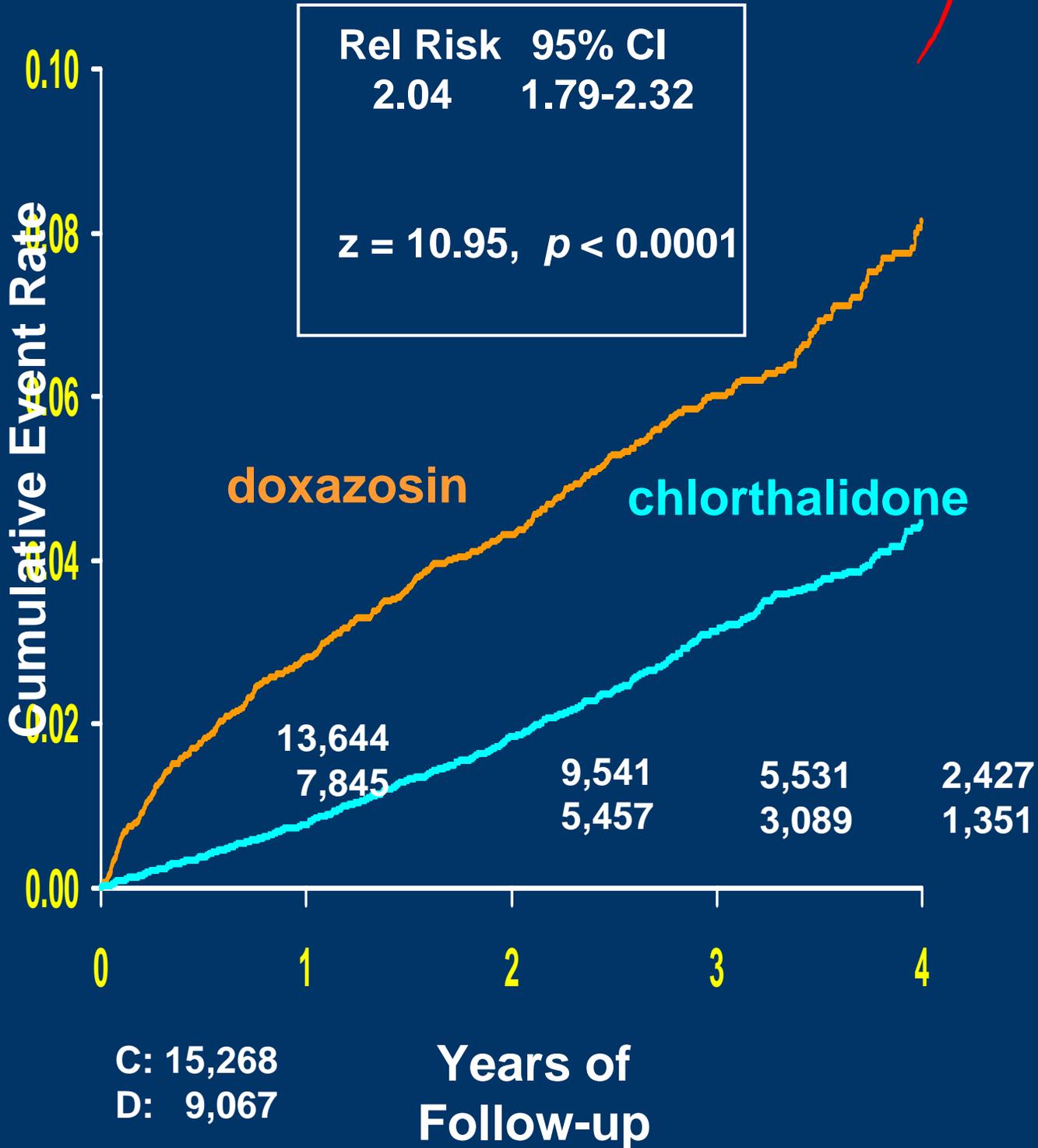
Follow for CHD and other outcomes until death
or end of study (up to 8 yr)

Cardiovascular Disease

ALLHAT



Heart Failure



Risks and benefits of estrogen plus progestin in healthy postmenopausal women

**Principal results of the
Women's Health Initiative
randomized controlled trial**

Presented by

Sylvia Wassertheil-Smoller, PhD

Albert Einstein College of Medicine

CDN Webcast 2003 - www.CDNetwork.org

Based on:

Writing Group for the **Women's Health Initiative** Investigators
Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal
Women: Principal Results From the Women's Health Initiative Randomized
Controlled Trial *JAMA* 2002 288: 321-333



WHI Hormone Program Design

Hysterectomy

Women who had
no uterus at
start of study

YES

N= 10,739

Conjugated equine
estrogen (CEE)
0.625 mg/d

Placebo

Women who had
a uterus at
start of study

NO

N= 16,608

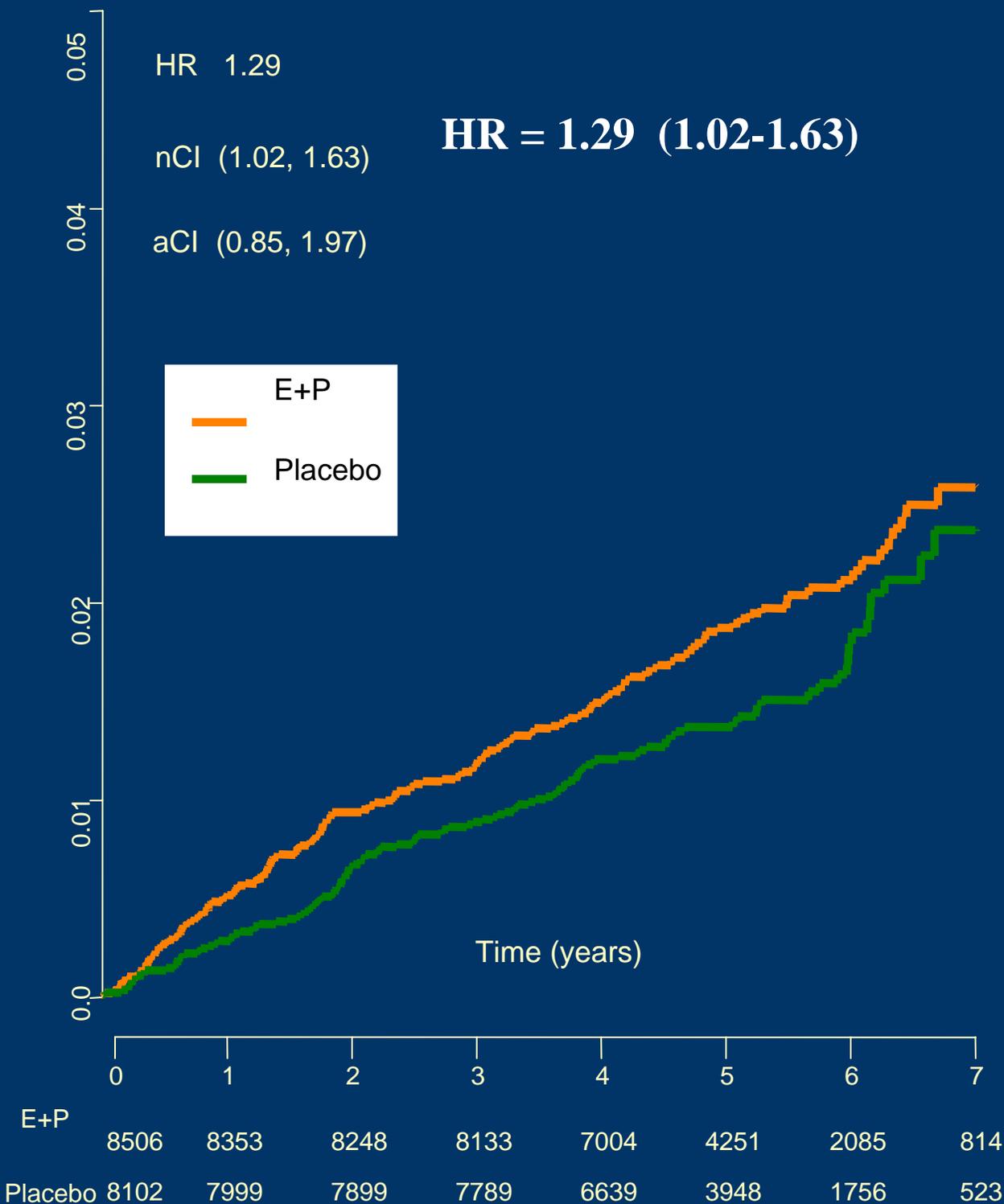
CEE 0.625 mg/d +
medroxyprogesterone
acetate (MDA) 2.5
mg/d

Placebo



Kaplan-Meier Estimates of Cumulative Hazards for CHD

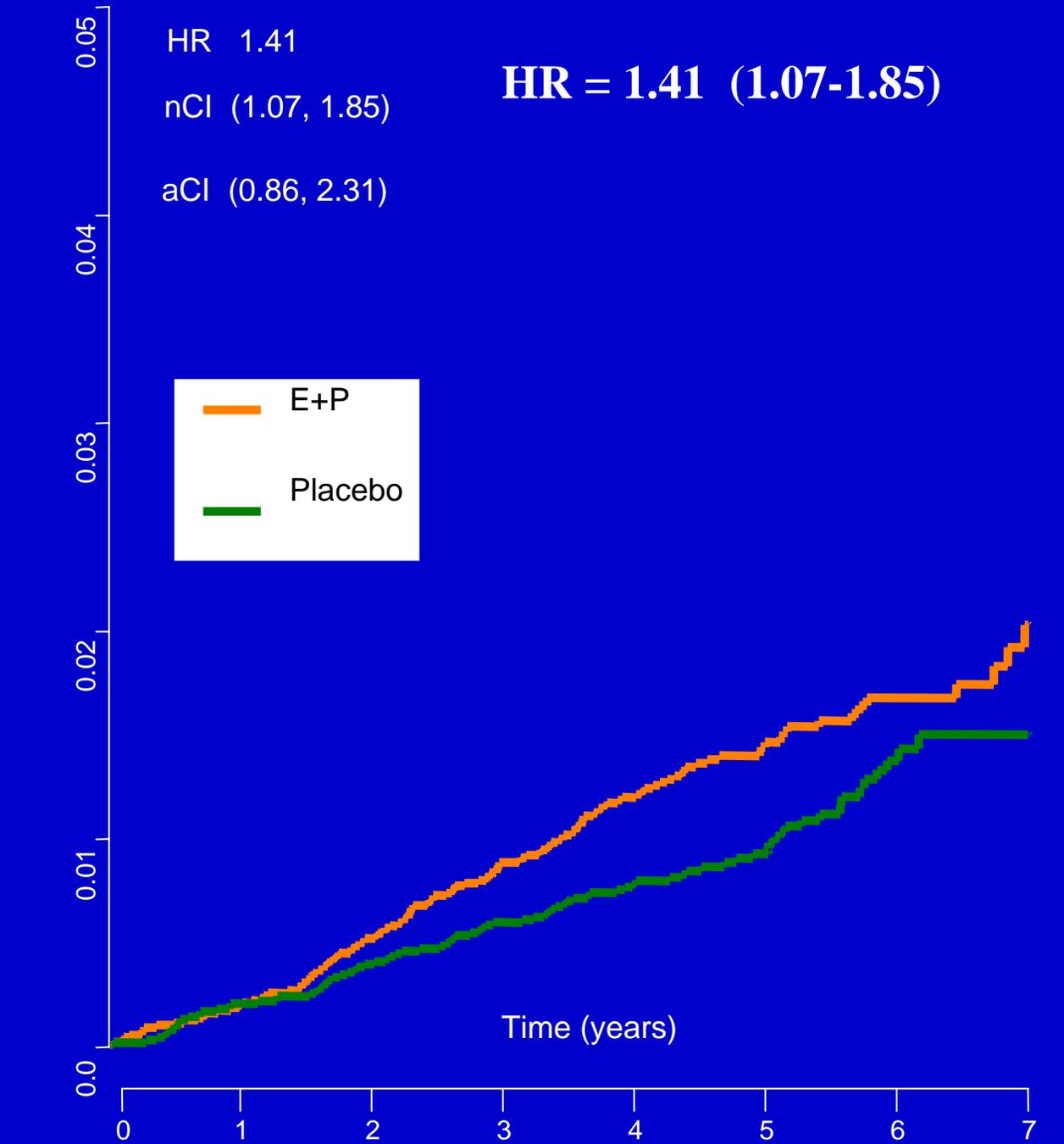
CHD



WOMEN'S
HEALTH
INITIATIVE

Kaplan-Meier Estimates of Cumulative Hazards for Stroke

Stroke

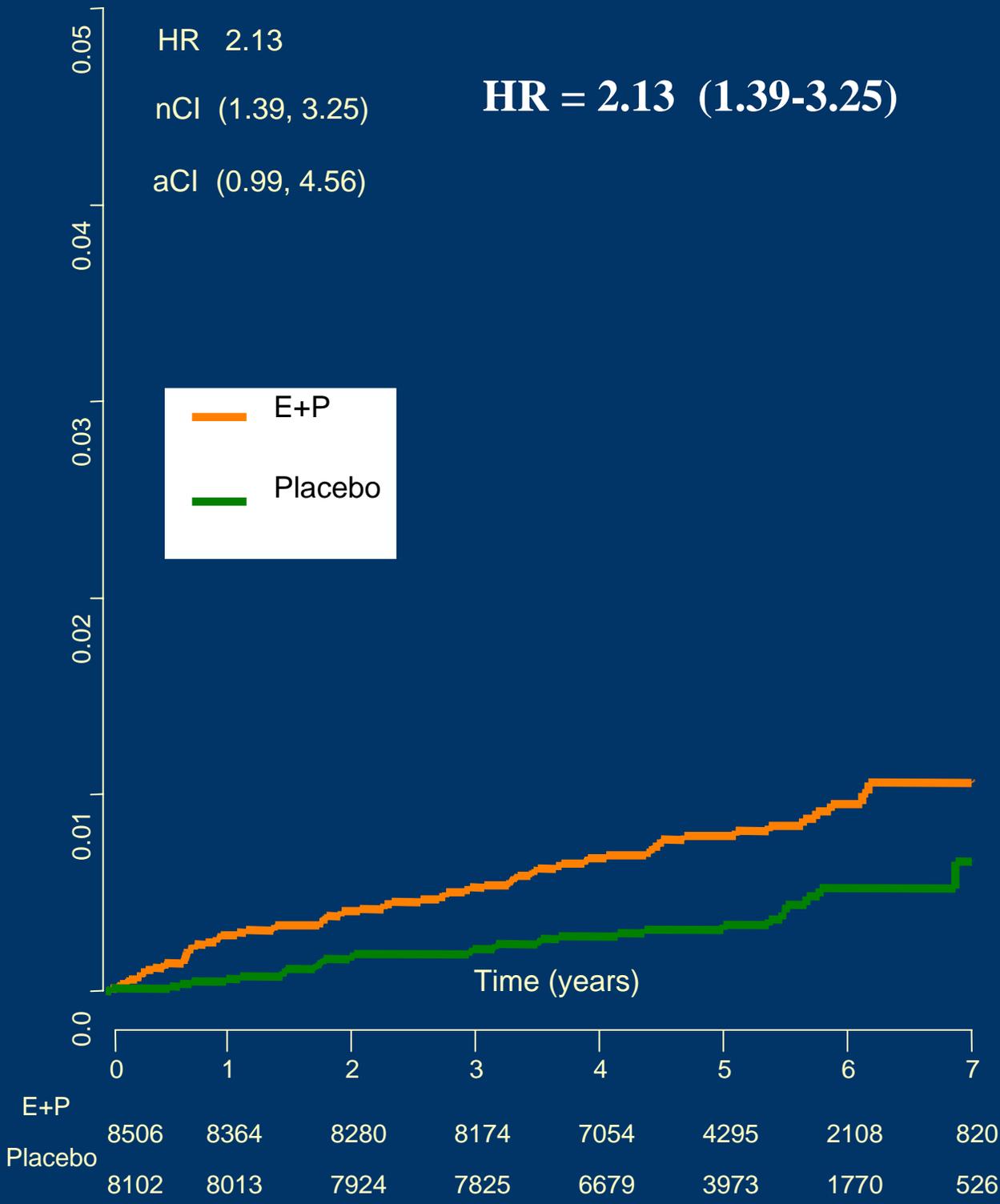


| | | | | | | | | |
|---------|------|------|------|------|------|------|------|-----|
| E+P | 8506 | 8375 | 8277 | 8155 | 7032 | 4272 | 2088 | 814 |
| Placebo | 8102 | 8005 | 7912 | 7804 | 6659 | 3960 | 1760 | 524 |



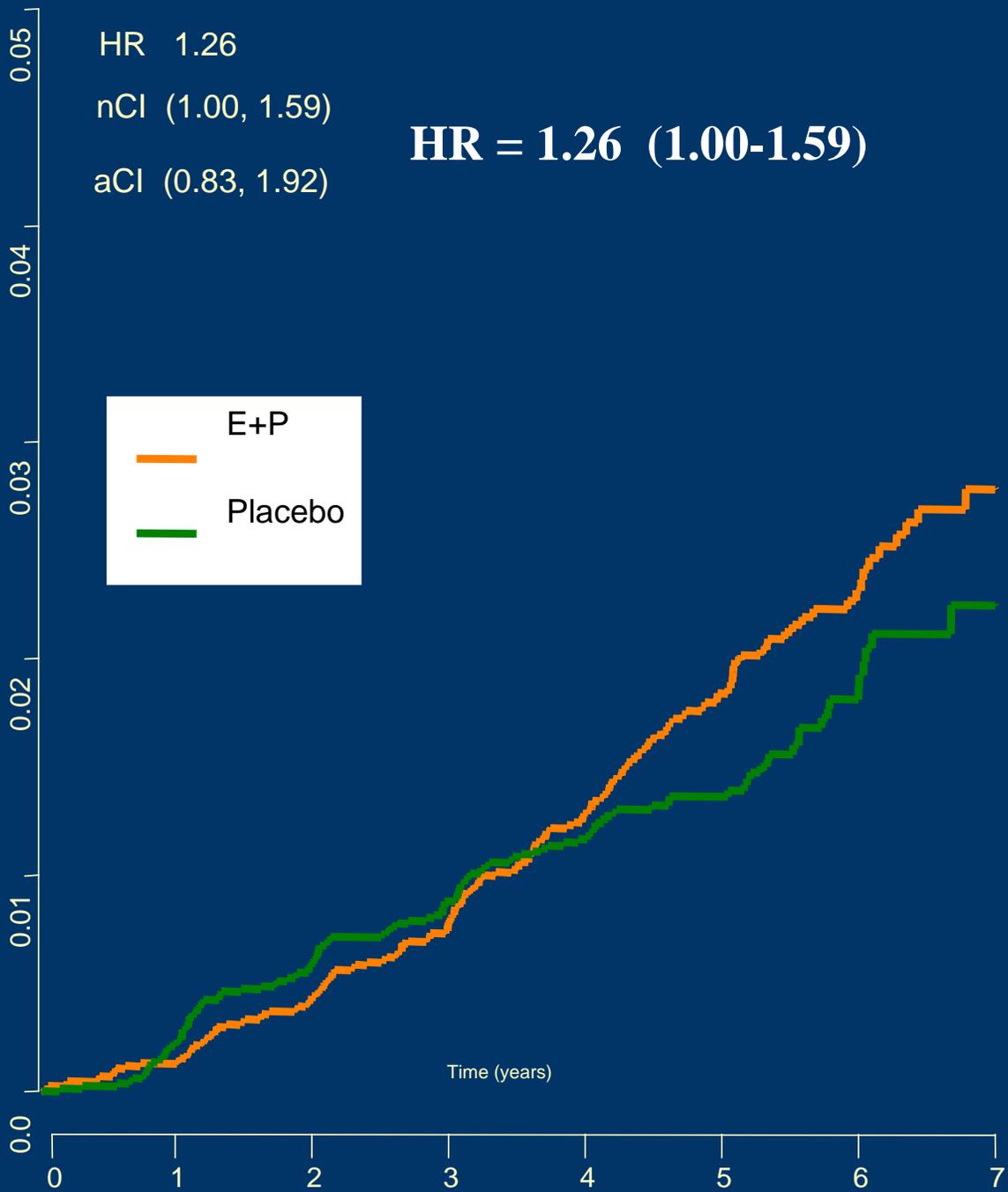
Kaplan-Meier Estimates of Cumulative Hazards for PE

PE



Kaplan-Meier Estimates of Cumulative Hazards for Breast Cancer

Invasive Breast Cancer

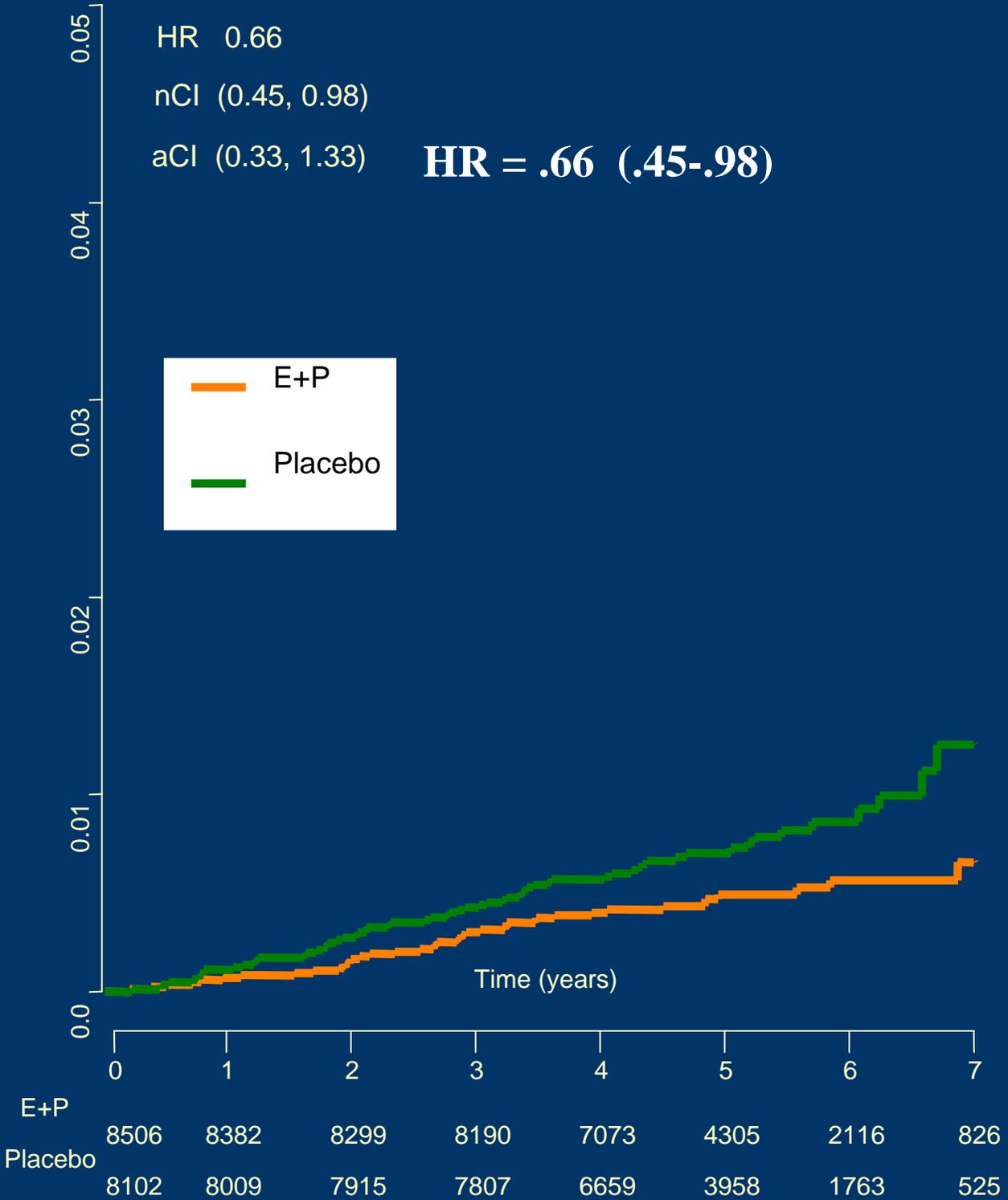


| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---------|------|------|------|------|------|------|------|-----|
| E+P | 8506 | 8378 | 8277 | 8150 | 7000 | 4234 | 2064 | 801 |
| Placebo | 8102 | 8001 | 7891 | 7772 | 6619 | 3922 | 1740 | 523 |



Kaplan-Meier Estimates of Cumulative Hazards for Hip Fracture

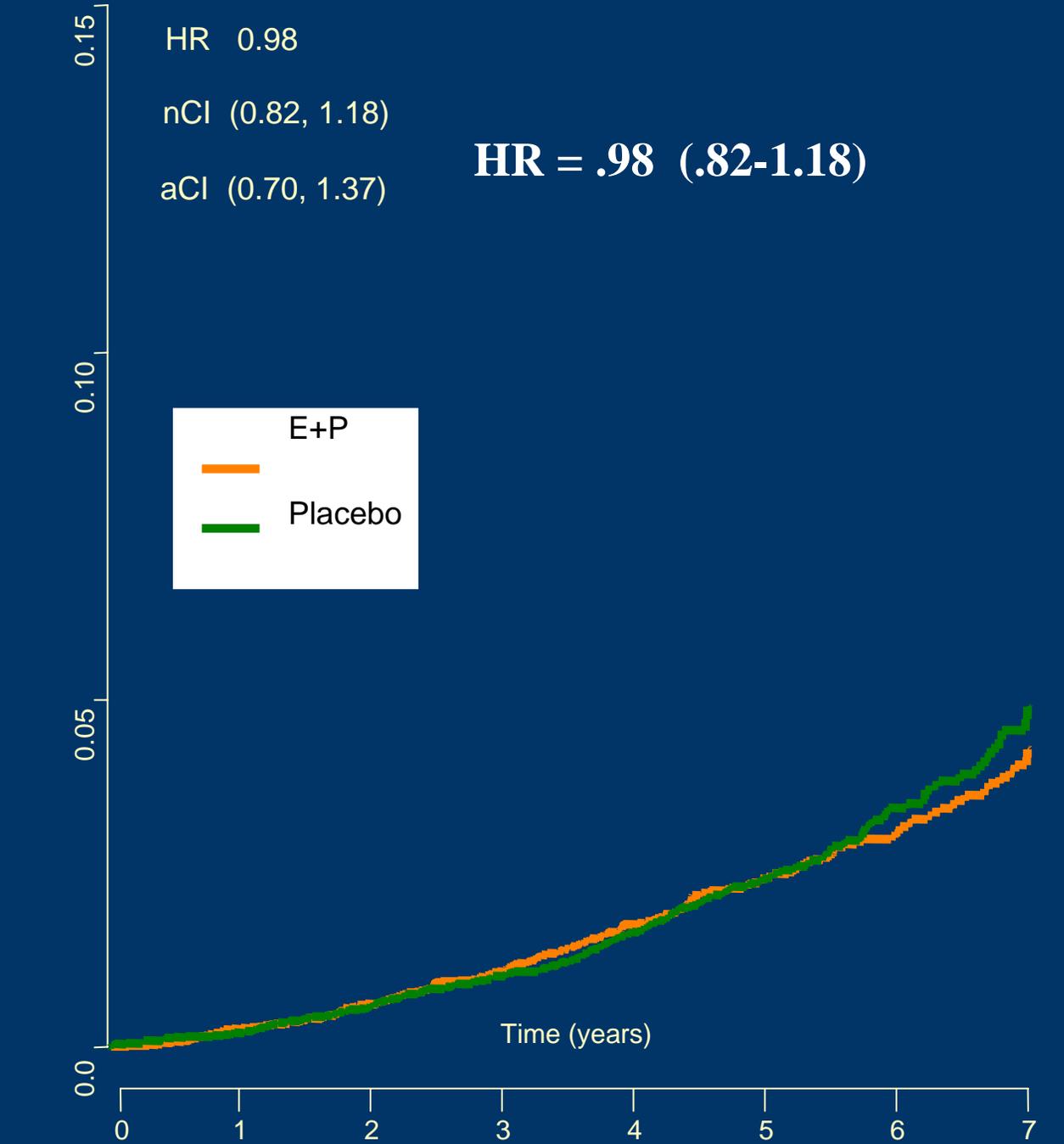
Hip Fracture



Kaplan-Meier Estimates of Cumulative Hazards for Death

The number of women at risk are presented below the horizontal axis for each treatment arm.

Death



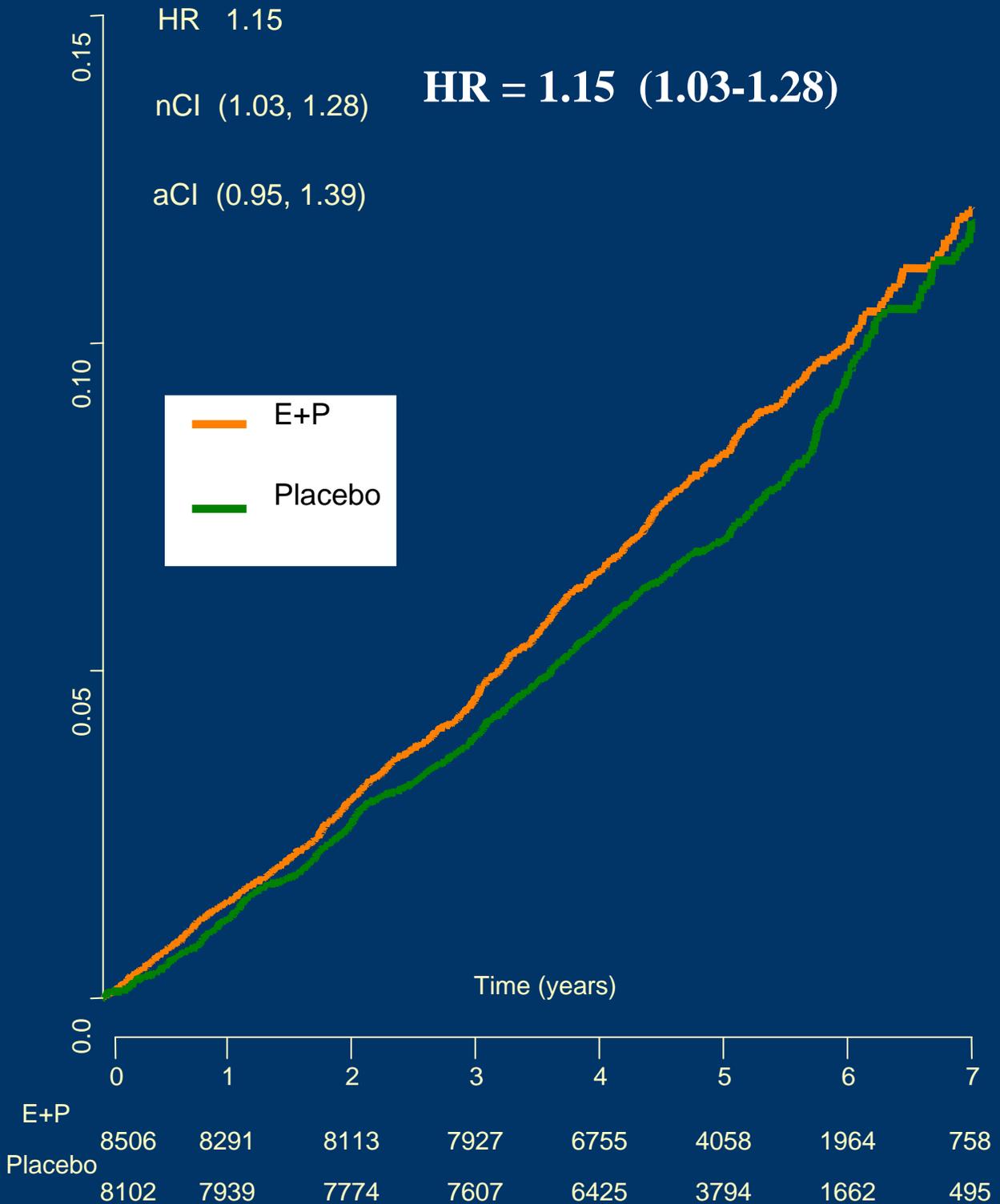
| | | | | | | | | |
|---------|------|------|------|------|------|------|------|-----|
| E+P | 8506 | 8388 | 8313 | 8214 | 7095 | 4320 | 2121 | 828 |
| Placebo | 8102 | 8018 | 7936 | 7840 | 6697 | 3985 | 1777 | 530 |



Kaplan-Meier Estimates of Cumulative Hazards for the Global Index

The number of women at risk are presented below the horizontal axis for each treatment arm.

Global Index



Why Did the DSMB Recommend Stopping Early?

**The risk of invasive breast cancer
crossed the monitoring boundary**

AND

**The global index supported a
trend toward overall harm**

The Data & Safety Monitoring Board's Decision

Looking at 5.2 years of study data, the DSMB recommended that women in the study of:

Estrogen+Progestin

Stop study pills

Estrogen alone

Continue study pills. At this time, no increased risk of breast cancer has been seen in women taking estrogen alone.

Session Outline - Recap

1. Background on Research Ethics

- IRB/Belmont Report
- HIPAA/Privacy Boards/Protected Health Info
- DSMB/Interim Analyses/Early Stopping Rules

2. Trial Monitoring: Statistical Issues

- Power (1-beta)
- Sample Size (alpha)
- Effect Size (ES) & Clinical Significance
- Variability/Heterogeneity (VAR)

4. DSMB: Establishment of a priori Early Stopping Rules: Policies & Procedures

- Stopping for Harm
- Stopping for Benefit

5. Examples of Early Trial Terminations

1. B-HAT
2. ALLHAT
3. WHI



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CONCLUSIONS

SAFETY FIRST:

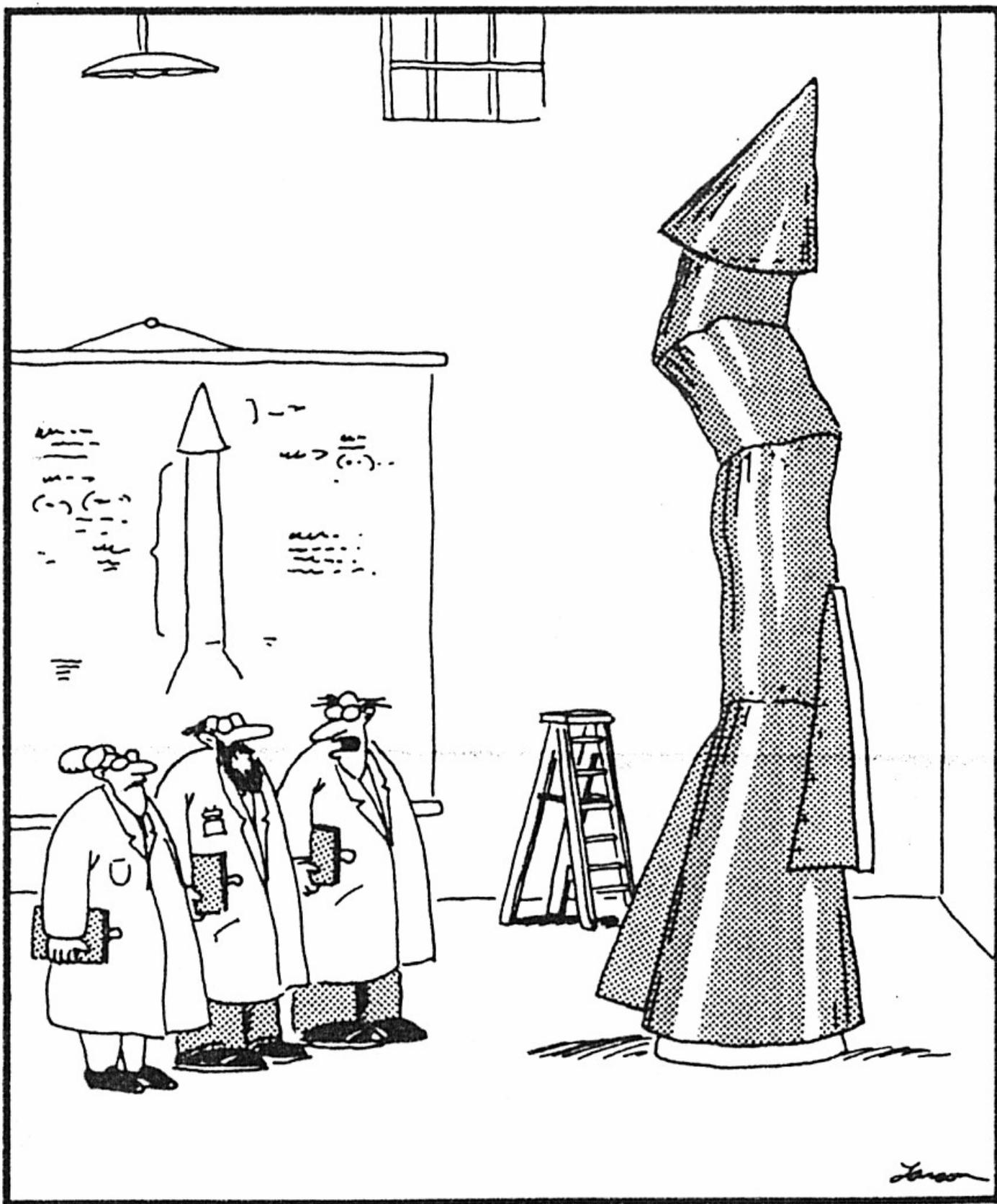
1. Test relevant behavioral & social science theories in real world, culturally diverse settings
3. Improve systems of care
4. Contribute to patient care
5. Improve health outcomes for underserved populations
6. Following appropriate strategies and statistical methodologies to increase the likelihood of making correct decisions

In a Nutshell
(Standing on One Foot)

Follow the Golden Rule:

Do Unto Others...

All else is Commentary



"It's time we face reality, my friends. ...
We're not exactly rocket scientists."

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- [Assessing Adult Immunization Rates in Your Practice: Online ACASA Demonstration - 12/05/2002 11:58](#)
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President/CEO

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