

The Medication Approval Process – Evaluation of Efficacy and Safety

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OBJECTIVES

- **To familiarize the audience with critical terminology used in clinical trials studies**
- **To familiarize the audience with strengths and weaknesses of various clinical research study designs**
- **To provide the audience with a fundamental basis for attempting to understand the significance of public reports of clinical research findings**

ISSUES

- **Key Definitions**

- **Efficacy** – **Does the intervention work?**

- **Effectiveness** – **Efficacy in actual practice**

CARTOON

- Deleted from this document for
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DILEMMAS

- **Estrogen deficiency and risk of Alzheimer's disease in women.**
 - **Am J Epidemiol 1994 Aug 1;140(3):256-61**
 - **“This study suggests that the increased incidence of Alzheimer's disease in older women may be due to estrogen deficiency and that estrogen replacement therapy may be useful for preventing or delaying the onset of this dementia.”**

DILEMMAS

- **Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. Alzheimer's Disease Cooperative Study**
 - **JAMA 2000 Feb 23;283(8):1007-15**
 - **“CONCLUSIONS: Estrogen replacement therapy for 1 year did not slow disease progression nor did it improve global, cognitive, or functional outcomes in women with mild to moderate AD. The study does not support the role of estrogen for the treatment of this disease. The potential role of estrogen in the prevention of AD, however, requires further research.”**

DILEMMAS

- **Effect of postmenopausal hormone therapy on cognitive function: the Heart and Estrogen/progestin Replacement Study.**
 - **Am J Med 2002 Nov;113(7):543-8**
 - **“CONCLUSION: Among older postmenopausal women with coronary disease, 4 years of treatment with postmenopausal hormone therapy did not result in better cognitive function as measured on six standardized tests. Whether these results also apply to elderly women without coronary disease cannot be determined from this study.”**

DILEMMAS

- **A Placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia**
 - **JAMA 1997 Oct 22/29;278(16):1327-32**
 - **CONCLUSIONS.** “EGb was safe and appears capable of stabilizing and, in a substantial number of cases, improving cognitive performance and the social functioning of demented patients for 6 months to 1 year. Although modest, the changes induced by EGb were objectively measured by the ADAS-Cog and were of sufficient magnitude to be recognized by the caregivers in the GERRI.”

DILEMMAS

- **Ginkgo for memory enhancement. A randomized controlled trial**
 - **JAMA 2002 Aug 21;288(7):835-40**
 - **CONCLUSIONS.** “The results of this 6 week study indicate that ginkgo did not facilitate performance on standard neuropsychological tests of learning, memory, attention, and concentration or naming and verbal fluency in elderly adults without cognitive impairment. The ginkgo group did not differ from the control group in terms of self-reported memory function or global rating by spouses, friends and relatives.”

DILEMMAS

- **Ginkgo biloba for prevention of dementia. A randomized controlled trial**
 - **JAMA 2008 Nov 19;300(19):2253-62**
 - **CONCLUSIONS.** “In this study, G biloba at 120 mg twice a day was not effective in reducing either the overall incidence rate of dementia or AD incidence in elderly individuals with normal cognition or those with MCI.”

DEFINITION

- *Clinical Trial*

A prospective study that compares the effect and value of intervention(s) against a control in human beings.

Clinical Trial

- **Key words:**

Prospective

Intervention

Control

TIMING OF CLINICAL TRIALS

- **ISSUES**

- **Drift in practice habits**

- **Experience with the intervention**

- **Stability of the pathological process to which the intervention is addressed**

Elements of the Study Protocol

- **Study Design**
 - **Who?** - the study cohort
 - **How many?** - a statistical calculation
 - **How long?** - depends on frequency of adverse event
 - **What?** - validity of endpoint (surrogate vs. definitive)

SOURCES OF ERROR

- **Alpha error** – accepting efficacy when it doesn't exist
- **Beta error** – assuming lack of efficacy when an intervention is effective
- **Sample size** – planning a study that is too small to accommodate alpha and beta errors

The Study Population

Who will be studied?

How will study subjects be selected?



Feasibility

Generalizability

The Study Population

- **Issues Affecting Inclusion Criteria**
 - **Heterogeneity of the health problem**
 - **Mild**
 - **Moderate**
 - **Severe**
 - **Categorical vs. continuous inclusion measures**

The Study Population

- **Fundamental Point**
 - **The study population should be defined in advance, stating unambiguous inclusion (eligibility) criteria. The impact that these criteria will have on study design, ability to generalize, and participant recruitment must be considered.**

Clinical Trial

- **Key Elements:**

Randomization of participants

Blinding of patients and investigators

RANDOMIZATION

- **Purpose:**
 - **To produce comparable groups with a study group assignment procedure that tends to respect known and unknown risk factors**
 - **To minimize investigator bias**
 - **To guarantee the validity of statistical tests**

TESTS OF COGNITIVE FUNCTION

- **ADAScog** – **Score out of 70** – **Categorical**
 - Initial clinically important difference “10 points”
 - After drug studies reduced to “4 points”
 - Many interventions “3 points”
- **MMSE** – **Score out of 30** – **Categorical**
 - Lower score worse. Dementia only if score < 24
- **ADS-CGIC** – **Seven point scale** – **Categorical**
 - Lower score better
 - Score of “4” = no change

Reporting and Interpreting of Results

- **Interpretation Issues**
 - **Clinical Implications**
 - **Generalization of findings**
 - **Surrogate endpoints**
 - **Economics – numbers needed to treat**

THE BOTTOM LINE

- **Statistical significance vs. clinical relevance**
 - **Efficacy vs. effectiveness**
 - **Intention to treat vs. **study completers****
 - **Number needed to treat**
 - **Adverse events burden**
 - **Cost to the health care system**