ADAPTIVE DESIGNS IN CLINICAL DRUG DEVELOPMENT : Opportunities & Challenges

A Patient/Advocate Perspective

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Topics

- Advocates
  - Who are we?
  - What do we do?
- Clinical Trials
  - Issues from an Advocates perspective
  - Examples of collaboration & innovation
- Conclusions

Who Am I?

Jane Perlmutter
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- Twenty-one year breast cancer survivor
- Active, informed, and opinionated advocate
- Ph.D. in experimental-cognitive psychology
- Professional experience in academia and industrial R&D
- Currently, independent consultant

All Advocates Want Rapid Access to Effective Treatments

- Treatments are especially needed for:
  - Life-threatening diseases
  - Where no other treatments are available
- But, patients are concerned about side-effects especially when:
  - Non-reversible
  - Unknown
  - Disease is not life-threatening
  - Alternative treatments are available

Advocates Do NOT Speak With One Voice

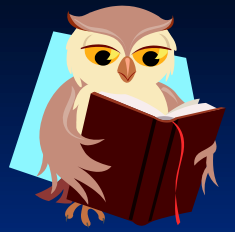
- Some focus on rapid availability of experimental drugs, at least for life threatening illnesses[1]
- Others are committed to evidence-based medicine and guard against approaches they believe will undermine scientific integrity, including early stopping of trials[2]

[1] Abigail Alliance (http://abigail-alliance.org/index.html)
[2] National Breast Cancer Coalition (http://www.stopbreastcancer.org)

Innovative Experimental Designs

- Can have widespread impact on drug development by:
  - Increasing speed--reduce number of patients and/or speed their accrual
  - Improving quality—target optimal treatment conditions and patient sub-groups
  - Decreasing cost

- **Note:** *Innovative design* does not mean *creative analysis*

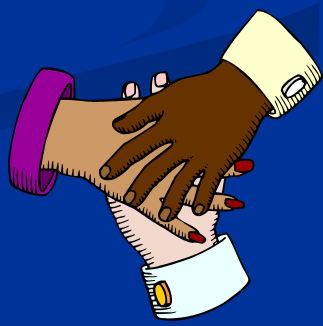


Knowledge & Power

- Not all advocates have a thorough understanding of the scientific and regulatory processes
- Many advocates have significant (and increasing) impact on research strategy and funding, approval of drugs, and health policy
- Increased understanding between scientists and advocates will help them most effectively achieve common goals

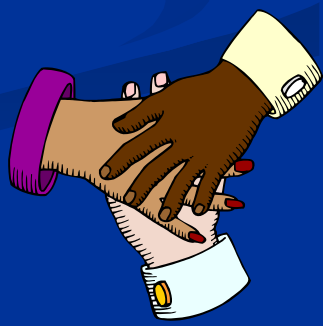
Advocates Can Be Important Allies

- Clarify values and provide a sense of urgency
- Increase public awareness and understanding of science in general and randomized clinical trials in particular
- Lobby for appropriate political action
- Partner with scientists and clinicians on design and implementation of research



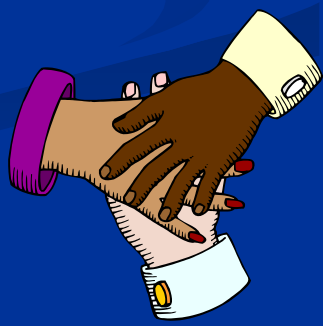
Examples: Advocates Influence Policy

- Lobby for policy change—e.g.,
  - Registration of clinical trials
  - Changes in drug approval process
  - Direct-to-consumer prescription drug advertising
  - Privacy of health and genetic information
  - Universal access to quality care
- Sit on advisory committees (e.g., NIH, FDA, Cooperative Groups)
- Help secure research funding



Examples: Advocates Influence Research

- Sit on research strategy and priority-setting committees (e.g., grant reviews)
- Sit on IRBs and DSMBs
- Provide an outside, but highly motivated, and often educated perspective on experimental priorities and designs
- Provide patients' perspective on protocols, informed consent process & outreach materials
- Help to recruit and support patients
- Communicate results to advocate community



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Clinical Trials—Ethical Issues

- Balancing responsibility toward:[1]
  - Patients in the trial
  - Current patients needing treatment, but not in the trial
  - All future patients
- Belief in equipoise[2]
  - Who?--researcher, clinician, patient
  - When?—beginning or throughout trial

Participants' focus

Some Advocates' focus

Scientists' focus

Adaptive Trialists, Bayesians

Traditional Trialists, Frequentists

[1] Belmont Report (1979)

[2] Helsinki Declaration (1964)

Clinical Trials—Statistical Issues

- Trade-offs between α and β Errors
  - *Scientists:* Protect against "false truths" at all costs (minimize α)
  - *Patients:* Do not miss any potentially lifesaving treatment (minimize β)
- Converging evidence
  - Frequentist vs. Bayesian perspectives
  - Levels of evidence
- Subset analysis

Clinical Trials—Endpoint Issues

- Primary endpoints may not be available during patient recruitment
- Surrogate endpoints may not be available or widely agreed upon
- Secondary endpoints may be of considerable interest and may not co-vary with the parameter used by the adaptive algorithm

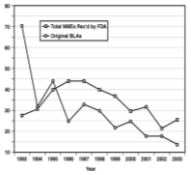
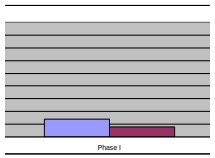
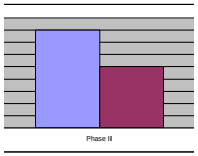
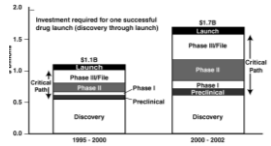
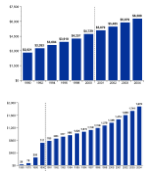
Clinical Trials—Tissue Issues

- Validating a biomarker vs. treatments
  - Targeted treatments will be approved with tests of biomarkers
  - But biomarkers may need to be independently validated
- Patients support banking tissue, but are concerned about access to the tissue

Clinical Trials—Practical Issues

- High costs associated with large designs
- Selecting treatment arms
  - Combination therapies
  - Dosages
  - Delivery schedules
- Establishing eligibility requirements
- Accruing patients to randomized trials

Drug Development Reality

Trend	~ 10 Year Change	Figure
Increasing investment in U.S. Biomedical Research	+ 250%	
Lack of new products available to patients	- 55%	
Decreasing success of compounds entering Phase I	- 5 % points - 50%	
Decreasing success of Phase III trials	- 30 % points - 35%	
Major increases in medical product development costs	+ 65%	
Major rise in healthcare costs	+ 60% per capita + 2.5% points GNP + 20% GNP	

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Example: Bone Marrow Transplants for Women With Breast Cancer

- Much early hope and hype
- Many advocated for availability outside of trials
- Trials accrued slowly
- Many women did not survive treatment
- When trials concluded, no overall benefit was found

This was a watershed experience for many advocates

Mayer, M. When Clinical Trials Are Compromised: A Perspective from a Patient Advocate. *PLoS Medicine*, 2005, 2(11), e358.

Example: Herceptin for Women With Breast Cancer

- An experimental treatment in trouble:
  - Recruitment for critical trials was stalled
  - Genetech approached NBCC
  - With NBCC's involvement accrual rapidly increased

An important and innovative therapy was approved and incorporated into clinical practice

NBCC's Expectations for Partnerships*

Advocates Provide

- Input on study design & implementation
- Input on outreach materials
- Publicity to support recruitment
- Publicity to support expanded access, if appropriate

Advocates Expect

- Important, ethical trials
- Opportunities for meaningful input
- Information on all relevant trials
- Updates on trial progress, status & results
- Publications of results, regardless of outcomes

*http://www.stopbreastcancer.org/bin/index.asp?strid=150&btnid=1&depid=7

NBCC
National Breast Cancer Coalition
grassroots advocacy in action

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Opportunities of Adaptive Trials: An Advocate's Perspective

- More effective treatments for more of the patients enrolled in clinical trials
- More rapid completion of trials, approval of effective treatments, and abandonment of non-effective treatments
- More efficient use of resources:
  - Patients
  - Money
  - Scientists time

Challenges of Adaptive Trials: An Advocate's Perspective

- ***Public/Patients/Advocates:*** Suspicious of science in general and randomization in particular
- ***Clinical Researchers:*** Lack awareness or understanding of adaptive designs
- ***Regulators & Journal Editors:*** Appear ambivalent about adaptive designs
- ***Drug Developers:*** Unwilling to risk lack of approval by regulators

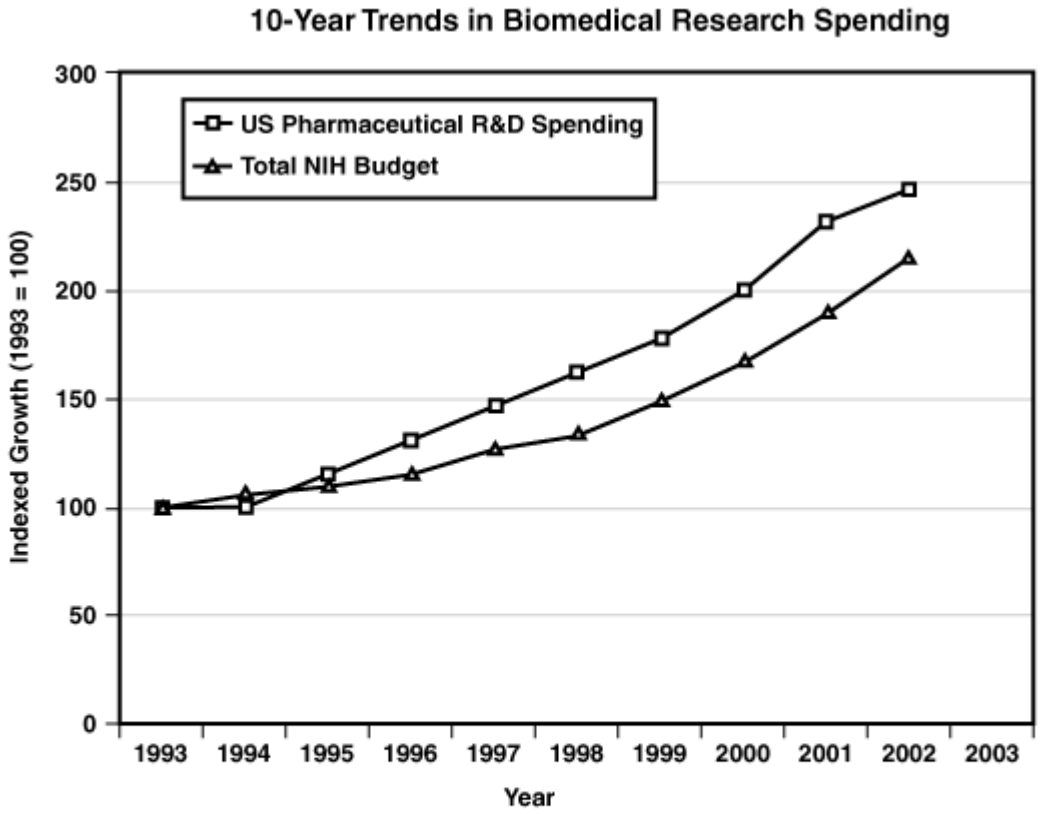
Take Home Points

- Advocates can be important allies in research
- Find and educate advocates in your area
- Let them know what you need and have them help you get it:
  - Patients' perspectives on research
  - Recruitment and support of patients
  - Public understanding of randomized clinical trials, in general, and adaptive designs in particular
  - Public support of research priorities
  - Public policy changes

Backup

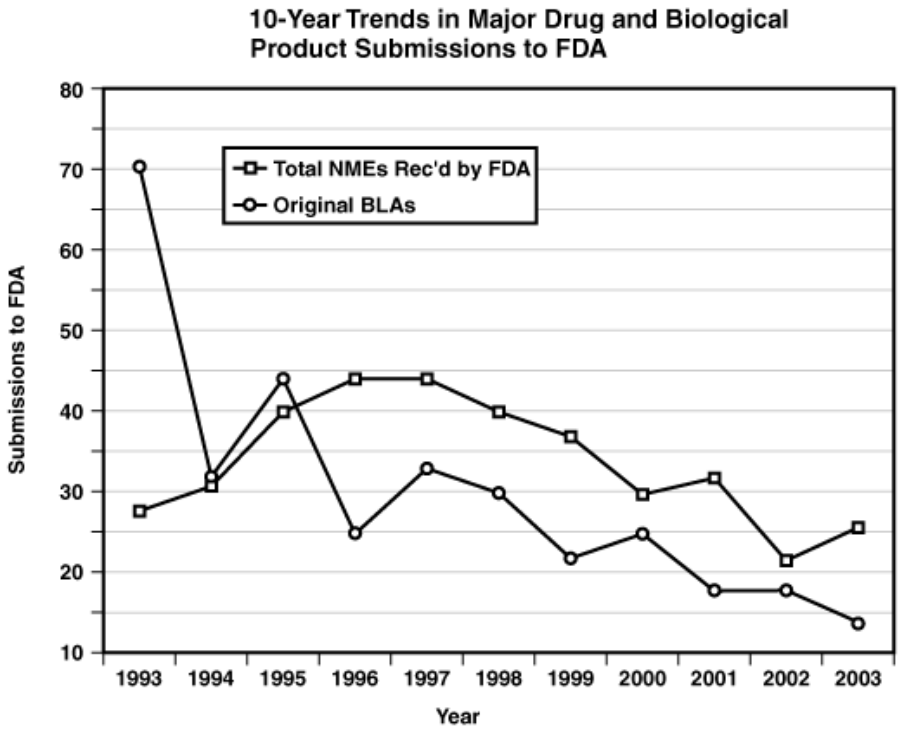
- Research Investment
- New Products
- Clinical Trial Success Rates
- Medical Development Costs
- Healthcare Spending

Increasing Investment in U.S. Biomedical Research



The figure shows 10-year trends in biomedical research spending as reflected by the NIH budget (Budget of the United States Government, appendix, FY 1993-2003) and by pharmaceutical companies' research and development (R&D) investment (PAREXEL's Pharmaceutical R&D Statiststical Sourcebook 2002/2003).

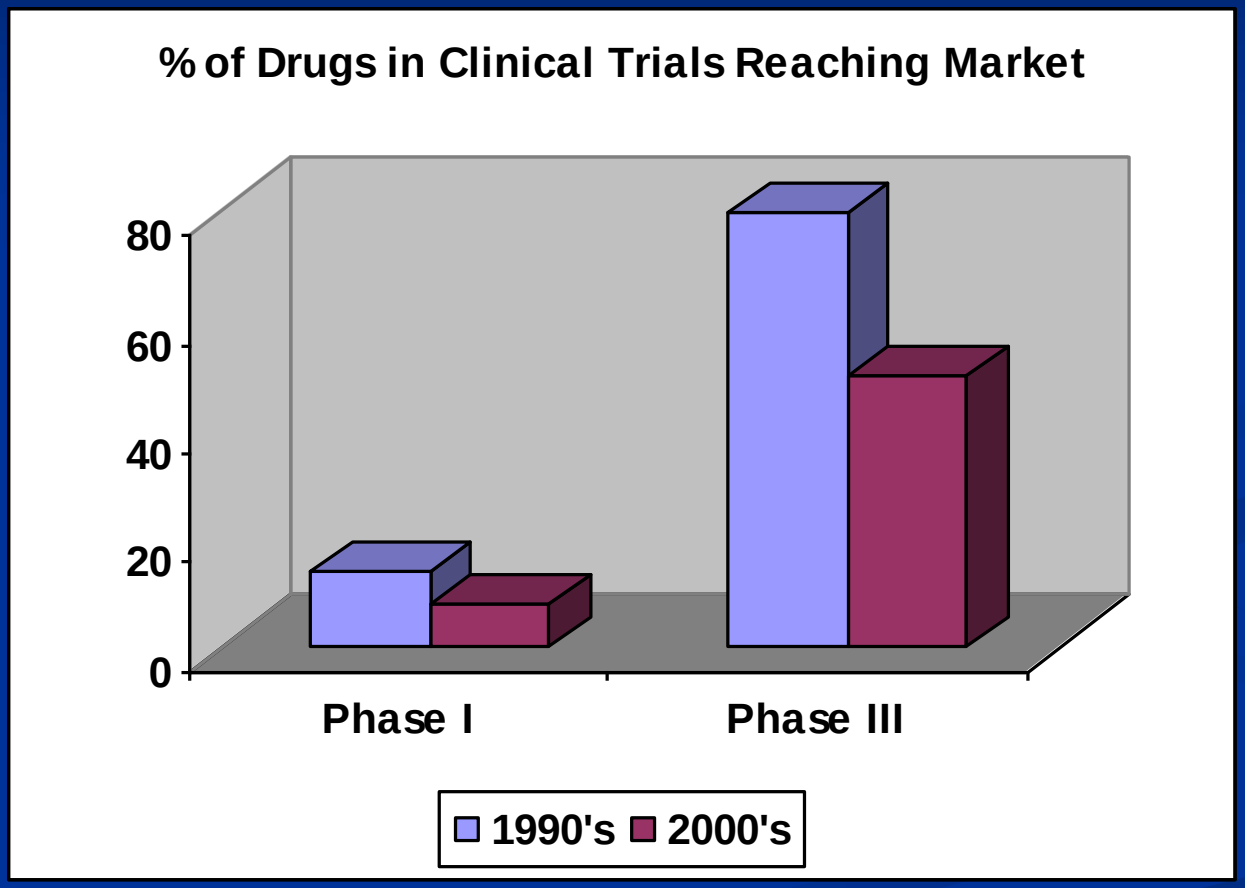
Lack of New Products Available to Patients



The figure shows the number of submissions of new molecular entities (NMEs) — drugs with a novel chemical structure — and the number of biologics license application (BLA) submissions to FDA over a 10-year period. Similar trends have been observed at regulatory agencies worldwide.

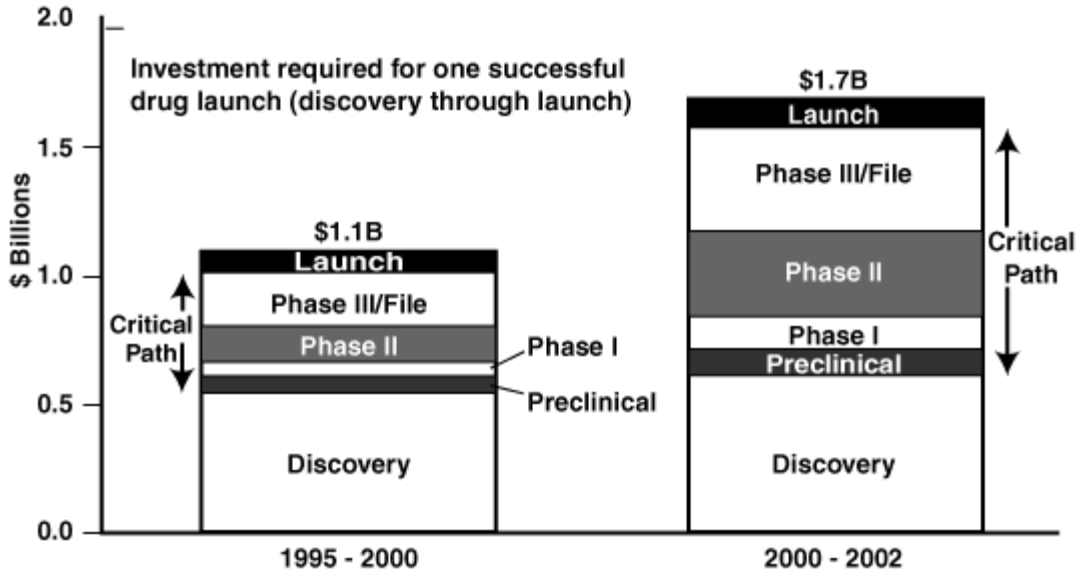
FDA White Paper: Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products, 2004.

Lower Success Rate in Clinical Trials



Woodcock, J. Accelerating Cancer Therapeutic Development—The FDA Critical Path Initiative, AACR, 2006.

Increases in Medical Product Development Costs



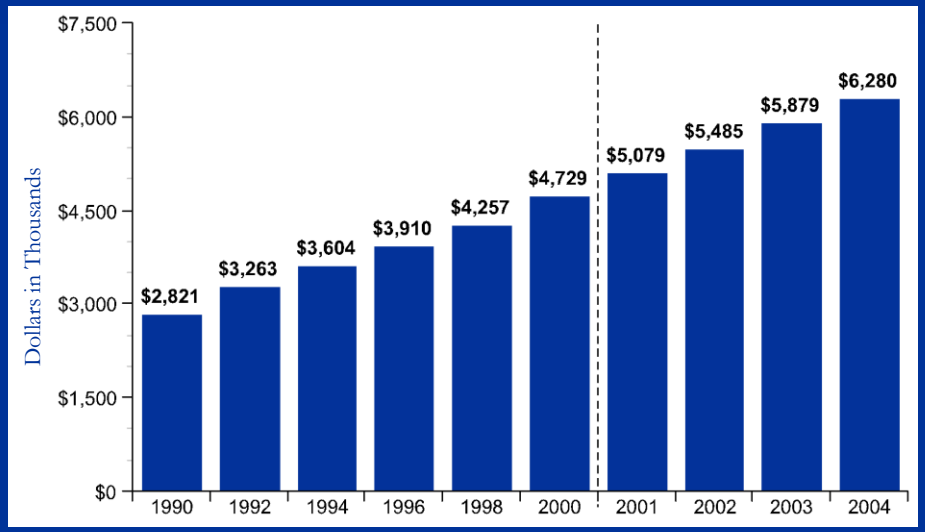
SOURCE: Windhover's In Vivo: The Business & Medicine Report, Bain drug economics model, 2003

The figure shows one estimate of the total investment required to "launch" (i.e., market) a successful drug in two time periods. Most of the recent cost increases are within the "critical path" development phase, between discovery and launch.

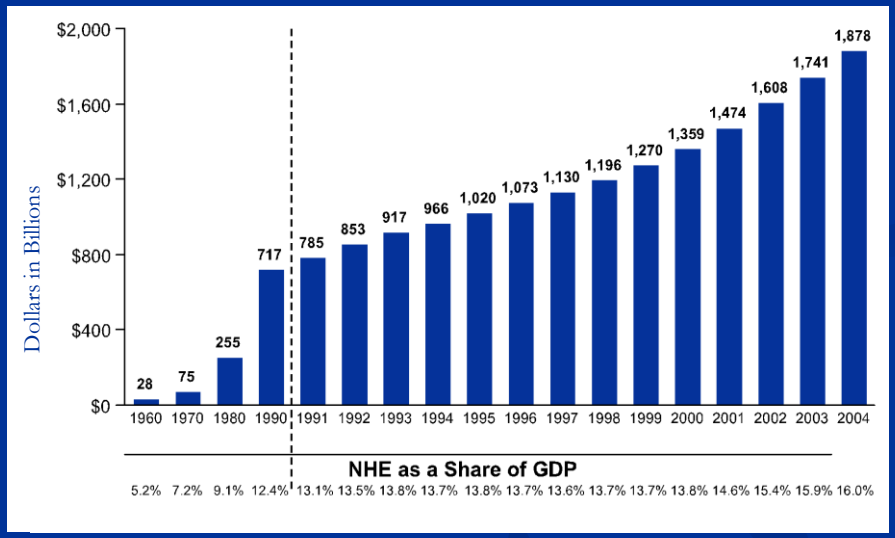
The overall increase between 1995 - 2000 and 2000 - 2002 is estimated to be 55 percent.

Rise in U.S. Healthcare Costs

National Health Expenditures per Capital



National Health Expenditures and % Gross Domestic Product



Source: Centers for Medicare and Medicaid Services, Office of the Actuary, National Health Statistics Group, at http://www.cms.hhs.gov/NationalHealthExpendData/