Clinical Trials: Moving Multiple Perspectives toward Common Ground

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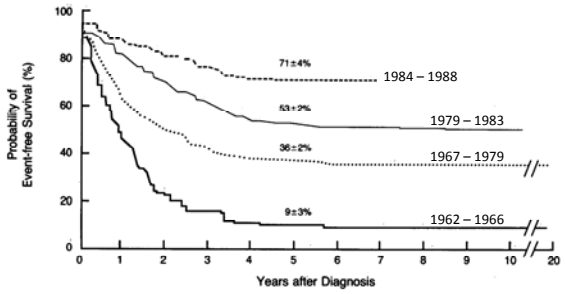
Topics for Discussion

- Stakeholders
- Importance and value of clinical trials
- Phases of clinical trials and associated risks and benefits
- Ethics of testing unproven treatments
- Barriers to enrollment
- New Washington State rules for coverage of clinical trials
- Allocation of costs between sponsors and carriers

Stakeholders

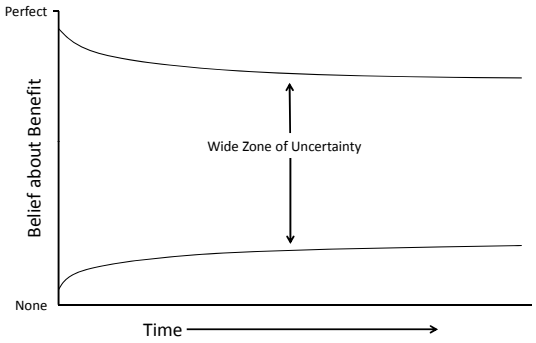
- Patients and family members
- Physicians in academic and private practice
- Private and public insurance providers
- Sponsors
  - Academic individuals and cooperative groups
  - Pharmaceutical and device industry
- Regulatory agencies
- Tax-payers
- Public at large

Treatment for Acute Lymphoblastic Leukemia in Children

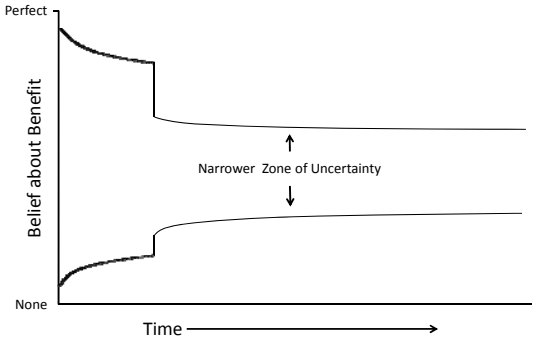


Rivera et al. New England Journal of Medicine 329:1289, 1993

Gain of Information in the Absence of Clinical Trials



Gain of Information in the Presence of a Clinical Trial



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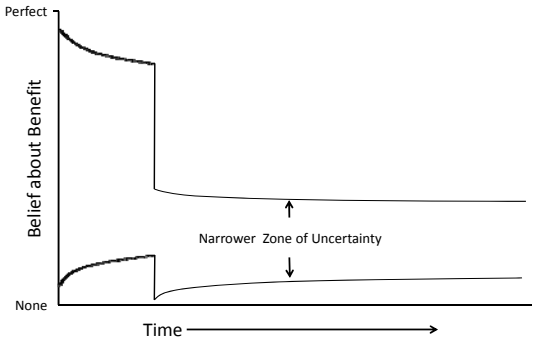

Preliminary Steps in Drug Development

- Screening of chemical compounds for biochemical effect
- Medicinal chemistry—turning a compound into a drug
  - Absorption
  - Distribution
  - Metabolism
  - Elimination
- Manufacture according to regulatory requirements
- Toxicology—assessing the potential side effects
  - Rodents
  - Rabbits
  - Other
- Pharmacokinetics
  - Amount in body related to dose and time after administration

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- Review by FDA and beginning of clinical trials 10

Phases of Clinical Trials

Phase	Purpose	Number of Patients
I	Find a safe dose Decide how treatment should be given Measure effects the human body	15 – 30
II	Measure effect on specific type of cancer Measure effects on the human body	30 – 100
III	Compare new treatment with current standard treatment	100 – 3000
IV	Assess long-term safety and effectiveness	500 – 5000

National Cancer Institute Website

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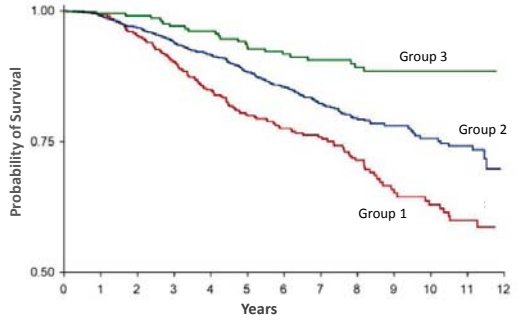
National Cancer Institute Website

Patients Benefit from Participating in Clinical Trials

- 1727 women with localized breast cancer in Canada
  - Group 1: Treatment without trial and not consistent with guidelines
  - Group 2: Treatment without trial but consistent with guidelines
  - Group 3: Treatment according to a clinical trial
- Results
  - Group 2: 30% reduction in risk of death compared to Group 1
  - Group 3: 55% reduction in risk of death compared to Group 1

Hebert-Croteau et al. Breast Cancer Research and Treatment 91: 279, 2005

Survival after Diagnosis



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The Fundamental Ethical Question in Clinical Trials

- The aim of a clinical trial is to develop generalizable knowledge by means of scientific investigation involving groups of patients
- The aim of medical care is to benefit particular patients
- Can these aims be reconciled with each other?

Joffe and Miller, Journal of Clinical Oncology 19:2987, 2006

Arguments about Ethics of Phase I Clinical Trials

- Purposes
  - Critics: limited to assessment of dose and toxicity
- Probability of benefit
  - Critics: no reasonable prospect of benefit
- Validity of consent
  - Critics: purposes are misconstrued, benefits are overestimated

Arguments about Ethics of Phase I Clinical Trials

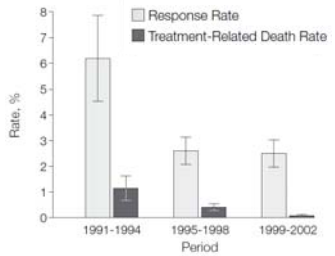
- Purposes
  - Critics: limited to assessment of dose and toxicity
  - Defenders: participants can benefit
- Probability of benefit
  - Critics: no reasonable prospect of benefit
  - Defenders: chances of benefits are small, but real
- Validity of consent
  - Critics: purposes are misconstrued, benefits are overestimated
  - Defenders: consent can be valid if participants are given information

Response Rates in Phase I Cancer Trials

	Author and Year of Publication	
Measure	**Decoster 1990**	**Estey 1986**
Number of agents evaluated	87	54
Number of patients	6639	6447
Agents with at least 1 response, %	61	65
Agents with >15% response, %	5	3
Agents with 10 – 15% response, %	6	9
Agents with 5 – 10% response, %	21	20
Agents with <5% response, %	30	30
Agents with no response, %	39	35

Risks and Benefits of Phase I Cancer Trials

- 6474 cancer patients
- 213 phase I clinical trials
- Results reported at ASCO Meeting 1991 – 2002



Roberts et al. JAMA 292:2130, 2004

Risks and Benefits of Phase I Cancer Trials

- 11,935 cancer patients
- 460 clinical trials sponsored by National Cancer Institute
- 1991 – 2002
- Four groups evaluated
  - Group 1: Single investigational agent
  - Group 2: Multiple investigational agents
  - Group 3: Combination of investigational and FDA-approved agents
  - Group 4: Only FDA-approve agents

Horstmann et al. New Engl J Med 352:895, 2005

Responses and Deaths in Phase I Cancer Trials

Group	Number of Trials	Percent of Patients	
		Responses	Deaths*
1	193	4.2	0.34
2	54	7.1	0.37
3	184	15.8	0.65
4	29	27.4	0.65

*possibly, probably or definitely related to treatment

Horstmann et al. New Engl J Med 352:895, 2005

Grade 4 Toxic Events in Phase I Cancer Trials

Group	Number of Trials	Patients with Grade 4 Toxic Event, %*	Average Number per Patient
1	20	15	1.6
2	3	4	2.0
3	17	45	1.8
4	3	34	2.4

*possibly, probably or definitely related to treatment

Horstmann et al. New Engl J Med 352:895, 2005

Grade 3 or 4 Toxic Events in Phase I Cancer Trials

Author and Year	Number of Trials	Number of Patients	Grade 3 or 4 Toxicity, %
Roberts, 2004	213	6474	10.3
Wheler, 2012	82	1181	10.3

Choices Facing End-Stage Cancer Patients

- Palliative care
  - Intended only to relieve or control symptoms
- Approved cancer treatments
  - Relieve or control symptoms
  - Decrease the burden of malignant cells
  - Possibly prolong survival
  - Usually exhausted when patients reach end stage
- "Off-label" treatment
  - Based on personal experience or preliminary published reports
  - Toxicities generally well understood
  - Benefits uncertain
- Phase I clinical trial
  - Based on preclinical testing
  - Toxicity uncertain
  - Benefits uncertain

Frustration for Physicians

- "Perhaps no reason for failure to accrue is more frustrating to the clinical investigator than the inability to enter an otherwise eligible patient because of denial of insurance coverage. Particularly galling is that the same insurance coverage would be unquestionably granted for similar (or in some cases, precisely the same) therapeutic and management plan, if only it were not on a clinical trial. Even more difficult to accept is that reimbursement is unquestionably granted for these agents, tests and procedures even if they are known to be ineffective, so long as the words 'clinical trial' are not utilized."

Edelman, Cancer Journal 10:288, 2004

Why Patients Do Not Participate in Clinical Trials

Perceived Reason	Patient (%)
Not aware of any appropriate trials	65
Current treatment is better or more effective	23
Did not meet the criteria to participate	19
Fear of possible side effects	14
Did not want to change doctors	11
Did not want to wait to begin treatment	11
Fear of getting placebo	10
Concern about insurance or coverage problems	10
Inconvenient location	6
Time commitment was too much	5
Out of pocket expenses were too high	5

Fenton et al. Community Oncology 6:207, 2009

Why Patients Do Not Participate in Clinical Trials

Perceived Reason	Patient (%)	Doctor (%)
Not aware of any appropriate trials	65	
Current treatment is better or more effective	23	27
Did not meet the criteria to participate	19	
Fear of possible side effects	14	61
Did not want to change doctors	11	
Did not want to wait to begin treatment	11	45
Fear of getting placebo	10	67
Concern about insurance or coverage problems	10	38
Inconvenient location	6	59
Time commitment was too much	5	34
Out of pocket expenses were too high	5	33
Patient too weak or too ill to participate		47

Actual Reasons for Not Enrolling in a Clinical Trial

- 263 lung cancer patients seen for initial consultation
  - 10 did not need treatment
- 253 with active disease
  - 26 already started treatment
- 227 not previously treated
  - 44 had no trial that matched diagnosis and stage of disease
- 183 had appropriate diagnosis and stage
  - 101 did not meet eligibility criteria
- 82 were eligible to participate in a trial
  - 57 did not enroll
- 25 enrolled (14%)

Baggstrom et al. J Thoracic Oncology 6:98, 2011

Actual Reasons for Not Enrolling in a Clinical Trial

Reason	Percent
Patient not eligible	55
Patient eligible but did not enroll	31
Refusal	9
Travel distance	7
Insurance problems	6
Compliance problems	1
Other or unknown	8

Baggstrom et al. J Thoracic Oncology 6:98, 2011

Medicare Coverage Determination for Clinical Trials

- Established in 2001
- Covers "routine costs" for items and services typically provided in the absence of a clinical trial
  - Administration of the investigational product
  - Clinically appropriate monitoring
  - Prevention of complications
  - Treatment of complications
- Items and services not included
  - Investigational item or service itself
  - Data collection and analysis not used in direct medical management
  - Anything inconsistent with widely accepted and established standards

Requirements for Qualification of Clinical Trials

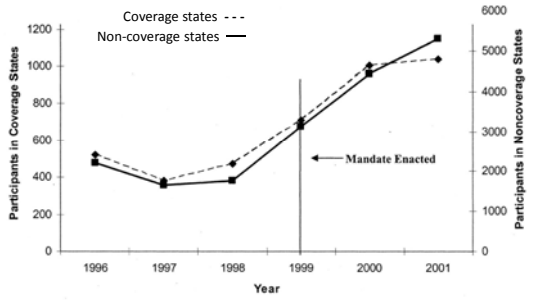
- Item or service
  - Must fall within a Medicare benefit category
  - Must have therapeutic intent
  - Must enroll patients with diagnosed disease
- Desirable characteristics
  - Intention to test effect on health outcomes
  - Supported by scientific or medical information
  - Does not unjustifiably duplicate existing trials
  - Design is appropriate to answer the question
  - Sponsored by a credible organization or individual
  - Compliance with Federal regulations for protection of human subjects
  - Conduct according to appropriate standards of scientific integrity
- Automatic qualification
  - Direct or indirect funding by Federal agencies
  - Conduct under an Investigational New Drug application

Effect of State Mandates on Enrollment in Trials

- Illinois, Louisiana, New Jersey, Virginia
- Mandates to reimburse for clinical trials mandated in 1999
- Analyzed enrollment in NCI-sponsored studies
  - Cancers of breast, colon or rectum, lung, prostate
  - Phase II
  - Phase III
- Results compared to 35 states with no mandate before 2002

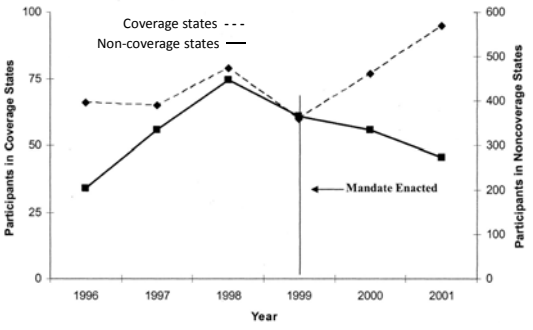
Gross et al., Journal of the National Cancer Institute 96:1063, 2004

Results—Phase III Trials



Gross et al., Journal of the National Cancer Institute 96:1063, 2004

Results—Phase II Trials



Gross et al., Journal of the National Cancer Institute 96:1063, 2004

Effect of State Mandate in California

	Number and Percent of Patients	
Step in process	**Before Mandate**	**After Mandate**
All patients	276 (100)	216 (100)
Considered for trial	171 (62)	119 (55)
Appropriate trial available	91 (33)	63 (29)
Patient eligible	76 (28)	52 (24)
Patient agreed	39 (14)	35 (16)

Martel et al. Cancer Journal 10:294, 2004

Washington State OIC Rule, Effective Nov 8, 2012

- Carrier must not restrict coverage of "routine costs"
  - Items and services consistent with and typically covered outside a clinical trial
- Limitations to use of network services may be applied
- Carrier may refuse coverage if the patient does not meet eligibility requirements of the trial
- Coverage includes prescription medications other than the investigational product itself
- Items and services not covered
  - Investigational item or service itself
  - Anything used only for data collection or analysis
  - Anything not used in direct medical management
  - Anything inconsistent with widely accepted and established standards

WA State OIC Definition of "Clinical Trial"

- Phase I, II, III, IV
- Prevention, detection or treatment of cancer or other life threatening disease or condition
- Funded or approved by
  - One of the National Institutes of Health
  - Cooperative group with NIH-approved peer-review program
  - Department of Defense or Veterans Affairs
  - An institutional review board with assurance approved by OHRP, or
  - A qualified research entity eligible for NIH Center Support Grant
- Definition of "life-threatening"
  - Any disease or condition from which the likelihood of death is probable unless the course of the disease or condition is interrupted

Premera Policy

- Life-threatening condition
- Therapeutic intent—not for diagnosis or supportive care
  - OIC rule allows "prevention" or "detection" trials
- Phase I, II, III or IV clinical trials
- Written research protocol
- Approved by institutional review board
- Approved by a national body
  - Not required by WA State OIC rule
- Signed informed consent in medical record
- Device or drug must have final approval or be allowed for investigation by FDA

Patient Protection and Affordable Care Act—March 2010

- Carrier may not deny participation in a clinical trial
  - Also applies to out-of-state, in-network participation
  - Applies to out-of-network participation if the plan provides out-of-network benefits
- Carrier may not deny coverage for routine costs in a trial
  - Routine costs defined as in Medicare and OIC rule
  - Exclusions defined as in Medicare and OIC rule
- Carrier may not discriminate against patients in a clinical trial
- Qualified patient
  - Eligible to participate in an approved trial
- Definition of approved clinical trials
  - Phase I, II, III or IV, in relation to prevention, detection or treatment of cancer or other life-threatening disease or condition, defined as in OIC rule
  - Direct or indirect Federal funding, or
  - Conduct under investigational new drug application, or
  - Exempt from investigational new drug application

Testing Done in Phase I and Phase II Cancer Trials

- 49 Phase I trials
- 41 Phase II trials

	Average Number of Tests During First 4 Weeks	
Test	**Phase I**	**Phase II**
Physical exam	3.2	2.2
Vital signs	5.6	2.8
Electrocardiogram	4.4	0.8
Laboratory tests	18	10
Measurement of drug level	15	1.0

Craft et al: Cancer 115:1592, 2009

Effect of Clinical Trials on Costs of Care—Methods

- 83 Institutions
  - 34 academic medical centers
  - 24 oncology practices
  - 25 other types of practice
- Observation period: October 1, 1998 to December 31, 1999
- 932 patients enrolled in an NCI-sponsored trial
  - 777 in phase III trials
  - 155 in phase I and phase II trial
- 696 patients not enrolled in a clinical trial
- Costs estimated by applying prices to to utilization data
- Follow-up for an average of 2.5 years

Goldman, JAMA 289:2975, 2003

Effect of Clinical Trials on Costs of Care—Results

Patient Group	Treatment Costs, $		Percent Difference
	Participants	Nonparticipants	
ALL	35,418	33,248	6.5
Phase of trial			
III	32,686	31,569	3.5
I and II	40,898	36,679	12.8
Institution type			
Academic	38,449	35,693	7.7
Other	32,766	31,108	5.3
Vital status			
Alive	34,369	33,199	3.5
Dead	39,420	33,432	17.9

Goldman, JAMA 289:2975, 2003

Reasons for Differences—All Patients

Service	Average Use		P Value
	Participants	Nonparticipants	
Hospital days	7.4	8.2	.27
Intensive care unit days	0.61	0.66	.84
Ancillary services	22.0	17.9	<.001
Expensive diagnostics	4.6	3.6	<.01
Pathology reports	7.6	6.3	.02
Laboratory tests	48.5	39.7	.10

Goldman, JAMA 289:2975, 2003

Reasons for Differences—Deceased Patients

Service	Average Use		P Value
	Participants	Nonparticipants	
Hospital days	17.9	17.4	.86
Intensive care unit days	1.5	1.9	.80
Ancillary services	13.1	7.0	<.01
Expensive diagnostics	5.1	3.5	<.01
Pathology reports	6.8	4.2	.01
Laboratory tests	66.7	54.5	.24

Goldman, JAMA 289:2975, 2003

Conclusions of Cost Analysis

- 19,000 patients enrolled in NCI sponsored studies in 1999
- Estimated direct treatment cost: $268 million
- Estimated cost if not enrolled: $252 million
- Difference: $16 million
- Only 3% of adult cancer patients participate in NCI-sponsored studies
- Total expenditure for cancer treatment: $8.4 billion

Goldman, JAMA 289:2975, 2003

Questions for Insurance Carriers and Medical Providers

- In clinical trials, how do we determine
  - Which services are medically necessary and appropriate?
  - Which services are provided only for data collection and analysis?
  - What is the "standard of care" outside a clinical trial?
    - "What I usually do"
    - NCCN guidelines or other published standards
- Examples
  - Repeated EKG tests to assess QTc abnormalities in a phase I trial
  - Repeated imaging tests to assess certain cancer endpoints
    - Duration of response in patients with response
    - Disease-free survival in patients with complete response
    - Time to progression of cancer in all patients
    - Progression-free survival in all patients

One Possible Direction for the Future

- "Trench warfare" between two armies
  - On one side: Patient financial services representatives
  - On the other side: Case managers
  - Patient-specific pre-authorization requests and negotiations for each questioned service or item in the clinical trial document

A Better Direction for the Future

- Negotiation and agreement between clinical trial sponsors and a national board of insurance carrier representatives
  - During the design phase of each clinical trial
  - Use of widely accepted published clinical guidelines and standards to determine which items are medically necessary and appropriate
- Elements in the "treaty"
  - A calendar of trial-associated activities charged to insurance
  - A calendar of trial-associated activities charged to the sponsor
- Advantages
  - Takes medical providers and case managers out of the discussion
  - Much improved efficiency for everyone
  - Much less waste and needless friction for everyone

Conclusions

- Clinical trials are the treatment of tomorrow given today
- Ethical principles for clinical trials have been established
- Limitations in eligibility criteria create the largest barriers to participation in cancer clinical trials
- Insurance carriers can no longer exclude patients from participation in clinical trials for cancer
- New insurance rules will not greatly increase enrollment in cancer clinical trials or costs of coverage
- A new approach is needed for adjudicating the allocation of costs in clinical trials