The hijacking of clinical trials

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Center for Clinical Trials seminar

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The hijacking of clinical trials

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The prevailing research "culture"

- One roof model
- Institutional Review Board
- Principal investigator
- Grant funding
- Fierce independence
- Unfettered rights to data and to prerogative of publication

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Propelling historical forces

- Post WWII prosperity
- NIH
- Kefauver-Harris Act of 1962
- Push for evidence-based medicine
- The "multicenter age"

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NLM full length publications*

	CTs	All pubs	% CTs
1970-75	11,997	818,507	1.5
1976-80	14,891	830,085	1.8
1981-85	22,438	1,001,099	2.2
1986-90	36,417	1,228,224	3.0
1991-95	62,474	1,404,737	4.4
1996-00	93,773	1,616,501	5.8
2001	19,052	366,687	5.2
2002	19,352	376,212	5.1
2003	20,670	395,277	5.2
Total	**301,064**	**8,037,329**	**3.7**

* Full length English publications; limited to "humans"; courtesy of Ann Ervin

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Factors in the hijacking of trials

- The creation of a cowed investigatorship
- Multicenter trials
- The government as an initiator of trials
- The $500,000 limit on grant submissions
- Mandatory data deposit
- Congress
- Apartheid monitoring structures
- The "cooperative" mode of funding
- IRBs and ethicists

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The 64 million dollar question

Name a branch of science where those who design and carry out the study cannot be trusted to see the data they generate?

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Factors in the marginalization of the clinical investigator

- Brow beating re conflict of interest
- Naivety
- Love of money
- Randomization and masking
- Shielding

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Forces driving multicenter trials

- Public health significance of small benefits for large numbers of people
- Gaps in the FDA criteria for drug approval
- Ethics of underpowered trials
- Globalization

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The era of multicenter trials

- Streptomycin TB trial (1947 - 48; UK Medical Research Council)
- UGDP: University Group Diabetes Program (1960 - 75; investigator-initiated; grant supported)
- CDP: Coronary Drug Project (1965 - 75; investigator-initiated; grant supported; quasi cooperative agreement)
- MRFIT: Multiple Risk Factor Intervention Trial (1973 - 82; NHLBI initiated; contract funding)

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Multicenter trials* by time

	All CTs	MC CTs	%
1986 - 90	35,417	3,237	9.1
1991 - 95	62,474	7,974	12.8
1996 - 00	93,773	11,655	12.4
2001	19,052	2,585	13.6
2002	19,352	2,598	13.4
2003	20,670	3,048	14.7

* Counts from NLM database restricted to "human", full length articles, English publications; publication type: "clinical trial"

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NIH: The 500 pound gorillas

- Assumes an ever increasingly role in the initiation of trials
- Feels increasingly obliged to control funding via contracts and cooperative agreements
- Increasing use of RFAs and RFPs to initiate trials
- Ever more demanding with regard to control of the treatment effects monitoring process

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Congress at the design table

The perception that trials have favored men and their diseases and conditions caused Congress to require that the Director of the NIH ensure (for trials involving diseases or conditions common to men and women) that trials funded by the NIH be

> *designed and carried out in a manner sufficient to provide for a valid analysis of whether the variables being studied in the trial affect women or members of minority groups, as the case may be, differently than other subjects in the trial.* (NIH Revitalization Act of 1993)

Interpreted by the NIH to pertain to phase III and IV trials

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The $500,000 limit

History

Originated from NCI; announced in NIH Guide, Vol 22, no. 43, 26 Nov 1993; effective on announcement (revised 17 Dec 1993, vol 22, no 45)

NIH-wide effective 1 June 1996; announced in NIH Guide 3 May 1996, vol 25, no 14 (revisions announced 20 March 1998 and 16 October 2001)

16 October 2001 announcement

The National Institutes of Health (NIH) is updating its policy on the acceptance of applications requesting direct costs of $500,000 or more for any one year. Effective with the January 1, 2002 receipt dates, applicants must seek agreement to accept assignment from Institute/Center staff at least 6 weeks prior to the anticipated submission of any application requesting $500,000 or more in direct costs for any year.

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HIH data sharing requirements

"Starting with the October 1, 2003 receipt date, investigators submitting an NIH application seeking $500,000 or more in direct costs in any single year are expected to include a plan for data sharing or state why data sharing is not possible."

"As noted earlier, NIH recognizes that the investigators who collect the data have a legitimate interest in benefiting from their investment of time and effort. We have therefore revised our definition of "the timely release and sharing" to be no later than the acceptance for publication of the main findings from the final data set. NIH continues to expect that the initial investigators may benefit from first and continuing use but not from prolonged exclusive use."

Final NIH statement on sharing research data (26 Feb 2003)
(http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html)

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NIH cooperative agreement (U01 and U10)

NIH grant funding under the terms and conditions of a cooperative agreement

A financial assistance mechanism used when substantial Federal programmatic involvement with the recipient during performance is anticipated by the NIH Institute or Center
(http://grants1.nih.gov/grants/glossary.htm#C (general definition)

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Cooperative agreement

NIH GUIDE, Volume 23, Number 15, April 15, 1994

The National Institute of Allergy and Infectious Diseases (NIAID) announces that any new or competing continuation investigator-initiated clinical trial, prevention, education, or control intervention, or epidemiological study in which direct costs exceed $500,000 in any year will usually be awarded as a cooperative agreement (U01).

The $500,000 direct costs limit applies when either (1) a study is to be conducted at one institution or (2) a study proposing multi-institutional collaborative arrangements is submitted as either subcontracts to a single application or as separate applications. For single applications, the dollar limit excludes indirect costs of any subcontracts that are reported as a direct cost on the application budget page summary. Separate U01 awards usually will be made for individual applications submitted concurrently by institutions proposing a study involving a coordinated research effort.

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Cooperative agreement

Observations

- Often imposed as a condition of funding
- Terms and conditions spelled out in award
- Subject to fairly wide variation as to role of funding agency
- An almost certain point of contention will be in regard to treatment effects monitoring

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Initiation type and funding type for CCT trials

	Initiation type	Funding type
HPT	Inv	Grant RO1
GLT	Inv	Grant RO1
SOCA	RFA	Grant U10
IHDP	Inv	Grant
CAMP	RFP	Contract
NETT	RFP	Contract
CBET[1]	RFP	Contract
WGET[1]	RFP	Contract
ACRC	RFA	Contract
ADAPT[2]	Inv	Grant U10
NASH	RFA	Grant U10
DIADS-2[2]	Inv	Grant U10
MUST[2]	Inv	Grant U10
PVAT	Spon	Contract

[1] Investigator initiated converted to RFP
[2] Investigator initiated converted to cooperative agreement when funded

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IRBs and multicenter trials

- Archaic (designed assuming the "one roof" model for research as conveyed in name *institutional* review board)
- Largely nonfunctional (all IRBs are created equal; byzantine in multicenter trials)
- Hopelessly duplicative in some regards and hopelessly deficient in other regards
- AE system of reporting largely useless, especially in long-term treatment and prevention trials
- "Protections" demanded often not in subjects' best interests if not downright dangerous (eg, as in desire to severe linkage on completion of trial)
- Contributes to marginalization of investigators

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Alzheimer Disease Anti-inflammatory Prevention Trial (ADAPT)

1st submission
Study population: Cache County Utah cohort
Sample size: 3,100
Treatments: Ibuprofen and matching placebo
5 yr budget: $10,486,428
Submitted: 30 May 1997
Priority score: Disapproved

2nd submission
Study population: Cache County Utah cohort
Sample size: 2,800
Treatments: Ibuprofen and matching placebo
5 yr budget: $14,087,522
Submitted: 13 February 1998
Priority score: Approved but unfundable priority score

3rd submission
Study population: 4 clinics (Bal, Bos, Roc, Logan)
Sample size: 2,625
Treatments: Ibuprofen, celecoxib and matching placebos
5 yr budget: $25,121,319
Submitted: 1 March 1999
Priority score: Approved for funding

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Investigator initiation

Funding
Funded: 1 March 2000
Period of award: 5 yrs
Award amount (5 yr total): $25 million

Actual trial
Study population: 6 clinics (Bal, Bos, Roc, Sun City, Tampa, Seattle)
Sample size: 2,625
Treatments: Celecoxib, naproxen, and matching placebos

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Forces leading to removal of investigators from monitoring

- "Paternalism"
- Concerns regarding treatment-related feedback bias
- Worries about spilling the beans
- Appearances

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Marginalizing dogma re monitoring

- Separation/independence
- Masking
- Firewalls
- Stopping rules
- Decisional authority

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Points of contention

- Vetting and appointing authority
- Standing of nonvoting members
- Rules
- Responsibility and authority
- Route of communications
- Recommending or decisional

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Investigators of the world rise up and show your independence!
