Effect of a US National Institutes of Health programme of clinical trials on public health and costs

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Summary

Background Few attempts have been made to estimate the public return on investment in medical research. The total costs and benefits to society of a clinical trial, the final step in testing an intervention, can be estimated by evaluating the effect of trial results on medical care and health.

Methods All phase III randomised trials funded by the US National Institute of Neurological Disorders and Stroke before Jan 1, 2000, were included. Pertinent publications on use, cost to society, and health effects for each studied intervention were identified by systematic review, supplemented with data from other public and proprietary sources. Regardless of whether a trial was positive or negative, information on use of tested therapies was integrated with published per-use data on costs and health effect (converted to 2004 US$) to generate 10-year projections for the US population.

Findings 28 trials with a total cost of $335 million were included. Six trials (21%) resulted in measurable improvements in health, and four (14%) resulted in cost savings to society. At 10 years, the programme of trials resulted in an estimated additional 470 000 quality-adjusted life years at a total cost of $3·6 billion (including costs of all trials and additional health-care and other expenditures). Valuing a quality-adjusted life year at per-head gross domestic product, the projected net benefit to society at 10-years was $15·2 billion. 95% CIs did not include a net loss at 10 years.

Implications For this institute, the public return on investment in clinical trials has been substantial. Although results led to increases in health-care expenditures, health gains were large and valuable.

Introduction

The mission of the National Institutes of Health (NIH) in the USA is "…to uncover new knowledge that will lead to better health for everyone".[1] The final step in developing interventions that improve health is testing in clinical trials. The NIH has been a major sponsor of clinical trials, with an investment of US$2·9 billion in 2004, over 10% of the NIH budget.[2,3]

Examples of exciting basic discoveries and reductions in disease burden are often cited as evidence that government investment in medical research is worthwhile.[4,5] However, funding levels are vigorously debated and vary from year to year.[4,6] Some critics have pointed to the perceived failure of a recent doubling in the NIH budget to result in an increase in the rate of development of novel therapies.[7] Few attempts have been made to systematically evaluate the effect of medical research on the public, and no methodological standards have been agreed on.[8–11] One review concluded that five selected proven interventions alone justified the entire US health-care expenditure[12] and, thus, would justify the research needed to produce them. Most proven interventions that gain wide use in medicine have a greater return to society than their costs, on the basis of accepted valuations of health improvements, as shown in systematic cost-utility and economic analyses.[13] However, analyses have not generally included the costs of the underlying research. The effect of a public programme of research on medical care, public health,

and health-care costs has not been systematically studied.

Clinical trials that affect health care alter rates of use of the studied treatment. The effect of clinical trials on health and costs can be estimated by combining information on changes in rates of use with effect on health and costs for each use, derived from specific cost-utility or economic analyses. We analysed the effect of trials for one of the NIH institutes, the National Institute of Neurological Disorders and Stroke (NINDS), on the basis of a systematic review of publications and by creating a model for the effect of its entire programme of trials in which funding was completed before the end of 1999.

Methods

Data sources

NINDS provided a complete listing of its funded phase III clinical trials and their costs. We included all randomised trials with funding for the primary trial completed before Jan 1, 2000; more recent trials were excluded because information on implementation of the findings would be limited in time and accurate projections of use would not be possible.

To estimate the effect of a trial, we gathered data on use of each tested intervention and estimates of the effect of the intervention on health and costs with standard methods of systematic review.[14] Cost-utility analyses generally provide an estimate of the net cost and net

health benefits (measured as quality-adjusted life years, a unit equivalent to an additional year of healthy life) to society for each use of an intervention, so these publications were preferred over other published analyses of per-use effect.

Systematic keyword and author searches of PubMed and Biosis were done to identify the primary publication of the trial results (keywords derived from the grant title with principal investigator as an author; grant number was also searched). We used previously validated, highly sensitive search strategies to identify publications of pertinent cost and cost-utility analyses and usage of the tested medication or procedure before and after trial publication.[15] For cost analyses, we searched the tested intervention as a keyword combined with other keywords (cost, utility, or QALY) or Medical Subject Heading terms (cost-benefit analysis, costs and cost analysis, economics, or quality-adjusted life years). For usage data, we searched the intervention as a keyword combined with additional keywords (use, usage, rate, or trend) or with the Medical Subject Heading term utilization. We contacted the principal investigator when the primary publication could not be readily identified, and reviewed all references that cited the primary publication, which were identified from a search of the Web of Science. We also asked principal investigators to identify information on cost, health effects, or usage, when this was not identified in the primary searches.

When several publications on either cost or health implications of an intervention were identified, articles were reviewed independently by three physician clinical researchers, who were asked to select the most pertinent reference on the basis of three criteria: the analysis reflected the US economy and health-care system; standard measures and methods were used to assess effect on health (such as, willingness to pay or quality-adjusted life years); and the analysis took the perspective of society (that is, it included all costs of treatment and its consequences, including costs of side-effects, patients' lost wages, and health-system implementation, irrespective of the payer). Reviewers were also asked to abstract from each selected publication the best estimate of cost and health implications, which was considered to most accurately represent the target population of the trial, discounted (preferably by 3%) to take into account the lower value generally placed on costs and benefits that occur later in time.[13] Publications about use were reviewed similarly, using the criteria: the estimate of use was reported specifically for the intervention tested in the trial; and the publication reflected use in the USA. Since information on use before and after the trial was required, more than one publication could be identified. When no one study met all criteria, the reviewers were asked to identify the one closest to meeting these criteria. If at least two of the three primary reviewers did not agree on a publication or an abstracted value, a fourth physician reviewer chose between those previously identified.
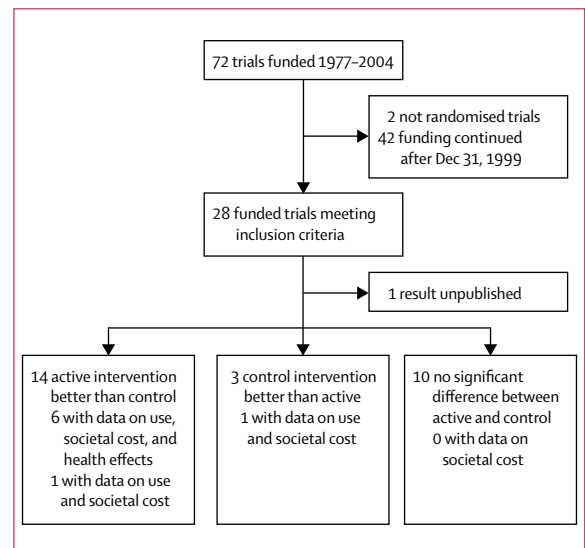
Figure 1: **Selection of randomised trials included in analysis**

When cost or use data were not identified from publications, we contacted organisations that pooled sales data (such as IMS Health), manufacturers (such as the makers of rectal diazepam), or disease-based nonprofit organisations (such as the National Multiple Sclerosis Society). When no report of the effect of trial results on costs of health care or on quality of life was available, the intervention was judged not to have affected health or costs. We made similar judgments for interventions for which data on use were unavailable. Costs of these trials were included in the model but no other effect was modelled. We assumed that trial findings were correct and that results were applied appropriately; thus, inclusion of the costs, but no estimate of benefit, of these trials would tend to underestimate the effect of the programme, although a negative net benefit of some of these trials cannot be ruled out.

Analytical model

We estimated that trials have an effect on society solely through its direct consequences for clinical practice, measurable as a change in use of the tested medical or surgical intervention. With this assumption, effect on society is measurable as the cost and health benefits associated with each use of an intervention (derived from published cost-utility and other economic models) multiplied by the additional uses prompted by trial results. This is a conservative assumption, since a trial could also affect use of similar interventions, could alter understanding of disease processes, or might have laid groundwork for development of other interventions.

We developed a health economic model designed to estimate US aggregate treatment costs/savings and effect on public health, measured in quality-adjusted life years or costs to society (defined as total related net expenditures, including health-care and productivity

costs, irrespective of the payer). We assumed that the true costs of a trial were shown by NINDS expenditures assigned to the trial.

Yearly use of proven treatments was projected to the US population for 10 years and 30 years, beginning in the first year after completion of funding (or after publication of primary trial results, whichever was first). Estimates were based on adjudicated publications or other sources. Rates of use were interpolated linearly between these estimates and were assumed not to change after the most recent estimate (since rates of use could have gone up or down after the last known rate). Population size and distribution was assumed to be constant after 2004. Total use at 10 years and 30 years was calculated by summing yearly rates. Yearly net costs and benefits were calculated by multiplying discounted per-use estimates from published work by net changes in use of the studied treatment before and after trial publication. For example, if an intervention was associated with a net cost of $1000 and a net gain of one quality-adjusted life year per use based on a published cost-utility analysis, and use data indicated that an

|	Reference	Active intervention	Control intervention	Target population	Superior intervention	Cost of trial
Randomized Indomethacin Germinal Matrix/Intraventricular hemorrhage Prevention Trial	20	Indomethacin	Placebo	Very low birthweight neonates	Active	$8 875 272
Diazepam for acute repetitive seizures	21	Diazepam rectal gel	Placebo	Acute repetitive seizure	Active	$1 563 303
Recombinant Beta Interferon as treatment for multiple sclerosis	22	Interferon beta-1a	Placebo	Relapsing-remitting multiple sclerosis	Active	$7 771 364
Asymptomatic Carotid Artery Stenosis Collaborative Study	23	Carotid endarterectomy	Medical therapy	Asymptomatic internal carotid artery stenosis	Active	$43 320 428
Stroke Prevention In Atrial Fibrillation I	24	Warfarin or aspirin	Placebo	Atrial fibrillation	Active	$16 093 548
Remacemide Inpatient Seizure Evaluation Trial	25	Remacemide	Placebo	Refractory epilepsy	Active	$1 115 095
North American Symptomatic Carotid Endarterectomy Trial	26	Carotid endarterectomy	Medical therapy	Symptomatic internal carotid artery stenosis	Active	$64 033 234
Tissue plasminogen activator in ischemic stroke	27	Tissue plasminogen activator	Placebo	Acute ischaemic stroke	Active	$18 774 365
Dilantin for seizure prophylaxis after brain trauma	28	Phenytoin	Placebo	Post-traumatic seizures	Active	$2 278 078
National Acute Spinal Cord Injury Study II	29	Methylprednisolone	Placebo	Acute spinal cord injury	Active	$6 330 642
National Acute Spinal Cord Injury Study III	30	Long-duration methylprednisolone	Short-duration methylprednisolone	Acute spinal cord injury	Active	$12 639 013
Deprenyl/Tocopherol in Parkinson Disease (DATATOP)	31	Tocopherol/deprenyl	Placebo	Early Parkinson's disease	Active	$34 015 598
Pallidotomy in Parkinson's disease	32	Unilateral pallidotomy	Medical therapy	Parkinson's disease	Active	$3 007 431
Nicotine/haloperidol therapy in Tourette syndrome	33	Transdermal nicotine	Placebo	Tourette's disorder	Active	$722 105
Aspirin and carotid endarterectomy	34	High-dose aspirin	Low-dose aspirin	Patients undergoing carotid endarterectomy	Control	$3 920 504
Stroke prevention In atrial fibrillation III	35	Low-dose warfarin+aspirin	Standard warfarin	Atrial fibrillation	Control	$18 695 305
Extracranial/Intracranial Arterial Anastomosis Study	36	Superficial temporal-middle cerebral artery bypass	Medical therapy	Ischaemic stroke or transient ischaemic attack	Control	$29 198 826
Valproate for seizure prophylaxis after brain trauma	37	Valproate	Phenytoin	Post-traumatic seizures	No difference	$5 475 726
Brain Resuscitation Clinical Trial I	38	Thiopental	Placebo	Cardiac arrest survivors	No difference	$3 783 150
Brain Resuscitation Clinical Trial II	39	Lidoflazine	Placebo	Comatose survivors of cardiac arrest	No difference	$5 296 353
Brain Resuscitation Clinical Trial III	40	High-dose epinephrine	Low-dose epinephrine	Cardiopulmonary resuscitation	No difference	$5 753 116
Randomised study of nicardipine SAH	41	High-dose nicardipine	Low-dose nicardipine	Aneurysmal subarachnoid haemorrhage	No difference	$9 793 659
Randomised trial Of Org-10172 in acute ischemic stroke	42	Danaparoid	Placebo	Acute ischaemic stroke	No difference	$15 023 629
Randomised trial of Tirilazad in acute stroke patients	43	Tirilazad mesylate	Placebo	Acute ischaemic stroke	No difference	$1 674 068
Stroke prevention in atrial fibrillation II	44	Warfarin	Aspirin	Atrial fibrillation	No difference	$7 941 150
National Acute Spinal Cord Injury Study I	45	High-dose methylprednisolone	Low-dose methylprednisolone	Acute spinal cord injury	No difference	$3 105 611
Conventional vs percutaneous discectomy—a clinical trial	46	Percutaneous discectomy	Conventional discectomy	Lumbar disc herniation	No difference	$3 559 807
Felbamate Concentration Response Trial	Not published	..	..	..	..	$1 363 384
Total	..	..	..	..	..	$335 123 767

Trial costs inflated to 2004 US$ on basis of medical services component of Consumer Price Index.[19]

Table 1: **Characteristics of clinical trials meeting inclusion criteria**

	Reference		
	Use	Quality of life	Societal cost
Randomized Indomethacin Germinal Matrix/Intraventricular Hemorrhage Prevention Trial	47*	48	48
Diazepam for acute repetitive seizures	49†	NA	50
Recombinant beta interferon as treatment for multiple sclerosis	51	52,53‡	52
Asymptomatic Carotid Artery Stenosis Collaborative Study	54–56*	57	57
Stroke prevention in atrial fibrillation I	58–61	62	62
North American Symptomatic Carotid Endarterectomy Trial	55,56,63	64	64
Tissue plasminogen activator in Ischaemic stroke	65,66	67	67
Extracranial/Intracranial Arterial Anastomosis Study	§	NA	68

NA=not available. *And US Centers for Disease Control and Prevention. CDC wonder web site. http://wonder.cdc.gov (accessed Oct 14, 2005). † And Martella D, Xcel-Pharmaceuticals, personal communication (April, 2005). ‡And Prosser LA, Harvard Medical School, personal communication (August, 2005). §And Barnett H, Robarts Research Institute, personal communication (March, 2005).

Table 2: **Model input data sources for clinical trials with available information on societal costs and benefits**
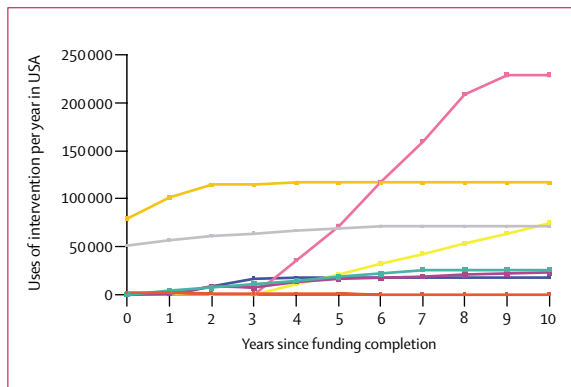
Figure 2: **Use of tested interventions in the USA for the eight trials with adequate data**
Year 0 corresponds to final year of trial funding. Interventions: diazepam for acute repetitive seizures (pink), endarterectomy for asymptomatic (orange) and symptomatic (grey) carotid stenosis, beta interferon-1a for multiple sclerosis (yellow), tissue plasminogen activator for ischaemic stroke (green), anticoagulation for atrial fibrillation (purple), prophylactic indomethacin for premature neonates (blue), and extracranial-intracranial bypass surgery for carotid occlusion (red). See table 2 for references.

additional 1000 procedures were done in the 10 years after the trial, the 10-year effect for this intervention would have been estimated as a $1 000 000 cost and a gain of 1000 quality-adjusted life years.

In some instances, use of an intervention could have been affected by results from more than one clinical trial. When other trials of similar interventions and populations were published within 2 years of the trial sponsored by the NINDS, the effect of the NINDS-sponsored trial was reduced: health costs and benefits were multiplied by the proportion of patients in all the trials enrolled in the NINDS-sponsored trial (that is, the number in the NINDS-sponsored trial divided by the total number studied in trials).

Total incremental net benefits of the programme were calculated at yearly time points after funding completion by combining trial costs and treatment costs with a

monetary value for a quality-adjusted life year, derived by valuing a quality-adjusted life year at per-head US gross domestic product ($40 310),[16] which estimates the average yearly economic productivity of a US resident, regardless of employment or age; such a standard has been recommended by the World Bank.[17] Although debated, this calculation probably gives a low estimate of the value of a quality-adjusted life year, judging by economic studies and taking into account the willingness of society to pay more for interventions that produce an additional year of healthy life.[13] However, expenditures on interventions that cost more than the gross domestic project per quality-adjusted life year would generally be expected to produce a net economic burden.[18]

All costs and benefits were converted to 2004 US$ with the Medical-U portion of the Consumer Price Index.[19] Overall societal effect for the programme of trials was estimated as the incremental net benefit: total net health benefit in quality-adjusted life years multiplied by gross domestic project, minus the increase in total costs related to the tested interventions minus the total cost of the programme of trials.

Bootstrap 95% CIs were calculated at the 10-year event horizon. 10 000 samples of 28 trials were sampled with replacement from the listing of included trials, and estimates of costs, health benefits, incremental cost-effectiveness ratios, and net incremental benefits were calculated with the R Software Package (version 2.2.0, Comprehensive R Archive Network, Vienna), and the 5th and 95th percentile outputs were identified with Stata (version 7.0, College Station, TX, USA).

Role of the funding source
The study was prompted by a request from the National Advisory Council for NINDS. Study design, data analysis, and preparation of the final version of the manuscript were independent of the sponsor. Staff of NINDS provided information on trial names, principal investigators, and costs, reviewed the initial study plan, and reviewed a draft of the manuscript. A panel of three health-policy experts independently reviewed the analysis plan, actual model, and final manuscript.

Results
Between the years 1977 and 2007, NINDS committed funding to 72 clinical trials at a combined cost of $959 million (figure 1). Of these, 28 were randomised phase III trials with funding completed before Jan 1, 2000 (table 1).[20–46] The costs of all 28 trials meeting inclusion criteria ($335 million) were included in the analysis. Trial costs ranged from $722 000 for a small trial of the effects of nicotine on Tourette's syndrome[33] to $64 million for the North American Symptomatic Carotid Endarterectomy Trial.[26]

The effects of a trial could be assessed if information on use and the intervention's effect on total costs and savings or quality of life were available; such information

was available for eight trials (table 2).[47–68] For the others, no information was available about cost to society or quality of life. Data for use of interventions were derived from publications for seven of the eight included trials and solely from an aggregator of US sales data for one (table 2). For four of the interventions, at least one other similar trial was published with 2 years of the NINDS-sponsored trial, and rates of use were reduced to reflect the proportion of patients in the NINDS-sponsored trial among all studied individuals (weighting for rectal diazepam for seizures, 44%; warfarin for atrial fibrillation, 48%; endarterectomy for symptomatic carotid artery stenosis, 46%; endarterectomy for asymptomatic carotid stenosis, 79%).[69–73]

All the included economic and health analyses took the perspective of society and discounted future effects on costs and health benefits, generally by 3–5%. All estimated the effect of an intervention, as evaluated in the clinical trial, applied to a typical patient or population and, thus, estimated the effect on society of each appropriate use of the intervention.

Use of tested treatments increased in seven of eight trials (figure 2), with rates reaching plateau an average of 7·1 years (range 3–11 years) after completion of trial funding. Rates of external-to-internal carotid artery bypass surgery for carotid artery occlusion decreased after publication of the negative trial results.

Data for intervention use were integrated with per-use estimates of effect on costs and health derived from published health economic analyses (table 3). Six trials had demonstrable benefits on health, with projected gains in quality-adjusted life years ranging from 4038 to 146 837 in the 10 years after funding was completed (table 3). Four trials were associated with a reduction in costs to society, whereas four increased costs. With quality-adjusted life years valued at per-head gross domestic product[16] and including the costs of the trial, six of the eight trials resulted in a net increase in value to

society at 10 years, ranging from $0·3 billion to $6·5 billion (figure 3). The net costs of recombinant interferon beta for multiple sclerosis[22] and of carotid endarterectomy for asymptomatic carotid stenosis[23] exceeded the economic benefit to health.

Overall, the entire programme of trials cost $335 million. Assuming conservatively that trials in which data on effect were unavailable had no direct implications for health, the effect on society would be shown by projections from the eight trials with adequate data (table 3). Thus, the programme of trials had a 10-year projected benefit of 470 339 quality-adjusted life years (95% bootstrap CI 96 875–916 968) at an additional cost of $3·3 billion (95% CI savings of $3·8 billion to cost of $13·5 billion). Including the cost of all the trials, this programme resulted in a net cost per quality-adjusted life year (incremental cost-effectiveness ratio) of $7713 (95% CI savings with health benefit to cost of $36 585), a cost for an additional healthy year of life that would widely be considered cost-effective, well below per-head gross domestic product. The overall incremental net benefit of the programme at 10 years was a projected gain of $15·5 billion ($0·67 billion to $34·49 billion). The 10-year return on investment was 4600% (200–11 300%).

Investment in the programme of trials was returned through health benefits within 1·2 years of completion of trial funding (figure 3). In sensitivity analysis, the programme of trials produced a net gain ($3·00 billion) at 10 years even when the two most beneficial trials were removed from the analysis. In the primary analysis, we assumed that rates of use before trial publication would have continued unchanged if the trial had not been done. In a sensitivity analysis, we altered this assumption to project rates of use based on their change before trial publication and used this to estimate the effect of trial results on use; overall model results were essentially unchanged ($15·7 billion net benefit).

	Quality-adjusted life years per use	Societal cost per use ($)	10-year projections			
			Total net uses	Quality-adjusted life years	Treatment costs ($)	Incremental net benefits ($)
Randomized Indomethacin Germinal Matrix/Intraventricular Hemorrhage Prevention Trial	1·00	–632	146 837	146 837	–92 857 340	6 003 009 978
Diazepam for acute repetitive seizures	NA	849	1 050 776		–891 839 458	890 276 155
Recombinant beta Interferon as treatment for multiple sclerosis	0·014	3213	297 256	4038	955 140 007	–800 131 189
Asymptomatic Carotid Artery Stenosis Collaborative Study	0·25	11 552	371 282	92 820	4 288 862 203	–590 564 802
Stroke prevention in atrial fibrillation I	0·24	984	147 736	35 457	145 402 116	1 267 774 453
North American Symptomatic Carotid Endarterectomy Trial	0·35	1819	163 669	57 120	297 716 385	1 940 786 211
Tissue plasminogen activator in ischaemic stroke	0·75	–6074	178 517	134 066	–1 084 314 904	6 469 781 905
Extracranial/Intracranial Arterial Anastomosis Study	NA	30 998	–10 500	..	–325 476 690	296 277 864
Total	..	..	..	470 339	3 292 632 319	15 477 210 576

NA=not available. Incremental net benefits include cost of trial, treatment costs, and quality-adjusted life years valued at 2004 per capita gross domestic product ($40 310). Products of per-use and net-use data vary slighted from 10-year projections because of rounding. See table 2 for references.

Table 3: Per-use estimates and 10-year projections of effect of clinical trials with available information on societal costs and benefits
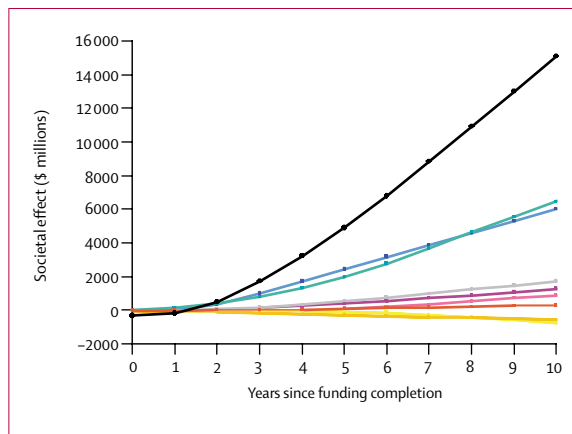
Figure 3: Societal effect of trials
Data shown by year after funding completion of clinical trial programme (black line) and by individual trials with adequate data: tissue plasminogen activator for ischaemic stroke (green), prophylactic indomethacin for premature neonates (blue), endarterectomy for symptomatic carotid stenosis (grey), anticoagulation for atrial fibrillation (purple), diazepam for acute repetitive seizures (pink), extracranial-intracranial bypass surgery for carotid occlusion (red), endarterectomy for asymptomatic carotid stenosis (orange), and beta interferon-1a for multiple sclerosis (yellow). See table 2 for references.

Discussion

The NINDS programme of randomised trials has generated major health benefits. Although the trials have led to increased expenditures on health, the resultant health benefits have a much greater value than these costs, even when valued conservatively, with an overall net benefit of the programme of $15·2 billion at 10 years. The yearly return on investment was 46%, which outpaces by nearly fourfold the expected return if these same resources were invested in the stock market, as indicated by average returns on the S&P 500 during the period of study. Thus, the investment in clinical trials seems to be well justified.

Our estimate of benefit probably underestimates the true benefit for several reasons. First, information on effect was available for only eight of 17 trials that showed one intervention was better than another. Some trials without complete information probably have had major public health effects; for example, the trial that showed neurological benefits of methylprednisolone in spinal cord trauma[29] led to great changes in practice, but the effect of this intervention on society has not been valued systematically. Second, our estimate of the value of a quality-adjusted life year is low. We valued a quality-adjusted life year at $40 310, to indicate the average yearly economic productivity of a person in the USA. However, for health interventions, costs exceeding $50 000 per quality-adjusted life year are well accepted, and even those exceeding $100 000 are common.[13] Furthermore, some economic evaluations have estimated the value of a quality-adjusted life year even higher.[74] Third, the estimates for the cost of drugs are high. We relied on estimates from published work, but none of these reports recognised that profit, taxes, and underwriting

development of future drugs are not true costs from society's perspective because they simply involve transfer of resources from one group to another; the true cost of a drug is shown by the materials and labour necessary to develop, make, and distribute it.[75] Finally, our definition of effect on society was narrow: benefits were measured only as the result of changes in use of the tested treatments. We made no attempt to evaluate the effect of trial results on interventions similar to those tested in the trials; for example, a negative trial of a heparinoid[42] probably resulted in reduced use of acute anticoagulation for acute ischaemic stroke, but this effect was not captured in our analysis. Also, we made no attempt to value the scientific discoveries and methodological advances gained from clinical trials; as some very highly cited publications were included in our analysis, this effect was probably substantial.

We cannot comment on the relative expenditures for basic research relative to clinical research. All the interventions from these clinical trials required understanding brought about through basic science research. Thus, the overall investment in basic and clinical research was important to achieving these health gains. Interestingly, however, the total budget of the NINDS during the 27-year period covered by this study was $29·5 billion[2] and the expected return over a similar time for the clinical trials in the programme was projected to be more than $50 billion. Thus, benefits from the clinical trials alone have been large enough to justify the entire programme of research, basic and clinical.

The effect of these trials could have been greater. Implementation of proven treatments was often delayed and incomplete. Rates of use were estimated to plateau more than 7 years after completion of funding. Furthermore, several interventions continue to be underused.[58,66] Although implementation is not part of the stated mission of the NINDS, additional focus on implementation of proven treatments is needed if the full promise of the research investment is to be realised.[76]

Our study has several limitations. We relied heavily on published work for our model inputs and, although we selected model inputs systematically, the choice of available studies was limited. Cost-utility analyses figured prominently in our analysis, and they are prone to bias and error.[77] Included cost-utility analyses used a range of methods for assessing effect of health and for measuring costs, so estimates are imprecise. Studies of the effect of several proven interventions could not be identified. Estimates of the dollar value of a quality-adjusted life year vary widely depending on the methods used for assessment,[74] producing uncertainty in the overall economic value of the programme; however, the overall cost-effectiveness ratio of the programme is well within current accepted standards of value. We assumed that trial results would be applied to a population similar to the target population of the trial; in fact, proven interventions

can be applied more broadly, with uncertain benefits in unstudied populations. Results of two trials produced very striking benefits that overwhelmed the benefits of the other trials; however, the effect of the programme was still very positive even when these trials were excluded. Our analysis focused on the USA, since the initial trial investment was made there; findings might not be generalisable elsewhere, since costs of implementation and the values of health states vary widely. Finally, our method applies to previous research and not to the specific value of future research projects; other methods have been proposed to weigh the potential benefits of competing funding proposals and may be more relevant in determining whether public funding could be more wisely used elsewhere.[10,78] Nonetheless, the conclusion that the investment in clinical trials was worthwhile seems difficult to contradict because of the size of the modelled benefit and conservative assumptions of the model.

Few studies have studied the effects of research and methodological standards have not been established.[8,10,79] The methods of health services and economic research, including cost-utility analysis, are attractive because they incorporate standard measures of health and economic benefit.[8,9] Further refinements will be necessary to create the best methodological standards to evaluate the effects of research. However, the potential reward is great, with more rigorous justification for funding and for setting research priorities.[80]

References
1   National Institutes of Health. NIH public access background information. http://publicaccess.nih.gov/publicaccess_background.htm (accessed Oct 13, 2005).
2   National Institutes of Health. The NIH almanac—appropriations, section 2. http://www.nih.gov/about/almanac/appropriations/part2.htm (accessed Oct 11, 2005).
3   National Institutes of Health. Estimates of funding for various diseases, conditions, research areas. http://www.nih.gov/news/fundingresearchareas.htm (accessed Oct 11, 2005).
4   Frist WH. Federal funding for biomedical research: commitment and benefits. *JAMA* 2002; **287:** 1722–24.
5   A political attack on peer review. *Nat Neurosci* 2005; **8:** 1273.
6   Fuster V. NIH funding: a roller coaster ride? Priorities if NIH funding increases. *Circulation* 1999; **99:** 2064–66.
7   Pollack A. Despite billions for discoveries, pipeline of drugs is far from full. *The New York Times* 2002 April 22; C1.
8   Buxton M, Hanney S, Jones T. Estimating the economic value to societies of the impact of health research: a critical review. *Bull World Health Organ* 2004; **82:** 733–39.
9   Murphy KM, Topel RH, eds. Measuring the Gains from medical research: an economic approach. Chicago: University of Chicago Press, 2003.
10 Fleurence RL, Torgerson DJ. Setting priorities for research. *Health Policy* 2004; **69:** 1–10.
11 Wooding S, Hanney S, Buxton M, Grant J. Payback arising from research funding: evaluation of the Arthritis Research Campaign. *Rheumatology (Oxford)* 2005; **44:** 1145–56.
12 Cutler DM, McClellan M. Is technological change in medicine worth it? *Health Aff (Millwood)* 2001; **20:** 11–29.
13 Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. Cost-effectiveness in health and medicine. New York: Oxford University Press, 1996.
14 Petitti DB. Meta-analysis, decision analysis, and cost-effectiveness analysis. 1st edn. New York: Oxford University Press, 1994.
15 Health Information Research Unit, McMaster University. Search strategies for MEDLINE in Ovid Syntax and the PubMed translation. http://hiru.mcmaster.ca/hedges (accessed Nov 8, 2005).
16 US Department of Labor. Comparative real gross domestic product per capita and per employed person, fifteen countries, 1960-2004 (page 9). Washington, DC: Bureau of Labor Statistics, 2005: 1–15.
17 The Global Alliance for Vaccines and Immunization. GAVI : health, immunization, and economic growth. http://www.vaccinealliance.org/General_Information/Immunization_informa/Economic_Impact/vacc_cost.php (accessed March 24, 2006).
18 Osteoporosis: review of the evidence for prevention, diagnosis and treatment and cost-effectiveness analysis. Introduction. *Osteoporos Int* 1998; **8** (suppl 4)**:** S7–80.
19 US Department of Labor. Bureau of Labor statistics data: prices and living conditions. http://www.bls.gov/data/ (accessed Sept 6, 2005).
20 Ment LR, Oh W, Ehrenkranz RA, et al. Low-dose indomethacin and prevention of intraventricular hemorrhage: a multicenter randomized trial. *Pediatrics* 1994; **93:** 543–50.
21 Dreifuss FE, Rosman NP, Cloyd JC, et al. A comparison of rectal diazepam gel and placebo for acute repetitive seizures. *N Engl J Med* 1998; **338:** 1869–75.
22 Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). *Ann Neurol* 1996; **39:** 285–94.
23 Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA* 1995; **273:** 1421–28.
24 Stroke Prevention in Atrial Fibrillation Study. Final results. *Circulation* 1991; **84:** 527–39.
25 Devinsky O, Vazquez B, Faught E, et al. A double-blind, placebo-controlled study of remacemide hydrochloride in patients with refractory epilepsy following pre-surgical assessment. *Seizure* 2002; **11:** 371–76.
26 North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991; **325:** 445–53.
27 The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995; **333:** 1581–87.
28 Temkin NR, Dikmen SS, Wilensky AJ, Keihm J, Chabal S, Winn HR. A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. *N Engl J Med* 1990; **323:** 497–502.
29 Bracken MB, Shepard MJ, Collins WF, et al. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. Results of the Second National Acute Spinal Cord Injury Study. *N Engl J Med* 1990; **322:** 1405–11.
30 Bracken MB, Shepard MJ, Holford TR, et al. Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. National Acute Spinal Cord Injury Study. *JAMA* 1997; **277:** 1597–604.

31   The Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 1993; **328:** 176–83.

32   Vitek JL, Bakay RA, Freeman A, et al. Randomized trial of pallidotomy versus medical therapy for Parkinson's disease. *Ann Neurol* 2003; **53:** 558–69.

33   Silver AA, Shytle RD, Philipp MK, Wilkinson BJ, McConville B, Sanberg PR. Transdermal nicotine and haloperidol in Tourette's disorder: a double-blind placebo-controlled study. *J Clin Psychiatry* 2001; **62:** 707–14.

34   Taylor DW, Barnett HJ, Haynes RB, et al, for the ASA and Carotid Endarterectomy (ACE) Trial Collaborators. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomised controlled trial. *Lancet* 1999; **353:** 2179–84.

35   Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. *Lancet* 1996; **348:** 633–38.

36   Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. Results of an international randomized trial. The EC/IC Bypass Study Group. *N Engl J Med* 1985; **313:** 1191–200.

37   Temkin NR, Dikmen SS, Anderson GD, et al. Valproate therapy for prevention of posttraumatic seizures: a randomized trial. *J Neurosurg* 1999; **91:** 593–600.

38   Brain Resuscitation Clinical Trial I Study Group. Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. *N Engl J Med* 1986; **314:** 397–403.

39   Brain Resuscitation Clinical Trial II Study Group. A randomized clinical study of a calcium-entry blocker (lidoflazine) in the treatment of comatose survivors of cardiac arrest. *N Engl J Med* 1991; **324:** 1225–31.

40   Abramson N, Safar P, Sutton-Tyrrell K, Craig MT. BRCT III Study Group: a randomized clinical trial of escalating doses of high dose epinephrine during cardiac resuscitation. *Crit Care Med* 1995; **23:** A178.

41   Haley EC Jr, Kassell NF, Torner JC, Truskowski LL, Germanson TP. A randomized trial of two doses of nicardipine in aneurysmal subarachnoid hemorrhage. A report of the Cooperative Aneurysm Study. *J Neurosurg* 1994; **80:** 788–96.

42   Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. Low molecular weight heparinoid, ORG 10172 (danaparoid), and outcome after acute ischemic stroke: a randomized controlled trial. *JAMA* 1998; **279:** 1265–72.

43   The RANTTAS Investigators. A randomized trial of tirilazad mesylate in patients with acute stroke (RANTTAS). *Stroke* 1996; **27:** 1453–58.

44   Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet* 1994; **343:** 687–91.

45   Bracken MB, Shepard MJ, Hellenbrand KG, et al. Methylprednisolone and neurological function 1 year after spinal cord injury. Results of the National Acute Spinal Cord Injury Study. *J Neurosurg* 1985; **63:** 704–13.

46   Haines SJ, Jordan N, Boen JR, Nyman JA, Oldridge NB, Lindgren BR. Discectomy strategies for lumbar disc herniation: results of the LAPDOG trial. *J Clin Neurosci* 2002; **9:** 411–17.

47   Hintz S, Kendrick DE, Vohr BR, Poole WK, Higgins RD, for the National Institute of Child Health and Human Development Neonatal Research Network. Changes in neurodevelopmental outcomes at 18 to 22 months' corrected age among infants of less than 25 weeks' gestational age born in 1993–1999. *Pediatrics* 2005; **115:** 1645–51.

48   Moya MP, Goldberg RN. Cost-effectiveness of prophylactic indomethacin in very-low-birth-weight infants. *Ann Pharmacother* 2002; **36:** 218–24.

49   O'Dell C. Reduction in number of emergency department visits with Diazepam rectal gel use. *Ann Neurol* 2004; **56** (suppl 8): S109.

50   Ritter FJ, Frost MD, Karney VL, Hoskin C. Cost savings and effectiveness of rectal diazepam for treatment of prolonged or acute repetitive seizures in children 5 years and younger. *Neurology* 2000; **54** (suppl 3): A295.

51   IMS Health. Annual sales of IFNB-1a, by disease. Fairfield: IMS Health, 2005.

52   Prosser LA, Kuntz KM, Bar-Or A, Weinstein MC. Cost effectiveness of interferon beta 1a, interferon beta-1b, and glatiramer acetate in newly diagnosed non primary progressive multiple sclerosis. *Value Health* 2004; **7:** 554–67.

53   Cooper GS, Stroehla BC. The epidemiology of autoimmune diseases. *Autoimmun Rev* 2003; **2:** 119–25.

54   Kresowik TF, Bratzler D, Karp HR, et al. Multistate utilization, processes, and outcomes of carotid endarterectomy. *J Vasc Surg* 2001; **33:** 227–34.

55   Gross CP, Steiner CA, Bass EB, Powe NR. Relation between prepublication release of clinical trial results and the practice of carotid endarterectomy. *JAMA* 2000; **284:** 2886–93.

56   Agency for Healthcare Research and Quality. HCUPnet— Healthcare Cost and Utilization Project. http://www.ahrq.gov/data/hcup/hcupnet.htm (accessed Oct 11, 2005).

57   Cronenwett JL, Birkmeyer JD, Nackman GB, et al. Cost-effectiveness of carotid endarterectomy in asymptomatic patients. *J Vasc Surg* 1997; **25:** 298–309.

58   Stafford R, Radley DC. The underutilization of cardiac medications of proven benefit, 1990 to 2002. *J Am Coll Cardiol* 2003; **41:** 56–61.

59   Fang M, Stafford RS, Ruskin JN, Singer DE. National trends in antiarrhythmic and antithrombotic medication use in atrial fibrillation. *Arch Intern Med* 2004; **164:** 55–60.

60   Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. *Arch Intern Med* 1995; **155:** 469–73.

61   Sudlow M, Thomson R, Thwaites B, Rodgers H, Kenny RA. Prevalence of atrial fibrillation and eligibility for anticoagulants in the community. *Lancet* 1998; **352:** 1167–71.

62   Gage BF, Cardinalli AB, Albers GW, Owens DK. Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation. *JAMA* 1995; **274:** 1839–45.

63   Halm E, Chassin MR, Tuhrim S, et al. Revisiting the appropriateness of carotid endarterectomy. *Stroke* 2003; **34:** 1464–71.

64   Kuntz KM, Kent KC. Is carotid endarterectomy cost-effective? An analysis of symptomatic and asymptomatic patients. *Circulation* 1996; **94** (9 suppl): II194–98.

65   American Heart Association. Heart disease and stroke statistics— 2004 update. Dallas: American Heart Association, 2004.

66   Reeves MJ, Arora S, Broderick JP, et al. Acute stroke care in the US: results from 4 pilot prototypes of the Paul Coverdell National Acute Stroke Registry. *Stroke* 2005; **36:** 1232–40.

67   Fagan SC, Morgenstern LB, Petitta A, et al, for the NINDS rt-PA Stroke Study Group. Cost-effectiveness of tissue plasminogen activator for acute ischemic stroke. *Neurology* 1998; **50:** 883–90.

68   Derdeyn C, Gage BF, Grubb RL Jr, Powers WJ. Cost-effectiveness analysis of therapy for symptomatic carotid occlusion: PET screening before selective extracranial-to-intracranial bypass versus medical treatment. *J Nucl Med* 2000; **41:** 800–07.

69   Cereghino JJ, Mitchell WG, Murphy J, Kriel RL, Rosenfeld WE, Trevathan E, for the North American Diastat Study Group. Treating repetitive seizures with a rectal diazepam formulation: a randomized study. *Neurology* 1998; **51:** 1274–82.

70   Boston Area Anticoagulation Trial for Atrial Fibrillation investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med* 1990; **323:** 1505–11.

71   Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. *Lancet* 1989; **1:** 175–79.

72   European Carotid Surgery Trialists' Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. *Lancet* 1991; **337:** 1235–43.

73   Hobson RW 2nd, Weiss DG, Fields WS, et al, for the Veterans Affairs Cooperative Study Group. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. *N Engl J Med* 1993; **328:** 221–27.

74   Polsky D. Does willingness to pay per quality-adjusted life year bring us closer to a useful decision rule for cost-effectiveness analysis? *Med Decis Making* 2005; **25:** 605–06.

75   Reinhardt UE. Perspectives on the pharmaceutical industry. *Health Aff (Millwood)* 2001; **20:** 136–49.

76   Lenfant C. Shattuck lecture–clinical research to clinical practice—lost in translation? *N Engl J Med* 2003; **349:** 868–74.

77   Jefferson T, Demicheli V, Vale L. Quality of systematic reviews of economic evaluations in health care. *JAMA* 2002; **287:** 2809–12.

78   Meltzer D. Can medical cost-effectiveness analysis identify the value of research? In: Murphy KM, Topel RH, eds. Measuring the gains from medical research: an economic approach. Chicago: University of Chicago Press, 2003: 240.

79   Reinhardt UE. Making economic evaluations respectable. *Soc Sci Med* 1997; **45:** 555–62.

80   Committee on the NIH Research Priority-Setting Process IoM. Scientific opportunities and public needs: improving priority setting and public input at the National Institutes of Health. Washington, DC: National Academy Press, 1998.