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Lessons learned: Infrastructure development and financial management for large, publically funded, international trials

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Abstract

Background/Aims—Randomized clinical trials are widely recognized as essential to address world-wide clinical and public health research questions. However, for many conditions, their size and duration can overwhelm available public and private resources. To remain competitive in international research settings, advocates and practitioners of clinical trials must implement practices that reduce their cost. We identify approaches and practices for large, publicly-funded, international trials that reduce cost without compromising data integrity, and recommend an approach to cost reporting that permits comparison of clinical trials.

Methods—We describe the organizational and financial characteristics of INSIGHT, an infectious disease research network that conducts multiple, large, long-term, international trials, and examine challenges associated with simple and streamlined governance and an infrastructure and financial management model that is based on performance, transparency, and accountability.

Results—It is possible to reduce costs of participant follow-up and not compromise clinical trial quality or integrity. The INSIGHT network has successfully completed four large HIV trials using cost-efficient practices that have not adversely affected investigator enthusiasm, accrual rates, loss-to-follow-up, adherence to the protocol, and completion of data collection. This experience is relevant to the conduct of large, publically funded trials in other disease areas, particularly trials dependent on international collaborations.

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Conclusion—New approaches, or creative adaption of traditional clinical trial infrastructure and financial management tools, can render large, international clinical trials more cost-efficient by emphasizing structural simplicity; minimal up-front costs; payments for performance; and uniform algorithms and fees-for-service, irrespective of location. However, challenges remain. They include institutional resistance to financial change, growing trial complexity, and the difficulty of sustaining network infrastructure absent stable research work. There is also a need for more central monitoring, improved and harmonized regulations, and a widely-applied metric for measuring and comparing cost efficiency in clinical trials. ClinicalTrials.gov is recommended as a location where standardized trial cost information could be made publicly accessible.

Keywords

Infrastructure development; financial management; large trials; publicly-funded trials; international trials

Introduction

The conduct of large, multi-center clinical trials can be expensive and complicated. As early as 1975, it was suggested that new standards and designs would affect large trial costs, and data were needed to evaluate benefits.¹ While large trials are now deemed essential to address worldwide clinical and public health research questions, treatment strategies, and drug registration, their size, duration, and regulatory burden can exceed public resources, making them unaffordable.²

Recent evidence confirms that conventional models for clinical trials are becoming price prohibitive. Average cost per participant between 2006-2008 for Phase III trials was more than \$10,000.³ Trial costs for pharmaceutical studies exceeded inflation by 7.4% annually over the last 20 years, discouraging development of new products and investigations of public health-inspired research questions.⁴ This is attributed to the high-cost of Phase III trials, typically accounting for 90% or more of drug development costs in the US. Pharmaceutical industry attention has shifted to drugs for rare diseases, where rules permit smaller trials, rather than medications for chronic conditions that more significantly drive health care costs and numbers of affected people.⁵

Trials also have become more international. Investigators regulated by the Food and Drug Administration (FDA) outside the US grew 15% annually since 2002, while US-based FDA regulated investigators decreased 5.5% annually.⁶ The average number of countries involved in Phase III trials grew from 19 in 2002-2006 to 34 in 2006-2010.³ Many practitioners cite the benefits of global trials: larger populations for rapid enrollment, particularly of treatment-naïve participants; results more broadly applicable to diverse settings and populations; expansion of institutional and individual collaborations; and the ability to examine results in differing sub-populations.⁷

But globalization faces challenges. Large, long-term, publicly-funded Human Immunodeficiency Virus (HIV) treatment strategy trials like Strategies for Management of AntiRetroviral Therapy (SMART)⁸ and Strategic Timing of AntiRetroviral Therapy (START)⁹ complement Phase III pharmaceutical trials and better inform us of risks and

benefits of life-long treatments, but encounter obstacles associated with their global scope. Absent uniformity, well-intentioned international regulatory requirements add cost and delay, but little added value.² Demands for trial insurance and indemnification have increased¹⁰ and ethical issues arise when research funded by resource-rich countries is conducted in resource-poor countries. The number of countries, sites, government layers, and reliance on contract organizations adds management complexity. Finally, geographic and cultural distance makes it difficult to fully assess site capabilities, scientific fit, and up-front needs.

INSIGHT infrastructure

New approaches, or creative adaption of past practices, can render large, long-term, international clinical trials more affordable without adversely impacting scientific objectives.¹¹ The International Network for Strategic Initiatives in Global HIV Trials (INSIGHT), funded primarily by the National Institute of Allergy and Infectious Diseases, has built a unique organization with financial practices that reduce costs without compromising quality or fulfillment of its mission defining optimal strategies for the management of HIV and other infectious diseases through a global network.¹² Since its formation, INSIGHT has completed two large, international trials, with a third underway (Table 1). Evaluation of Subcutaneous Proleukin in a Randomized International Trial (ESPRIT) was a Phase III clinical endpoint trial looking at a new indication for interleukin-2.¹³ SMART was a strategic trial on treatment interruption with clinical outcomes. The ongoing START trial examines when to begin treatment, again with clinical outcomes. ESPRIT, SMART, and START are the largest randomized HIV treatment clinical trials ever conducted.

INSIGHT has capitalized on a collaboration of four established research organizations, each with central administration of many clinical sites: the Terry Biern Community Programs for Clinical Research, affiliated with the US Department of Veterans Affairs' Institute for Clinical Research, Washington DC, US; the Medical Research Council Clinical Trials Unit, London, United Kingdom; the Copenhagen HIV Programme, Denmark; and the University of New South Wales' Kirby Institute, Sydney, Australia. Each is an experienced HIV research organization, has independently conducted trials, and has long-standing relationships with clinical site investigators. The four agreed to integrate their organizations into a larger network with co-located operations and statistical functions at the University of Minnesota's Coordinating Centers for Biometric Research, which had experience in large trials, including HIV trials.

Figure 1 depicts INSIGHT's hierarchical structure using a breakdown for the Sydney International Coordinating Center to show components. Countries and sites change with each trial, but the operations and statistical functions at the University of Minnesota, and the coordinating centers in Copenhagen, London, Sydney, and Washington, are constants. This structure mirrors the networked, coordinating center structure successfully used by the US/ Canadian Digitalis Investigation Group trial for selection and coordination of 116 sites.¹⁴ A similar approach was recommended to the National Heart, Lung, and Blood Institute in 2011

to improve research across multiple sites and sustain collaborations between central and site-based research organizations.¹⁵

INSIGHT's infrastructure still reflects the hub and spoke alignments of countries and sites, but subsequent modifications have accommodated both practical and political needs. Figure 2 shows the infrastructure, coordinating center, and country alignments for the START trial. The Operations and Statistical Center at the University of Minnesota is responsible, in collaboration with the international coordinating centers, for network wide operations, governance, finance, drug distribution, communications, meeting logistics, website management, community support, clinical site establishment, data management, external Data and Safety Monitoring Board reporting, statistical analyses, specimen storage, and laboratory analyses. The Operations and Statistical Center also contracts with the four international coordinating centers and with the Site Coordinating Centers in the London and Sydney regions. The international coordinating centers are responsible for regional protocol management activities, subcontracting with country-based coordinating centers and clinical research sites, selection of sites, collection of site registration and establishment materials, document translations, train-the-trainer protocol implementation, participant randomization, quality assurance and external site monitoring oversight, regional meeting logistics, and assistance with development of new study and substudy protocols. The country-based site coordinating centers are responsible for countrywide and site regulatory submissions, site training, quality assurance support, on-site external monitoring, assistance with translations and data query resolution, distribution of site payments, and enrollment and follow-up accountability. Although Figure 1 provides a simplified view, there is considerable variation in relationships at this level, as evidenced in Figure 2 and accompanying notes. Finally, the clinical research sites are responsible for human subjects protection submissions; adherence to human subjects protection and Good Clinical Practice standards; participant consent, enrollment, and follow-up; maintenance of local regulatory files and drug accountability logs; completion of case report forms and resolution of queries; and facilitation of external site monitoring. An international or a site coordinating centersubcontracts with each clinical site that provides participants with primary HIV care.

Five distinguishing strategies have evolved to reduce management complexity, cited as one of the most effective ways to lower trial expense:¹⁶ First, we build on existing research relationships. INSIGHT sought to preserve institutional and individual collaborations and alignments already established by the international coordinating centers, but was flexible in accommodating cultural and political needs. For example, Figure 2 shows that seven START sites in Brazil were assigned to two, rather than a single, Brazilian coordinating center; South African sites were divided between the centers in Washington and Sydney; and other African site coordinating centers were allocated to either London or Washington. The network also has adapted to fluctuations in country and site numbers that reflect trial size, geographic scope, investigator interest, and diversity, as evident in the Table 1 numbers for participating countries and sites in the different INSIGHT trials. This flexibility enhances the autonomy and capabilities of the coordinating centers.

Second, we maintained co-located operational and statistical functions. The Minnesota co-location of these functions streamlines communications and optimizes shared resources (e.g.

administrative staff, physical facilities, computing, databases, websites, supplies, etc.), and responsiveness. Network components act in a unified manner. Data management and analysis occurs centrally in Minnesota, but INSIGHT also supports some statistical expertise present in Copenhagen, London, and Sydney.

Third, we emphasize simplified governance. INSIGHT has a streamlined governance model. A small Executive Committee secures network funding, ensures breadth in network participation, and develops network policies. The Scientific Steering Committee sets the research agenda, monitors productivity, and disseminates study results. The Operations Steering Committee develops and implements structures and processes that enhance INSIGHT's mission. A Community Advisory Board supports protocol development and implementation, education and training, and recruitment. These committees include geographic representation from the four international coordinating centers, and the committee chairs serve on the Executive Committee. Any other advisory groups are linked to the steering committees. Simplified governance, with regular rotation of roles among leaders and frequently scheduled conference calls, fosters responsiveness and accountability, reducing time-to-action in a network that values consensus.

Fourth, we delegate communications and contracting. Neither the Minnesota Operations and Statistical Center nor INSIGHT's governing bodies contract or communicate directly with clinical sites. Minnesota subcontracts only with the various coordinating centers; these in turn subcontract with the sites. Contractor tasks, sponsor functions, and payments for services flow from Minnesota, through the coordinating centers, to sites. Network or committee communications pass through coordinating centers to sites, or originate in the coordinating centers before being passed on to sites. Time zone differences are minimized, and communications between the parties closest to the actual conduct of the trial reinforce lines of responsibility and contracting relationships.

Finally, we assign focused site-monitoring responsibilities to coordinating centers. Monitoring is cited as a significant driver of clinical trial cost,^{15,17} accounting for 25 to 30% of the cost.¹⁶ A recent survey of monitoring found significant variation in practices and reliance on site visits versus centralized monitoring.¹⁸ INSIGHT's use of coordinating center staff for monitoring reduces overall costs, including travel and dedicated time, and takes advantage of monitors already familiar with the protocol, manuals and procedures, case report forms, and site characteristics and performance. In addition, INSIGHT trains monitors to focus on collection of key data items; less time is spent on regulatory file review and source documentation.

INSIGHT financial management

While regulatory burdens related to human subjects protection, adverse event reporting, and site monitoring is the most frequently cited reason for rising trial costs,¹⁹ financial bureaucracy also adds expense, but receives less attention in the literature. Recognizing that simplified financial management could offset rising costs, INSIGHT concluded that a successful financial structure for large, long-term trials should be *collaborative*, with support from various public and private sources; *transparent*, with finances, and compensation

visible to funders and investigators; *risk-averse*, with limited up-front commitments; *accountable*, with contractor payments based on performance; uniform with a standardly applicable, fee-for-service structure; and *simple*, with contracts and procedures that lessen burdens on institutions and investigators.

Successful integration of these characteristics has led to standardized contracts, simplified budgeting and financial transactions, compensation based on performance, uniform cost structures, predictable payments, and research on research. Specifically, the Minnesota Operations and Statistical Center subcontracts with the four international coordinating centers and with the site coordinating centers in the London and Sydney regions. Minnesota subcontracts have standardized provisions to flow-down sponsor obligations and specific tasks at each contracting level. Contract templates were simplified and unnecessary boilerplate was jettisoned to shorten the time and resources spent negotiating with institutions. The coordinating centers subcontract with their clinical sites and flow the appropriate responsibilities on to these sites. The burden of oversight for hundreds of sites is spread out and takes advantage of coordinating centers that are geographically proximal to sites, fluent in their spoken languages, and familiar with their local regulatory environment.

Fee-for-service, rather than traditional cost-reimbursement, is the basis for all contractor payments. Quarterly payments are calculated using network wide, fee-for-service payment schedules incorporated in the contracts. Following bilateral execution of the initial INSIGHT contract for the first year of a project, annual modifications that extend the performance period are quickly and unilaterally issued by the Minnesota Operations and Statistical Center without alteration of the basic contract or renegotiation of budgets. Protocol activities, accrual, and submission of case report forms determine payments. Figure 3 shows the payment schedule for START. Compensation is spread over the trial duration, rather than weighted at the front, to encourage good follow-up and minimize missing data. Typical cost reimbursement issues (e.g. late invoices, insufficient expense documentation, currency conversions, translation needs, reconciliation of differences, and audit testing are eliminated. Services rendered and deemed acceptable trigger payments of scheduled amounts in US dollars without regard for currency fluctuations or the need for expense documentation. The internal allocation of payments is at the site's discretion.

All coordinating centers and clinical sites in START receive both fixed and variable payments based almost entirely on performance metrics. The payments provide limited start-up and training support as the study is initiated, accrual support as the study enrolls, and visit and procedure payments for the study's duration. The types of INSIGHT coordinating center and site support fall into three categories. Start-up and training support is provided to coordinating centers for translations, human subjects protection reviews, regulatory submissions, the hiring of INSIGHT-prescribed staff, and training. Sites receive early advances upon completion of site registration activities. Advances are limited to minimize the risk of unrecoverable payments if coordinating centers or sites fail to meet commitments. Accrual support is provided to coordinating centers as participants enroll at their sites. It reflects both the incremental cost associated with growing enrollment and, as a recruitment incentive, the economies of scale that coordinating centers may realize with more sites and participants. Study visit and procedure payments are provided to clinical sites when the

Minnesota Operations and Statistical Center deems case report form documentation “complete” for study visits or procedures (e.g. baseline-randomization and follow-up visits, major events, processing malignancy specimens, etc.).

Payment algorithms for advances, accrual support, and participant care are uniform and do not vary geographically, irrespective of locations where the trial work is performed (Figure 3). While overall budget parameters are defined, annual site revenue is determined solely by performance. Payment schedules are transparent and posted on the INSIGHT website. Uniformity eliminates site-specific budgeting based on local health care systems; private insurance payments; and varying standards of care, salaries, and living costs for hundreds of sites. Site-specific budgeting is also fraught with political consequences when sites are compensated differently for similar activities. If compensation exceeds local costs, recipients can use the excess to hire staff, purchase lab equipment, or otherwise enhance research capabilities, trial performance, and future collaborations where populations may have been under-represented.²⁰ Additionally, uniform payments can eliminate an appearance of exploitation at a time of growing sensitivity to global research that is sometimes viewed as unethical “moral imperialism” or “bioethics colonialism”.²¹

Regular quarterly payments build predictability into budgeting and fund transfers without dependence on contractor invoicing. Domestic check or international wire transfer payments occur within the month immediately following the quarter. Coordinating center contractors receive documentation showing categorical amounts of support paid, including site and participant breakdowns with line listings of visits, events, procedures, and case report forms and a listing of unresolved queries that is a periodic reminder of unrealized revenue.

Finally, large, long-term trials can be vehicles for complementary research on trial design and efficiency. Based on early START trial experience, INSIGHT advocated for regulatory change in European clinical trials.¹⁰ INSIGHT has ongoing internal reviews on characteristics of high-performing sites, language translation efficiencies, and models for centralized human subjects protection review. Also, two nested sub-studies examine alternatives to familiar clinical trial features. One compares the standard informed consent with a shorter, easier-to-read version. Another compares on-site monitoring with remote, centralized monitoring.

These practices have not compromised study quality. Although START is ongoing, review of ESPRIT and SMART study data for two performance measures (percent missed visits and percent lost-to-follow-up) show good data completeness and low participant loss (Tables 2 and 3). These measures were applied to different levels of country income and site enrollment, where the INSIGHT practices could have arguably affected performance. Most of the P values for the study groupings were statistically significant due to the large number of participants evaluated; however, the actual differences in percentages within the study groupings were relatively modest.

Challenges

Despite success with the INSIGHT model, challenges still arise. First, by default, recruitment of clinical sites focuses on locations with established research infrastructures.

Other locations might be desirable for scientific or recruitment reasons, but the risk of non-performance (e.g. insufficient enrollment, protocol deviations, loss-to-follow-up, good clinical practice compliance, etc.) can jeopardize effort and funds allocated to a new study. Similar difficulties were cited for infrastructure development for new tuberculosis (TB) trials;²² expanded infrastructure capacity where TB burden was greatest was estimated in 2007 to cost \$1-2 million per site per year.

Second, development of budgeting algorithms and payment amounts requires broad consensus – a challenge in a large network. Proposals are usually developed by the Operations and Statistical Center and vetted within governance committees and international coordinating centers. After obtaining preliminary agreement, the centers recruit sites interested in the scientific question and satisfied with proposed compensation. Site recruitment can result in fine-tuning of the payment algorithms, but INSIGHT may not have the resources that allow for significant revision of amounts.

Third, some institutions are uncomfortable with fee-for-service subcontracts, or resist arrangements where non-performance risk rests with them rather than the network. They may not like unilateral extensions, or may want to renegotiate standardized payment amounts. They also may not have the financial wherewithal to float expenses without payments in advance of performance.

Fourth, large research networks walk a fine line to maintain coordinating center and site capabilities and still operate cost-efficiently. A balance must be struck between early stages in a study, when fewer participants are followed, or at times with less concurrent studies or lower payment amounts, and later stages when payments are more substantial or augmented by other trials. Absent this balance, key site staff may be lost or resources squandered.

Fifth, payments need to be carefully calibrated to avoid shortfalls or windfalls when incremental funding in a network is spread over multiple trials and a larger number of total participants. However, clinical trials are rarely similar. Adjustment of payments may still be imprecise or retrospectively difficult, and subsidization of one study at the expense of another may occur. For example, higher pharmaceutical payments in cancer research may offset lower compensation offered for concurrent public research.²³

Sixth, simplicity is presumed to be a hallmark of large, long-term trials, but is often subservient to other priorities. In academic settings and publicly-funded trials, there is always tension between the need to simplify and the desire to maximize return on investment. Typically, investigators want to collect as much data and as many specimens as possible, irrespective of the added complexity.

Finally, clinical trial cost comparisons and benchmarking are inexact. The literature is limited, and the rapid rise in cost and complexity over the last 15 years quickly renders comparisons obsolete. More importantly, the great variation in trial characteristics (e.g. number of participants, follow-up length, trial phase, design and scope of interventions, site numbers and locations, private or public sponsor, donated drug, number of sub-studies, and internal vs. external monitoring) and lack of standardized cost metrics confound

comparisons, even where data are available. Most often, the metrics lack a time element that is critical for long-term studies.

Table 1 shows costs for INSIGHT's largest, long-term clinical trials and illustrates trial differences. SMART costs are higher than the costs for the other two trials because SMART had separate operations and statistical centers, a different infrastructure, and higher payments for coordinating centers and sites, which made the trial more costly prior to INSIGHT assuming study responsibility in 2006. ESPRIT and START costs are more indicative of INSIGHT infrastructure and financial management practices. Although START will conclude at a higher cost than ESPRIT, it is a more complex study, requires international distribution of many antiretroviral drugs in 35 countries, and is sponsored by the University of Minnesota rather than the National Institute for Allergy and Infectious Diseases.

Discussion

Infrastructure and financial measures can be introduced to make large, long-term, international clinical trials more efficient. Some may seem intuitively difficult to implement, especially if conventional financial arrangements are already in place, but they can be integrated without jeopardizing quality. Both ESPRIT and SMART were characterized by optimal adherence to protocols and data completeness with low loss-to-follow-up. Expectations are similar for START. These traits are not always achievable in large, long-term trials and indicate that cost efficiency does not necessarily hinder successful completion.

The need for increased efficiency in an era of limited resources will lead to innovative clinical trial methodologies. Financial support of coordinating centers and sites will continue to diminish as compensation is tied to performance. In addition, interest will grow in remote capture of participants and data with hybrid, registry-based randomized trials. Despite the promise of generalizable findings drawn from observational data, weaknesses related to data quality, privacy and informed consent, data accessibility, short-term follow-up, lack of standardization, and inherent bias in patient eligibility need to be addressed.²⁴ Other technological innovations, including online recruiting and data collection, video consents, and home-based reporting have yet to demonstrate superiority over more traditional methodologies, but offer adaptive strategies that may streamline trials.²⁵

Resilient research networks have a unique role to play. They can build their research agenda on multiple, concurrent trials that spread fixed costs over larger numbers of participants and on sequential trials that strategically capitalize on prior research and an established infrastructure. By doing so, they maintain the momentum and capabilities needed to conduct large trials and ensure that network durability is not adversely affected by a lack of continued work.

The call for harmonized international laws and regulations is a common, but largely unfulfilled, refrain. Politics, national pride, and local inertia often outweigh common sense. Regulatory costs associated with site monitoring and good clinical practice have been briefly

addressed here and more substantively elsewhere. Other costs related to the US Health Insurance Portability and Accountability Act, local human subjects protection review in multi-center studies, and redundant adverse event reporting, have grown without evidence of improvement in participant privacy and safety.²⁶ Draft guidance on site monitoring released by the FDA in 2011 acknowledged the need for risk-based approaches to site monitoring and recommended that monitoring requirements be tailored to trial needs.²⁷ Similar, risk-based approaches should be adopted by international organizations that promote good clinical practice guidance and participant privacy and safety.

The paucity of generally accepted metrics for clinical trial costs is a significant problem that makes comparison and validation of cost-efficient practices problematic. Adding standardized cost information (e.g. total trial cost, cost per participant, cost per participant year of follow-up) to the ClinicalTrials.gov website postings would be an important step. These costs should be based on comprehensive accounting of clinical and non-clinical work, overhead, contracting and regulatory expenses, planning, design, implementation pre-enrollment, and close-out and analysis post-follow-up. This reporting would inform comparisons among trial practitioners about traditional versus innovative trials that incorporate regulatory harmonization and design and technological advances to reduce cost.

Cost efficiency will be an essential attribute of future large trials. Some observers want comparisons to include cost-benefit analyses that measure broader public health impact and lives saved.¹⁷ For example, a value-of-information analysis might assess whether a randomized trial is warranted. The analysis would review current knowledge about a research question and quantify the value of the expected benefit, recognizing that uncertainty may still remain upon completion.²⁸ Collaborating with community representatives throughout clinical trial design, planning, implementation, and reporting also strengthens the focus on public health needs and has been a hallmark of publicly funded HIV/trials. INSIGHT's Community Advisory Board has been an essential contributor to the network's research agenda, helping to build community support and ensure that the research is both warranted and clinically relevant.

Others advocate comparative-effectiveness research trials and large, simple, pragmatic trials that combine operational efficiencies, adequate sample sizes, Bayesian and adaptive trial methods, and practicality to ensure outcomes that are broadly generalized, less costly, and more informative for clinicians and decision makers.²⁹⁻³¹ While no cost-benefit analysis was attempted here, making cost information an integral part of future clinical trial reporting will give researchers more context when weighing clinical research proposals, including large, long-term, publically funded, international trials.

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Figure 1.
INSIGHT infrastructure schematic with expanded view of Sydney ICC.
ICC: International Coordinating Center
SCC: Site Coordinating Center

¹ In the Copenhagen and Washington regions, the ICCs contract with Site Coordinating Centers (SCCs) and/or sites. In the London and Sydney regions, the Minnesota Operations and Statistical Center contracts with the Site Coordinating Centers (SCCs), and the SCCs contract with the sites.

² Number of clinical sites indicated parenthetically.

Figure 2.
INSIGHT infrastructure for the START trial.

International Coordinating Centers (ICCs)	Payment (US\$)
Annual European Sponsor Representative (payment to Copenhagen ICC) ¹	34,831
Annual Sponsor Delegation (payment/ICC) ¹	39,633
Annual Main Study Enrollment (payment/participant) ¹	195
Annual Sub-study Follow-up (payment/participant/sub-study) ¹	25
Countries or Site Coordinating Centers (SCCs)	
One-Time Advance (payment/new country and initial site) ¹	10,000
One-Time Advance Supplement (payment/country site after initial site) ¹	2000
Annual Main Study Follow-up (payment/participant) ¹	1105
Annual Sub-study Follow-up (payment/participant) ¹	75
Clinical Research Sites	
Baseline-Randomization Visit (payment/visit) ¹	1681
New Malignancy Informed Consent (payment/participant) ¹	100
M1 and Q4 Visit (payment/visit) ¹	785
Annual Visit (payment/visit) ¹	927
Major Event (payment/form with all documentation) ²	250
New Malignancy (payment/biopsy, blood, or both at ACSR) ¹	1000

¹Annual payments are prorated and made quarterly. Site participant care payments are based on forms received and accepted at the INSIGHT Operations and Statistical Center; payment is made in the month following the end of each quarter (Q1 Jun-Aug, Q2 Sep-Nov, Q3 Dec-Feb, Q4 Mar-May).

²Paid at end of study.

Figure 3.

Example of START main study payment schedule without sub-study detail.

Table 1

INSIGHT clinical trial characteristics and cost comparison.

Clinical Trial	Trial Duration (Months)	Participating Countries/Sites	Total Accrual	Participant Years of Follow-up	Total Trial Cost (US\$)	Total Cost/Participant Year of Follow-up (US\$)
ESPRIT ¹	03/2000-11/2008 (104)	25/259	4,150	28,000	71,850,000	2,566
SMART ^{1,2}	01/2002-07/2007 (66)	33/318	5,472	15,000	111,855,000	7,055
START ^{1,3}	04/2009-12/2016 (92)	35/215	4,688	22,034 (est.)	92,400,000 (est.)	4,194 (est.)

¹ Study costs were normalized by dividing the overall trial cost, without sub-studies, by the participant years of follow-up to yield a cost/participant year of follow-up (ESPRIT and SMART costs do not include expense for external monitoring conducted by NIAID contract organizations).

² SMART cost was estimated using information available before and after 2006, the year that INSIGHT was established. Before 2006, funding was divided among different grantees.

³ START costs for the duration of the study are estimated because follow-up is still on-going.

Performance measures for gross income per capita country quartiles for ESPRIT (104 months duration) and SMART (66 months duration).

Table 2

Income ¹	Total Quartile Participants		% Missed Visits		% Lost-to-Follow-up	
	ESPRIT	SMART	ESPRIT	SMART	ESPRIT	SMART
Highest Country Quartile	1,251	3,406	14.8	8.2	8.3	5.4
2 nd Country Quartile	540	842	12.3	11.8	4.4	3.7
3 rd Country Quartile	762	427	14.1	7.5	3.8	1.6
Lowest Country Quartile	1,004	650	10.4	5.4	4.2	0.8
	Study Mean		13.1	8.4	5.6	4.3
	P Value ²		<0.001	<0.001	<0.001	<0.001

¹ Participating countries for each study ranked from highest to lowest World Bank (Atlas Method) gross national income per capita for 2012 and divided into quartiles. Argentina enrolled participants in both ESPRIT and SMART, but was not included in country quartiles because no comparable World Bank data was available.

² P values for missed visits were calculated using missing CD4+ assay results as a surrogate in generalized linear models after arcsine transformation. P values for participants lost-to-follow-up were calculated using a logistic model.

Performance measures for sites grouped by size for ESPRIT (104 months duration) and SMART (66 months duration).

Table 3

Site Size Groups	Total Group Participants		% Missed Visits		% Lost-to-Follow-up	
	ESPRIT	SMART	ESPRIT	SMART	ESPRIT	SMART
1-9 Participants	591	660	15.8	8.1	7.6	2.7
10-19 Participants	913	1,134	13.2	9.8	5.5	5.6
20-49 Participants	1,556	2,395	13.5	9.3	5.2	4.5
50+ Participants	1,051	1,283	11.3	5.8	4.3	3.3
	Study Mean		13.2	8.3	5.4	4.2
	P Value ^d		<0.001	<0.001	0.007	0.55

^d P values for missed visits were calculated using missing CD4+ assay results as a surrogate in generalized linear models after arcsine-transformation. P values for participants lost-to-follow-up were calculated using a logistic model.