Recommendations for Standardizing Budgets for Clinical Trial Sites: Considerations for the Re-competition of the DAIDS HIV/AIDS Clinical Trial Networks

January 26, 2011

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EXECUTIVE SUMMARY

The Division of AIDS (DAIDS) within of the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) currently sponsors six HIV/AIDS clinical trials networks designed to address NIAID's high priority areas of research. The Networks are currently operating in the fifth year of seven year cooperative agreements with NIAID. DAIDS is currently contemplating the next cycle of competition for clinical trials networks that will be required to meet current and anticipated NIAID priorities; these new awards are anticipated to start in 2013. As part of this process for the re-competition, DAIDS is considering developing a uniform method for costing clinical trial protocols that could be applied to all Clinical Trial Unit/Clinical Research Sites (CTU/CRS) for all trials sponsored by DAIDS through any of its clinical trials networks. The purpose of this report is to recommend methods to DAIDS that would meet this objective.

A number of considerations were taken into account in developing the recommendations for costing new clinical trials in 2013 and thereafter. Specifically, the methods recommended should:

- Build upon best practices already developed and used by the DAIDS clinical trial networks under the current cooperative agreements;
- Be developed in consultation with the DAIDS clinical trial networks;
- Account for the significant diversity of protocols conducted by the networks;
- Account for the geographic and institutional diversity of the clinical research sites across the DAIDS networks;
- Recognize the balance between maintaining capabilities at clinical research sites and running cost-efficient protocols;
- Be informed by best practices in other areas of clinical trials (e.g., industry, cancer trials);
- Increase the flexibility of the network infrastructure (e.g., to investigate other infectious diseases, other co-morbidities, work across networks);
- Assure that site capacity and resources are linked as tightly as possible to trials conducted by the networks;
- Reinforce the agility of sites to engage rapidly in a number of trials;
- Be cognizant of new types of trials (e.g., "pragmatic" or Bayesian trials) that might be more commonly proposed and implemented during the course of the next cooperative agreement and that could impact trial budgets; and
- Result in efficient allocation of limited resources for conduct of protocols at the sites over the course of the next cooperative agreement (i.e., allow for efficient allocation and reallocation of resources for study conduct at the sites based on changes in protocols (e.g., stemming from DSMB reviews), projected versus actual enrollment and other scientific needs).

- Account for non-traditional sites that might be recruited during the course of the next cooperative agreement (i.e. the HPTN 065 sites).

An ad hoc working group (see Appendix A) was formed to help inform the issues and to develop and shape the recommendations. The working group represented participants from the current DAIDS networks, HANC, and DAIDS (specifically, the Office of Clinical Site Oversight (OCSO)). The Working Group was expanded for a second meeting to include Program Officers from the six current networks and the Grants Management Officer for NIAID. The working group met face-to-face twice: On September 13, 2010 the original group focused on describing how each network currently costs protocols and to review the issues that should be addressed in the development of recommendations. On October 27, 2010 the expanded group met to gain a better understanding of how the proposed CTU/CRS configuration in the new grant cycle might influence how protocols and site budgets for participating in protocols will be developed in the future. In addition, some broad direction for the recommendations – some stemming from feedback from the September 13 meeting – were considered and discussed. The results of these two meetings were used as the basis for developing the recommendations contained in this report. (Members of the working group also communicated via e-mail and telephone on an as-needed basis.)

The key recommendations for how to prepare budgets for participation of a CTU/CRS in clinical trial protocols under the new cooperative agreement are as follow[1]:

1) Develop and adopt a common budgeting template;
2) Use cost-per-participant as a common metric whenever feasible;
3) Retain some flexibility in specific costing elements;
4) Encourage capitation or fee-for-service reimbursement models;
5) Provide specification to Networks regarding costs covered by the CTU core award;
6) Retain flexibility in administration of domestic and international CTUs; and
7) Provide a mechanism for unexpected requests for resources and for reallocating costs based upon performance deviating from expectations.

The rationale for each of these recommendations is provided in the report.

[1] It is recognized that given the variety and number of trials sponsored by DAIDS across its networks, some trials will not fit the model being proscribed by these recommendations. It is the intent of the recommendations to be applied to the vast majority of trials; however, exceptions will have to be made for those situations for which the recommendations clearly do not apply.

INTRODUCTION

Background

The Division of AIDS (DAIDS) within of the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) currently sponsors six clinical trials networks designed to address NIAID's high priority areas of research. The Networks are currently operating in the fifth year of seven year cooperative agreements with the government. Commencing with the current grant cycle, starting in 2006, DAIDS initiated a funding mechanism that consisted of Clinical Trial Unit (CTU) Core funding and Protocol Implementation Funds (PIF). The CTU Core funding "…include(d) funds required to maintain the CTU Administrative Component, including Community Advisory Board support, and 'Core Costs' for each Clinical Research Site. The 'Core Costs' for a Clinical Research Site include(d) the funds for site administration as well as funds required to maintain the site and recruit, screen, enroll and follow sufficient participants in representative studies for each Network affiliation".[2] "Sufficient participants" was further defined to mean the average number of participants per month 'on study' is no less than 20 over a 12-month period.

The PIF funds were intended to provide Network Leadership "… managerial flexibility and (ability) to address unexpected scientific opportunities".[3] The PIF funds were designed to reimburse sites for the cost of implementing and running clinical trial protocols above and beyond maintaining the sufficient number (20) of participants on study. The availability of PIF funds to the CTU/CRS was to be contingent upon satisfactory performance measures and network priorities. The combination of the Core Award plus the PIF funds should be sufficient to allow a CTU/CRS to maintain site infrastructure and to actively engage in the trials initiated by the DAIDS network(s) with which the site is affiliated.

DAIDS is currently planning for the next cycle of competition for clinical trial networks that will be required to meet current and anticipated NIAID priorities; these new awards for Network Leadership Groups will be made in 2013, and those for Clinical Trial Units will be made in 2014. As part of its current thinking, DAIDS anticipates the research foci of the Networks will be expanded to include other infectious diseases, in particular tuberculosis and hepatitis, as well as to increase emphasis on co-morbidities of HIV/AIDS. Specifically, DAIDS is contemplating releasing four RFAs for HIV/AIDS Networks dealing with Vaccines, Therapeutics, Prevention, and Pediatric and Maternal Health; the research agenda will focus on HIV as well as on two major co-morbidities, tuberculosis and hepatitis. An RFA for a Network in non-HIV infectious diseases will also be sponsored by the Division of Microbiology and Infectious Diseases (DMID) of NIAID. Importantly, DAIDS is also contemplating having fewer Clinical Trial Units – approximately 25 –

[2] Language is from RFA-AI-005-002; 2005)
[3] Language is from RFA-AI-05-001, 2005)

each with between four to eight Clinical Research Sites associated with it. Some of these CRSs might be "protocol specific"; in essence a reserve site that can be accessed for surges in protocol activity. Each CTU is expected to be affiliated with three or more of the leadership networks. Each CTU would have administrative oversight for the CRSs within their CTU. One goal is to provide greater resource sharing among CRSs within the CTU, resulting in greater efficiency from this Network structure. DAIDS anticipates this revised structure will also increase the flexibility of the networks, so that CRSs could readily and cost-efficiently perform work across disease areas and across the spectrum of prevention and therapeutic clinical trials protocols. To facilitate this, in the next round of cooperative agreements DAIDS would like to have all the networks use a uniform method for determining the costs of a CRS to participate in a DAIDS-sponsored clinical trial. Such a system would allow a CTU to respond quickly and accurately to a budget request from network leadership for a CRS to participate in a protocol, regardless of the network making the request or the specific disease area that is the subject of investigation in the protocol. The ability of a CTU to respond quickly in terms of developing budgets for participating in a protocol will allow network leadership to expedite getting protocols implemented and into the field. Additionally, the CTU should be able to reallocate resources for their most efficient use. DAIDS tasked the HIV/AIDS Network Coordination (HANC) Project with developing recommendations for a uniform method of costing protocols that could be implemented in the next cycle of cooperative agreements, starting in 2013/2014.

Objectives

The overarching objective of this project is ***to recommend method(s) to DAIDS for developing the costs for CRS protocol participation that could be applied to all Clinical Trial Units/Clinical Research Sites for all trials sponsored by DAIDS through any of its Clinical Trials Networks.*** The recommendations should take into account:

- Current methods used by DAIDS Networks to develop protocol budgets for sites;
- A determination of what is currently working well and what can be improved upon in the DAIDS Networks for the development of protocol budgets;
- Lessons learned and processes that have served well in other clinical trial contexts (e.g., industry, NCI cooperative oncology trials);
- The dynamics involved in maintaining a clinical trial network of geographically distributed sites that are ready and capable of implementing clinical trials while assuring that trials are budgeted as efficiently as possible;
- The diversity of clinical trials sites in terms of geography, institutional infrastructure, mission of host institution, regional cost variation, local employment laws and regulations and other relevant factors;
- The need to be cost efficient when considering the number and variety of clinical trials that will be implemented over the course of the next set of cooperative agreements;
- The need to account for deviations from plans (e.g., retention issues, under-enrollment at a site, etc.);

- The need to assure transparency in site budgets and accountability for the use of funds provided to sites;
- The need to assure that the complexities arising from studies co-funded by different Institutes, Centers, or Agencies are adequately addressed;
- Trends in clinical trial design that might impact the types of trials that will be sponsored by DAIDS over the course of the next decade, and the need to assure that the uniform costing guidance will be applicable to these trials; and
- The need to reallocate funds as protocol enrollment deviates over time from initial projections or unexpected changes in protocols.

Issues Considered in Developing the Recommendations

Although the objective itself seems straight-forward, it was important that in developing the recommendations – which may guide how NIAID invests hundreds of millions of public dollars in clinical trials over a seven year period – to be aware of and sensitive to a number of issues inherent in the nature of the DAIDS-sponsored networks and the trials developed and implemented by these networks. Some of these were touched upon in the objectives section above. In addition, the following considerations and limitations were taken into account in developing the recommendations.

1. **Focus on Clinical Site Costs, not the Total Cost of Each Protocol.** It is important to note that this project actually has a narrower focus than developing a uniform method for the overall budgeting of clinical trial protocols. Specifically, the focus is on budgets prepared by or for the CTU/CRSs for participation by the site in a trial, and not on the full cost of a given clinical trial protocol. A different model might have broadened the focus extensively to examine the full costs of each clinical trial sponsored by the DAIDS Networks. At the extreme, such a model would have required allocating costs of the Network Leadership Core/Operations Center, the Network Central Laboratories, and the Network Statistical and Data Management Centers (SDMCs) to each trial initiated by these entities. Conceivably, under such a model, for example, the Network Leadership would solicit proposals not only from the CTU/CRSs for participating in a trial, but from a list of eligible Laboratories and SDMCs as well, wherein "eligible" might be determined by a pre-qualified list of interested and capable organizations. However, the recommendations described in this report are more circumscribed, and take into account the likely structure of the Networks under the re-competition – one in which each network will continue to have a Network Leadership Group, a Central Laboratory, and a SDMC, and in which a smaller number of CTUs than exist at present will each have greater administrative responsibilities. Under this structure, the key variable costs associated with a given protocol are the costs of the sites to participate in the protocol. Having a uniform method for developing site budgets for protocol participation will increase protocol cost transparency, allocate resources efficiently and will facilitate rapid completion of this part of the protocol development process.

2. **The CTU/CRSs Represent a Broad Diversity of Sites.** There are a number of ways in which the sites differ, including:
    - ***Geographic Diversity*** – The DAIDS networks of CTU/CRSs span five continents. This geographic diversity includes: regional variation in costs of labor, supplies and laboratory procedures and tests; regulations that apply to the local work-force; and the socio-economic well-being of the population where the CRS is located.
    - ***Institutional Infrastructure*** – While many of the CRSs are located in academic institutions and their associated medical schools, others can be better characterized as free standing clinics. The type of institution might impact the ability of the CTU/CRS to respond rapidly to requests for initial and revised budgets.
    - ***Strength of Linkage to Primary Institution*** – Some CRSs are tightly linked to their host institution, while others might be more loosely associated with the host. Conceivably, this could impact the degree to which the host institution would provide support – administrative, financial and otherwise – to the CRS.
    - ***Primary Mission of Institution*** – Many of the CRSs have a primary focus on research, while others also provide care and prevention services.
    - ***Experiential Diversity*** – some CRSs have years of experience in Good Clinical Practices and conducting clinical trials, while others are newer to the process.
    - ***Other facets of diversity*** – There are myriad of ways in which CRSs might differ from one another, but most will not impact the focus of the present report, i.e., the ability of the CTU to respond rapidly and accurately to budget requests from Network Leadership.

3. **Maintain Balance between Cost Effective Protocols and Sustaining Capabilities at Networks.** In the typical "Pharma Model", most CRSs are entities focused on their own missions (treatment, research), and take on clinical trials as an "add-on" activity. Hence, the Pharma sponsor is not responsible for maintaining the basic infrastructure of the CRS, but frequently will pay for marginal costs to the site for running the clinical trial, as well as incentive payments to the site for willingness to take on the trial. This is frequently implemented in terms of a cost per participant that forms the basis for the contract with the site; in some cases, this cost might be negotiated with the individual site.

   The model for the relationship between DAIDS and its clinical trials networks, including their affiliated CTU/CRSs, is quite different in most cases. For many of these sites, without the support of DAIDS, staff would be unfunded, equipment would not be purchased, and, in general, the site would be unable to operate. Any uniform method for costing protocols applied by Network Leadership to the sites must be cognizant of this difference between the DAIDS model and the typical Pharma Model. In general, the

Pharma Model presumes a strong clinical or institutional existent infrastructure that is independent of individual study funding.

The goal of DAIDS and Network Leadership should be to assure that budgets for protocols are reasonable and accurate, but also to assure that the necessary site infrastructure required to engage in a number of protocols over the course of the cooperative agreement is not compromised. For example, at the extreme, one could envision a Pharma Model applied to the CTU/CRSs, in which they are paid for participating in a protocol, and in between protocols, funds are not provided for maintaining necessary site infrastructure. This would result in the site releasing and re-hiring staff repeatedly (assuming job-appropriate staff are readily available for re-hiring). The training costs, loss of experience and knowledge involved in such a system would far outweigh the benefit having the most cost-effective protocol. Hence, while the recommendations for a uniform method of costing protocols do not explicitly include considerations for sustaining site infrastructure, any such recommendations must take into account that protocol-specific funding is an essential component to maintaining the research capacity of the clinical trial networks. (Even in the event that key staff – e.g., those who are hard to replace or in whom significant training resources have been invested – are retained, disruptions to the site can be significant). In general, site capacity should be linked as tightly as possible to the trials conducted by the DAIDS networks, recognizing that there will be a natural ebb and flow to the numbers of clinical trial participants that the site follows during any given time period; there is neither interest nor the means to pay for unused capacity.

Related to the issue of assuring maintenance of site capacity is NIAID's interest in seeing that sites in resource limited settings continue to build capacity to implement and run clinical trials. These clinical trial settings may pose issues that are not normally found in other settings. Members of this Working Group have heard of problems dealing with such things as: differences in employment laws causing problems (i.e., many nations do not have the flexibility that the US has to hire staff for short periods of time corresponding to the needs for these staff on a given protocol); the requirement to provide significant severance pay for staff who are let go; and the problem of investing in training staff for technical positions who use the new skills to market themselves for better paying positions, resulting in high turnover for key positions at the site.

4. **Clinical Trial Logistics.** Clinical trials rarely go exactly as planned. Some sites may under-enroll or enroll much more slowly than anticipated, while other sites might over-enroll and enroll more rapidly than anticipated. Some sites might experience more drop-outs than others. There may be unexpected safety visits at one or more sites. The quality of the data and specimens will likely vary across sites. Once a protocol opens, sites may make unexpected requests for resources. The DSMB, in its independent review, may call for major modifications to the trial. In any event, a budget model

should have the flexibility to account not only the budget for a trial that goes exactly as planned, but also deviations from the plan. The recommendations should also take into account the extent, if any, to which superior performance at a site is rewarded, and, conversely, to which sub-par performance is penalized. In addition, significant costs are incurred at a site even prior to the protocol opening, even if no patients are ever enrolled at the site.

The recommendations should also consider the phases of protocol planning, implementation, and close out. While PIF are not awarded to a site until the IRB approves the protocol, sites still have protocol preparation costs prior to IRB approval. The recommendations should take into account how best to budget for and reimburse a site for these implementation costs.

5. **Changes in Clinical Trial Design.** The recommendations will impact how protocol budgets are prepared for up to 10 years (i.e., the new Cooperative Agreements will likely run until ~2020-2021). Therefore, to the extent possible, the recommendations should be flexible enough to accommodate new types of clinical trial designs that are expected to emerge over that time period. One trend that appears to be emerging, based to some extent on frustration with the costs and time associated with the traditional "gold standard" Randomized Clinical Trial (RCT), is the use of what is referred to as Bayesian, pragmatic, or adaptive designs in clinical trials. The FDA issued Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials" in February, 2010 and also issued Draft Guidance for Industry on Adaptive Design Clinical Trials for Drugs and Biologics in February, 2010. The key characteristic of so-called adaptive designs is the *prospectively planned* modification of trial design characteristics based upon pre-specified analyses of the data (usually interim data) from participants in the study. These modifications could result in the following: changes in sample size in one or more arms of the trial or of the overall trial; addition or deletion of arms of the trial; changes in the treatment regimens for the various arms of the study; changes in the number of study visits in one or more arms; and a host of other changes as specified *a priori* in the adaptive trial design (FDA, 2010a; FDA, 2010b). Obviously, all of the example modifications mentioned above have implications for the cost of a trial. Any budget guidance developed in the recommendations should be flexible enough to accommodate changes in the trial design during its course, whether these changes are specified *a priori* based upon meeting certain trial parameters, as in adaptive trials, or whether these changes are due clinical trial logistical or regulatory issues (see section 4, above).

6. **Account for *all* Costs.** In the funding model described above, and under the current cooperative agreement, the two primary sources of funding for a CTU/CRS are CTU Core Funds to maintain the CTU Administrative Component and support an average of 20 participants on study; and the PIF intended to reimburse sites for the cost of implementing and running clinical trial protocols above and beyond maintaining the 20

participants on study accounted for by the Core Funds. However, sites engage in activities that appear to be at the nexus of site infrastructure costs and protocol specific funding. For example, consider the advertising costs associated with raising public awareness of the site, versus advertising for a particular trial – these costs would overlap when a site has only a single large trial during a given year. Similarly, staff training costs that potentially benefit all trials, but may only be applied to a specific trial during the course of the year, might be difficult to categorize as either infrastructure or protocol specific, and therefore might be inadequately covered by either source of funds. Similar issues can arise for equipment, supplies, and a myriad of other expenses that a site incurs. To the extent possible, assuring that all legitimate costs are covered by an available funding mechanism and clearly delineated– whether they are protocol costs or Core costs – is in the best interests of all stakeholders.

A recent assessment by the Institute of Medicine (IOM) of the National Cancer Institute's Clinical Trials Cooperative Group Program can be instructive for DAIDS-sponsored trials. This assessment found that only 60% of NCI-sponsored phase III trials are actually completed, representing a waste of financial resources. One of the problems underlying this less than stellar track record, according to the IOM report, is that about half of the costs of these cancer clinical trials are borne by the clinical investigators and clinical care providers, causing them to seek supplemental funding to complete trials. As a result, one of the recommendations of the IOM is that the NCI provide adequate funding to site and trial PIs to cover the time required for involvement and leading trials (IOM, 2010). Extrapolating this to DAIDS-funded trials, it is important to assure that the costs of trials – including, but not limited to the time and effort of PIs – are fully accounted for in trial budgets; such assurance will increase the likelihood of successfully completed trials. Support for scientific effort at the site level has been raised by CTU PIs as a major challenge under the current funding mechanism.

7. **Minimize Disruption.** It must be emphasized that in developing the recommendations the goal was to build upon what is working well in the networks and to use "lessons learned" in constructing the proposed method(s) for costing protocols. Unless there are compelling reasons to do otherwise, the recommendations include incremental changes to what is currently being done in the networks, with an eye toward minimizing disruption and the need for Network leadership as well as CTU/CRS staff to learn entirely new methods for constructing protocol budgets. In addition, it was important to anticipate any consequences of changes were represented in the recommendations, so that Network and CTU/CRS staff could prepare for and deal with the consequences well in advance.

METHODS

Overview

The recommendations developed in this report were based upon a variety of inputs. These included:

- Literature searches, especially on costing for clinical trials and alternative research designs ("adaptive", "pragmatic", or "Bayesian" designs).
- Review of materials from the Networks, including SOPS, relevant portions of MOPs, and sample budgets for trials.
- Deliberations at two face to face meetings of the Protocol Costing Working Group (membership shown below).
- Additional meetings, conversations, and input on an ad hoc basis with members of the Working Group.
- Feedback from a variety of sources within DAIDS and in the DAIDS networks on earlier drafts of the recommendations.

Literature Review and Industry Contacts

We conducted literature searches on MEDLINE using combinations of the terms "clinical trials", "budgets", and "costs". After weeding out numerous articles on cost effectiveness, there were few articles remaining dealing with costs of clinical trials, and none dealing with budgets. A few articles were helpful (Emmanuel et al, 2003; Evans et al, 2000; Roche, 2002) in terms of delineating the tasks and associated time spent on various phases of clinical trials, but the information was not additive to the information already used by the Networks in developing protocol budgets for site participation in a trial. The literature on alternative clinical trials, and especially the FDA Guidance documents, provided insight into the types of adaptations that might take place in "Bayesian" trials; while these adaptations clearly would have impact on the budget for a trial, we could find no literature that specifically addressed the budgetary impact of Bayesian trials – other than the general sense that such trials would afford answers to research questions sooner, and thereby reduce trial costs.

In addition, we contacted a few industry or quasi-industry organizations. For example, we reached out to the Clinical Trials Transformation Initiative (CTTI) to ascertain whether they had any initiatives dealing with budgeting for clinical trials (they did not). We also contacted clinical trial software vendors to gain insight into the types of costs they include in their budgeting models. Again, the information gleaned was not additive to the information already used by the Networks. Finally, in a few industry contacts, we found that they consider their budgetary practices to be proprietary, and were reluctant to share information.

Network Materials

Fiscal representatives from the various networks were asked to send SOPS or other relevant documents to HANC for their review. In addition, HANC staff reviewed relevant portions of

materials (e.g., MOPs) on the networks' websites. These materials were used to familiarize HANC staff with protocol budgeting similarities and differences across networks. These processes were discussed by each of the Network representatives as part of the agenda at the first face-to-face meeting on September 13, 2010 in Seattle, WA (see below).

Face-to-Face Meetings

Two face-to-face meetings of the Protocol Costing Working Group were held. The first meeting, held in Seattle, Washington on September 13, 2010, provided a forum for the networks to share protocol costing procedures and processes with one another, to discuss the issues they each faced in developing protocol budgets, to share what had been working well and what they thought could be done better, and to discuss the desired approaches that DAIDS should consider in developing a uniform system for developing protocol budgets at the CTU/CRS level. (The agenda for this meeting, as well as a list of attendees, is shown in Appendix A). The deliberations of the meeting as well as some additional post-meeting thoughts that were e-mailed to HANC over the subsequent several weeks are summarized in a brief report, shown in Appendix B.

The second face-to-face meeting was held in Arlington, Virginia on October 27, 2010. The timing of this meeting was arranged to follow the NIAID sponsored Town Hall Meeting on October 26, which discussed the restructuring of the NIAID clinical trial networks for HIV/AIDS and other infectious diseases. Attendees at this meeting included the Network representatives at the earlier September meeting as well as two additional people from OCSO, the Program Officers for the Networks and the Grants Management Officer for NIAID. (See Appendix C for a list of attendees at this meeting). The purpose of this meeting was to review and discuss the similarities and differences among the Networks in terms of their approaches to protocol costing, especially in light of the information obtained from the Town Hall meeting regarding restructuring of the networks (reviewed at the meeting), and to delineate possible solutions to meeting the objectives of the project.

RECOMMENDATIONS

General Considerations

The recommendations described in this section need to be consistent with the intended revised network structure currently planned under the new set of cooperative agreements for the Network Leadership and for the CTUs. In particular, as described above and elaborated upon at the NIAID Town Hall meeting on October 26, 2010, there will be fewer (approximately 25) CTUs than currently exist, each associated with four to eight CRSs. Each CTU will have to be associated and have scientific competency to conduct clinical trials with at least three of the five networks, although at present it is not anticipated that a CRS will need to be "pluripotent".

DAIDS anticipates that funding will flow to the CTU from DAIDS (analogous to the current "Core CTU" funding) and from the Network (analogous to the current "PIF" funding). The CTUs will have greater administrative responsibility than at present; in particular, all funds to a CRS will come from the CTU with which it is aligned. Hence, under this planned scenario, neither DAIDS nor the Network Operations Center will provide funds directly to the CRS – they will all flow through the CTU. At present, it is anticipated that the Networks will have "Consortium Agreements" with the CTU *and* with the CRS; among other things, these agreements will specify the nature of the work to be performed and the requirements that the CTU and CRS must meet to receive funds. Note the consortium agreement between the Network and the CRS is not associated with funds from the Network, but specifies the conditions the CRS must meet in order to receive funds that the Network has provided to the CTU. (It should be noted that members of the working group expressed concern about the ability of Network Leaderships' host institutions to initiate and negotiate a large number of consortium agreements with CRSs when there are not funds accompanying them).

With the foregoing as background, the following recommendations are offered for consideration:

1. **Develop and Adopt a Common Budgeting Template**
   Five of the six current DAIDS Networks use some sort of budgeting template to guide development of budgets to estimate the costs of a site to participate in a clinical trial protocol; the sixth network indicated its willingness to use a template for developing budgets. As described in the report summarizing the September 13, 2010 meeting (see Appendix B), the ACTG and IMPAACT use the same basic template, the HVTN and HPTN each uses their own study-specific templates, and INSIGHT – while not calling it a template per se – obtains a time and events schedule for the protocol and assigns costs to these events using standardized labor, device, procedure, and lab costs. With the planned requirement in the re-competition that each CTU be associated with at least three Networks, the use of a common budgeting template will facilitate collaboration across the Networks.

As discussed later, development and adoption of a common template does not necessarily imply that all networks will *use* the template in the same manner. Issues of costing the elements in a template and how CTUs will be reimbursed – in terms of structure and timing of reimbursements – are not dictated by the use of a common budgeting template. Decisions regarding whether or not all Networks will be required to adopt uniformity on these issues is separate from a requirement that all Networks use the same budgeting tool. The elements for the common budgeting template are described below.

a. Elements of a Common Budgeting Template

i. Schedule of Visits: The protocol-related visits must be specified. Below is an example from part of a budget template used for HVTN 205.

Schedule of Visits and Procedures											
Visit	1	2	3	4	5	6	7	8	9	10	11
Day		D0	D14	D56	D70	D112	D126	D168	D182	D273	D364
Month		M0	M0.5	M2	M2.5	M4	M4.5	M6	M6.5	M9	M12
Visit Type	Screen	VAC1	Follow-up	VAC2	Follow-up	VAC3	Follow-up	VAC4	Follow-up	Follow-up	Follow-up

This particular protocol had a screening visit to determine eligibility and obtain informed consent, a vaccination visit on Days 0, 56, 112, and 68, and scheduled follow-up visits on Days 14, 70, 126, 182, 273, and 364. It is clear that the different visits involve procedures requiring disparate amounts of site personnel time (both clinic and lab staff) and various clinic supplies, resulting in different amounts of site laboratory procedures and analyses. Specifically for each visit, the following must also be specified:

ii. Personnel Costs:

1.) Clinic-related Personnel – including Physician, Nurse, Pharmacist, Recruitment/Retention counselor, Data Management staff, Phlebotomist, etc. (Specific staff involved in the clinic will vary by protocol and by type of visit within a protocol);
2.) Lab-related Personnel – Lab technician(s);
3.) Administrative Personnel – P.I.; Clinic Coordinator; Administrative support.
4.) Community Education Costs - Costs associated with community education that is specific to the individual protocol and not already accounted for by the site's Core budget.

iii. Laboratory Costs:

1.) A complete listing of procedures, assays, and tests required at the on-site laboratory for samples collected at each visit;
2.) Listing of any specialty laboratory requirements for each of the visits;
3.) Other laboratory-related costs (e.g., facility fees).

iv. Supplies: These should include laboratory, clinic, and other supplies that are required for each visit.

v. Specimen Storage: Any costs associated with the requirement to store specimens obtained during the trial need to be specified.

vi. Travel: Travel associated specifically with the protocol should be specified.

vii. Participant Reimbursement: Costs associated with reimbursing participants for each type of visit (some types of visits might have different reimbursements than others) should be specified.

viii. Advertising Costs: Costs associated with recruiting participants into the specific protocol (as opposed to general advertising about the site) should be specified.

ix. Equipment: Sites generally will use existing equipment when available; if protocol-specific equipment is required by a site, justification should be provided for this purchase.

x. Consultants: If the protocol is likely to require capabilities not typically contained within the core CTU or CRS staff, accommodations may need to be made to include consultant assistance.

xi. Other Expenses: All other expenses associated with performing the clinical trial (e.g., shipping specimens, translation of documents) that are not normally paid for by the CTU Core award should be specified.

(See recommendation 3a below - Re: the desirability of standardizing costs as much as possible, while retaining some flexibility in costing to allow for local differences. This first recommendation deals specifically with assuring that all costs are identified).

b. **Screening Ratios and Protocol Costs.** An important driver of protocol costs is the ratio of the people screened to those who actually enroll in a trial. People who show up to a site to be screened may not go on to become enrollees in a protocol for a number of reasons, including personal decisions not to enroll after learning more details about the trial, as well as not being eligible for further participation due to any of a host of reasons uncovered during the screening visit. Nonetheless, the costs of screening people – even though they may not become participants in a trial – are part of the cost of a protocol and therefore need to be included in the budgeting template. In using a budgeting template, this is often implemented by recognizing that for each enrollee screened, there were a number of other potential participants, and reimbursing for this effort accordingly. Estimating the ratio of the number of people screened versus those who eventually enroll in a protocol should take into account prior knowledge about the screening/enrollment ratio as well as what is known about the inclusion/exclusion criteria for the protocol and the likely impact this will have on the ratio. Accurate estimates of this ratio will result in more accurate protocol budgets.

c. **Developing the Common Budgeting Template.** We suggest that fiscal representatives from the networks (ACTG, HPTN, IMPAACT, HVTN, INSIGHT, and MTN) meet under the auspices of HANC to develop a common budgeting template, taking into account the elements described above as well as the practices they have developed and honed over the past five years.

2. **Use Cost-per-Participant as a Common Metric Whenever Feasible**

A common budgeting template readily lends itself to the use of a common metric to compare costs. Specifically, regardless of the decisions regarding flexibility allowed CTUs for specifying specific cost elements in the budget template (see number 3 below) or how CRSs are reimbursed (see number 4 below), once the budget template is completed for a CRS, the total cost divided by the proposed number of enrollees for that site provides a very useful metric – the cost-per-participant. The use of this common metric allows for a number of useful comparisons, such as the cost between CRSs within a CTU, the costs between CTUs within a Network, the costs between protocols, and the costs of a DAIDS-sponsored trial relative to trials sponsored by other organizations. The latter type of information will facilitate trial budgeting when there are agencies in addition to DAIDS co-funding the trial. Nonetheless, it must be recognized that some types of trials – e.g., prevention trials done at community level – are not amenable to calculating cost-per-participant.

3. **Retain Some Flexibility in Specific Costing Elements**
As described above, the budgeting template is a tool for assuring that all protocol-related costs are included in estimating the cost for a CRS to participate in a protocol; it does this by delineating all the cost-associated elements that go into a protocol. However, the template itself is "neutral" as to how the cost associated with each element is established and entered into the budgeting template. For example, consider a study nurse's time required for a screening visit. The budget template might specify that a study nurse is involved in a screening visit. But how much of his/her time should be specified for the visit, and at what hourly rate? The networks currently differ in their approaches to the amount of flexibility allowed across sites on costing these elements. Some of the networks currently work individually with their CRSs to tailor both the time and the cost of that time so as to accommodate the local conditions at the CRS.

Other networks – especially the larger networks with many CRSs – take a different approach. They have fixed the amount of time and the cost per time so that all CRSs receive the same amount of funds, although for some networks, differences are made for domestic US CRSs versus international CRSs. These networks have neither the time nor the resources to "negotiate" individually with each of their many CRSs, yet the budgeting system appears to work well for them. Alternatively, the system of individually tailoring costs to each CRS appears to work well for those networks using that system. Using this information as a guide to discern and retain what is working well, the recommendation is that the networks retain flexibility in *how* the common budgeting template is used. That being said, there are a number of areas that can likely be standardized across networks (taking into account domestic versus international sites), thereby increasing flexibility of CTUs to respond to budget requests made by any of their affiliated networks.

   a. **Standardize Direct Costs of Common Procedures to the Extent Possible.**
   Procedures that could prove amenable to cost standardization across networks include:
      - Intake physical exam;
      - Most site laboratory procedures – e.g., hematology, chemistry, liver, pregnancy, HIV screening, etc.;
      - Some specimen storage and shipping costs.
      - Regulatory submission costs.

The list should include other items as determined by fiscal representatives from the current networks and these representatives should reach consensus on the costs assigned to these common procedures. Only direct costs should be pre-specified, as sites will differ in their indirect rates.

4. Encourage Capitation or Fee-for-Service Reimbursement Models

Just as the use of a common budgeting template does not necessarily require entering common costs into the template for activities across CRSs, CTUs or Networks (see section 4.3 above); neither does it dictate the manner in which sites will be reimbursed for their work on a trial. The use of a common budgeting template, especially with the calculation of the common cost-per-participant metric, could be combined with a per capita method, a fee-for-service method, or a cost reimbursable method for reimbursing a site for their work on a protocol. Specifically:

- For a ***capitation reimbursement model***, the cost/participant would be used to calculate the budget for a site based upon the number of participants expected in the trial. The site would only be reimbursed for the actual number of participants recruited into the trail, regardless of the number expected.

- For a ***fee-for-service reimbursement model*****,** the budgeting template would be used to calculate the cost associated with each visit in a protocol; the site would be reimbursed only for those visits and those procedures during a visit that actually occur. For example, if an enrollee misses a visit, there is no reimbursement associated with that visit as there were no incurred costs.

- For a ***cost-reimbursable model***, the budgeting template would be used to calculate the cost/participant for a site. Specifically, the annual budget would be determined by the number of participants expected multiplied by the per-participant cost, and prorated for the portion of the protocol expected to be performed at the site that year. The site would then prepare a budget indicating levels of effort, materials, supplies, travel, etc., that is commensurate with that budget, and would be reimbursed accordingly. Unless the budget is modified as a result of performance that differs from expectations (e.g., fewer participants enrolled than expected), the site will be reimbursed according to the budget.

At present, five of the six networks use a cost reimbursement model to disburse funds to sites, even though four of these five networks use a budgeting template. The sixth network uses a fee-for-service model (see Table 1 in Appendix B).

Advantages/Disadvantages of Capitation and Fee-for-service Models. The advantage of a fee-for-service and, to only a slightly less extent, a per capita reimbursement model, is that it enhances accountability; (i.e., sites get paid for performance; if they do not perform - e.g., do not enroll the expected number of participants - they do not get paid). Hence, accountability appears to be high. Also, to a certain extent, both of these are easier for the contracting organization to administer, in that there are fewer elements to review in order disburse funds to a site.

One potential disadvantage of these two models from the CRS perspective is that the funds might be distributed in a "lumpy" fashion (as participants enroll and/or visits occur), while the staff requirements for sites (which usually account for most of a protocol's costs) are relatively steady. Hence, there might be a mismatch between the disbursement of funds and the incurrence of costs, resulting in "cash-flow" problems at a site. Unless significant funds are provided as part of the CTU/CRS core award to maintain site capacity (see Recommendation 5, below), these cash-flow problems could be significant for some sites. A second potential disadvantage of these methods is that the host institutions for the CRSs are, in many instances, much more familiar with dealing in a "grant" environment, in which forms such as PHS 398 or PHS 2590 are used as the basis for determining budgets for a project. There may be institutional resistance at the grants offices of some organizations in moving to a capitation or fee-for-service model for contracts, especially when these are proposed on a fixed-price basis. Yet a third potential disadvantage for some institutions is that fee-for-service may bear lower F & A costs for the institution, so that the total value of the contract to the institution is less than it might be under some other arrangement. (Note that if the fee-for-service is designated as 'patient care', the cost for patient care already has the F & A folded into many institutions' cost structure).

Advantages/Disadvantages of a Cost-reimbursable Model. The potential advantages and disadvantages of a cost-reimbursable model – especially one that is predicated on a budgeting template –essentially mirror the advantages and disadvantages of capitation and fee-for-service models. That is, the advantages include familiarity with the model by the grants office of the CRSs' host institution. Also, it allows a CRS to receive funds on a regular basis, which more accurately reflects how actual costs are incurred during the year. However, accountability is more difficult to achieve. Rather than being paid on the basis of *actual performance*, CRSs are paid based on *intended effort for* the year. If the effort does not result in the expected performance (e.g., the number of participants enrolled in a trial), there will be mismatch between pay and performance. In the extreme, a site can be paid for the full cost of enrolling their allotted number of participants without actually even enrolling a participant into the trial. Therefore, use of a cost-reimbursable model requires careful monitoring by the contracting organization to oversee performance and amend the agreements accordingly. This places an administrative onus on the contracting organization; this has been successfully navigated by several of the networks.

In sum, although capitation and fee-for-service models offer advantages over the cost reimbursement model, the recommendation is to *strongly encourage* the use of these reimbursement models rather than to require them. This takes into account the possible institutional unfamiliarity and concomitant resistance with these models by the host institutions of some CRSs, and recognizes that, by closely monitoring performance of CRSs and amending agreements accordingly, cost-reimbursable models can be used to attain accountability approaching that obtained by the other two models.

5. **Provide Specification Regarding Costs Covered by the CTU Core Award**
   One of the common themes of the protocol costing working group meetings is the need for greater budget transparency so that networks can better understand the flow of revenues to sites. This goal can be achieved by several actions:

   a. **Protocol Start-up Costs Funded at CTU/CRSs**. It has been suggested that in the new awards, DAIDS will provide costs associated with starting a study irrespective of planned enrollment. By having a clearly defined "bucket" of funds earmarked for pre-IRB approval protocol start-up costs, this will remove pressure on the Networks to provide these funds as part of their protocol funds and allow them to focus on the costs of actually running the protocol. These protocol start-up costs could be allocated to Networks to administer in a manner similar to the PIF awards, so that the Networks will have control of all funds associated with their protocols.

   b. **Share Budgeting Assumptions with Networks.** The amount of funds that is awarded to each CTU as part of their CTU Core award is predicated in large measure on algorithms dealing with expected proportions and types of staff and other costs that should be covered in the Core award. Providing that information to the Networks will better enable the Networks to assure that staffing and other cost elements for protocols initiated by the Network are adequately accounted for by a combination of the Core award and the protocol funds. In addition, it is important for the Network Leadership groups and the CTUs to understand that *all reasonable* non-protocol, site infrastructure costs are being covered by the CTU award (e.g., funds for replacing broken or worn out equipment; facility rental costs; etc.)

   c. **Provide a Mechanism for Post-Close-out Costs.** Even after a protocol is closed, there may be some costs associated with the protocol (e.g., data and specimen storage, commitments to provide HIV testing to vaccine participants – i.e., to deal with the issue of vaccine-induced seropositivity, etc). It is important for these funds to be provided – either through the Core award or through the Networks as part of their protocol administered funds.

6. **Retain Flexibility in Administration of Domestic and International CTUs**
   There is great diversity among the CRSs in the DAIDS networks, and there will continue to be so under the renewal. One important aspect of diversity is the difference between most US sites and international sites, especially those in resource limited settings. The ability of the host institutions in resource limited settings to bear or carry costs differs substantially from most domestic institutions. In addition, issues of staff turnover and the concomitant need to train staff, the ability to hire part-time staff, the nature of

employment contracts for staff, etc., are quite different in resource limited settings. Any revised mechanism for costing and funding protocols – as well as for funding CTUs – must take this diversity into account and allow for flexibility in how funds are administered in order to accommodate local conditions.

7. **Provide a Mechanism for Unexpected Requests for Resources and for Reallocating Costs Based upon Performance Deviating from Expectations**

   A budget is a statement of expectation for expenditures. The actual costs for implementing a trial may differ from the budget for a number of reasons. One major reason for budget deviations is that the protocol does not go according to plan (in terms of enrollment rates, retention, unexpected safety visits, etc.). Hence, in addition to the possibility that a budget may not accurately reflect the costs a site might incur even if the protocol goes exactly according to plan, there will be deviations from the budget due to unexpected issues that arise during protocol implementation that impact costs. The CTUs and/or the Network Operation Centers should set aside contingency funds to deal with protocol-driven unexpected requests for resources. Conversely, funding at CRSs should reflect deviation from plans – e.g., lower than expected enrollment; poor retention of participants; changes triggered by DSMB reviews. In addition, Network Operations Centers need to be provide the flexibility necessary to reallocate funds from one protocol to another should performance on a given protocol deviate markedly from expectations (e.g., very slow enrollment on a given protocol might be taken as a signal to reallocate funds to a more promising protocol).

SUMMARY AND CONCLUSIONS

A uniform method for estimating the costs of participation of a CRS in a DAIDS sponsored protocol will provide many benefits. It will facilitate the development of budgets by Networks and CTUs, thus expediting this part of the protocol development process. It should also reduce ambiguity that occasionally occurs when different networks ask a CTU/CRS to prepare budgets; one outcome of this reduced ambiguity should be increased budget accuracy.

At the behest of DAIDS, HANC took the lead in developing recommendations for a uniform protocol costing methodology. We worked closely with fiscal representatives from current DAIDS networks as well as numerous people within DAIDS. Although a literature review did not provide additional information not already contained in network approaches in estimating budgets for sites to participate in a protocol, it was one of the considerations that went into developing the recommendations.

HANC developed a series of recommendations that will result in greater uniformity in the development of protocol budgets. The most important of these is the need for networks to use a common budgeting template based upon the best features of templates currently used by most of the networks. However, rather than proscribe a Procrustean solution that requires every network to *use* the budgeting template identically (in terms establishing common cost elements across networks and reimbursing sites), HANC proposes allowing the networks to retain some flexibility for using the template in order to best accommodate local conditions and network-specific needs. Nonetheless, the recommendations provide a common metric – the cost–per-participant – that flows easily from the budgeting template and allows for a number of important comparisons (e.g., costs of protocols, costs across sites, costs to various co-funders of a study, etc.).

ACKNOWLEDGMENT

This project was supported by supplemental funds from the National Institutes of Allergy and infectious Diseases to grant U01 AI068614-01 Leadership Group for a Global HIV Vaccine Clinical Trials (Office of HIV/AIDS Network Coordination).

Appendix A: Ad Hoc Working Group on Protocol Costing Face-to-Face Meeting

September 13, 2010; Seattle, WA

Agenda

8:00-8:30	All	Working Breakfast, Welcome, Introductions
8:30-8:50	Jeff Schouten	Genesis of Protocol Costing Project
8:50 –9:20	Maureen Power	Current perspectives from DAIDS/OCSO
9:20-9:40	Rich Shikiar	Goals of Today's Meeting
9:40 – 12:25	Networks	Current Practices at Networks
9:40-10:05	ACTG Reps	ACTG Processes
10:05-10:30	HPTN Reps	HPTN Processes
10:30-10:45	BREAK	
10:45-11:10	HVTN Reps	HVTN Processes
11:10-11:35	IMPAACT Reps	IMPAACT Processes
11:35- 12:00	MTN Reps	MTN Processes
12:00-12:25	INSIGHT Rep	Insight Processes
12:25-12:50	BREAK and retrieve lunch	
12:50-1:30	Rich Shikiar; Group	Discussion of Issues to Consider in Developing Recommendations
1:30-4:00	Group	Next Steps for Development of Draft Recommendations

Attendees:

Linda Berman	**ACTG**
Linda Boone	**ACTG**
Kathy Hinson	**HPTN**
Gloria Pherribo	**HPTN**
Banks Warden	**HVTN**
Larry Smith	**HVTN**
Kimberly Hitchcock	**HVTN**
Brandy Price	**IMPAACT**
Jill Utech	**IMPAACT**
Carol Vincent	**IMPAACT**
Melissa DeGore	**MTN**
Judy Jones	**MTN**
Gregg Larson	**INSIGHT**
Maureen Power	**DAIDS**
Richard Shikiar	**HANC**
Christie Villa	**HANC**
Jeff Schouten	**HANC**

Unable to Attend Meeting:

Manizhe Payton	**DAIDS**
Teri Greenfield	**DAIDS**

Appendix B: Summary Report of Ad Hoc Protocol Costing Working Group Meeting

September 13, 2010

Introduction. During the first meeting of the Ad Hoc Protocol Costing Working Group held in Seattle on September 13, 2010, representatives from each of the Networks made presentations describing how each of their networks determines the budgets for clinical research sites to participate in their respective network's protocols. (See Attachment A for a list of the participants at the meeting). In addition, the OCSO representative at the meeting gave a presentation highlighting the current environment at DAIDS and the current thinking about the future of Clinical Trial Units (CTUs) and Clinical Trial Sites (CRSs). The purpose of this document is to *briefly* summarize the approaches of the six networks and to compare and contrast them in terms of key aspects involved in determining protocol budgets. As a caveat, it should be noted that the short summaries that follow cannot fully capture the richness and nuances of the presentations, nor the ensuing discussions about each presentation. However, while lacking the comprehensiveness of the full presentations, the summaries and the summary table that follows should accurately reflect key similarities and differences among the networks.

OCSO Summary for Current CTU Structure and Funding Areas for Improvement, CTU Funding Goals, Proposed CTU Funding and DAIDS Protocol Costing Goals:

Current CTU Structure and Funding Areas for Improvement

1. Multiple budget processes and funding mechanisms
    - Current Network RFA required Networks to develop own approach
    - Confusing to CTU & CRS; sometimes related to poor internal CTU communications
    - Requires significant effort at all levels
2. Aligning fund availability with need
3. Few incentives for cost containment
4. Capacity modifications
    - Adding capacity (new CRS) complicated and expensive
    - Subtracting capacity (closing poor performing, poor fit CRS) complicated
5. Transparency: Who's got what

CTU Funding Goals

1. Achieve efficiencies in funding and resource utilization
    - Encourage cost containment
    - Encourage resource sharing
    - Site capacity more tightly linked to trials

2. Clear lines of fiscal and programmatic authority and accountability
    - NIAID, Network, CTU and CRS
3. Introduction of project management discipline
    - Improved study projections, milestone driven, contingency planning
    - Work with host countries to improve the efficiency and timeliness of the research approval process
4. Provide core funding to:
    - Maintain and replace infrastructure
    - Provide staff stability at CTU/CRS
5. Facilitate partnerships and collaborations

Proposed CTU Funding

1. Core funding
    - Recalculate algorithm
2. Protocol Start Up Funds
    - Costs associated with initiating a study at a CTU/CRS irrespective of planned enrollment
3. Protocol Implementation Funds
    - Capitated per participant enrollment

DAIDS Protocol Costing Goals

1. Develop harmonized definitions of Protocol costs and costing mechanisms
2. Align use of PIF across Networks
3. Simplify and rationalize process for CTU/CRS
4. Focus on true costs, rather than estimates: gain better awareness of overall and true costs
5. Develop separate costing schemes for Start-Up and PIF capitation costs
    - Share resources when possible, avoid creation of redundant infrastructure
6. Provide funding at time of need
7. (Timely reporting of cash flow, use of funds)

Network Summaries – Determining Budgets for a CRS to participate in a protocol.

ACTG

1. Uses a template to calculate site costs for protocols
    - One template for U.S. sites and High-cost Non-U.S. sites; a second template for Low-cost Non-US Sites.
2. Templates include:
    - **Staff costs** (M.D., nurse, pharmacist, data manager), obtained by time spent (in hours) in each protocol activity by each category of staff multiplied by the hourly rate for that category of staff (e.g., nurse is $100/hour in U.S. template and $12/hour in Non-U.S. Low cost template).
    - **Clinic costs**, including supplies, facility usage fees, subject reimbursement, and costs for procedures (e.g., X-rays).
    - **Site Lab costs**, with cost for most safety assays set either by consensus of representative ACTG sites or by HHS Fee Schedule. (These costs are the same in both templates).
    - **Shipping costs**, determined by domestic versus international as well as by the type of shipment (e.g., CO_2).
    - **Storage Costs,** calculated per collection, and is set at different values in the two templates.
3. Site is awarded PIF allocation based upon a rolling average of enrollment, calculated separately by international and domestic enrollments. For example, if a site accounted for 8% of the enrollments in its category (e.g., domestic), it would be awarded 8% of the total PIF (domestic) budget for new protocols for the coming year.
4. For on-going protocols, site is awarded an amount for the year based upon % of protocol to be completed that year.
5. Site PIF budget also includes a small amount for scientific credit awarded to the site for activities such as publications, committee participation, etc, as determined from the annual site evaluations.
6. In sum, budgets are not tailored to individual site cost parameters. A site is primarily provided PIF budget for the year based upon whether they are U.S./High-Cost Non-U.S. or Low-Cost International, and their % of enrollees in their category over the prior years.

HPTN

1. Multiple funders from different NIH Institutes for each study presents distinctive issues, as a result, a "hybrid" model for developing protocol budgets has evolved.
2. A study-specific template is developed by the Operations Center.
3. Formal written guidance is provided to the sites, bolstered with informal discussions, so that the sites can complete the template.
4. The result of this is an estimate of the average cost of a study per site.

5. In many cases, the Protocol Chair or other investigators (e.g., supplemental RO1 funds for the protocol) will get involved in the development of the protocol budget as well.
6. The budget goes through several iterations – from a ball park estimate when the idea is presented as just a capsule concept; to a more precise estimate when it is a formal concept; to a detailed budget when the version 1.0 of the protocol has been set. This evolution (of both the science and the budget) often results in increased costs that are intended to reflect the realistic costs for carrying out the science.
7. Budget for a site is determined in part on the site's response to the written guidance document provided to the site. Based upon their response, budget may be altered to accommodate specific site requirements.

HVTN

1. Uses a protocol-specific template, determines costs per type of visit (including screening, vaccination, and follow-up visits).
2. For each visit, type of staff involved in the visit, the local laboratory procedures and supplies required during the visit, and specimen processing requirement for the visit (if any) are specified.
3. The template is provided to the site; each site customizes the template by filling in local salaries, fringe benefit rates, indirect cost rate, local costs of supplies, and participant reimbursement rate. They can also include other costs that were not included in the template (e.g., protocol-specific advertising costs). Finally, they also fill in the time requirements for each protocol activity by staff participating in that activity.
4. The basic metric used to compare across sites (as well as across protocols) is the per-participant site for each protocol.
5. The Core Operations Center reviews the resultant costs across all sites; if a site is an outlier in terms of numbers and/or amount of time allocated for staff on the protocol, or for other costs identified by the site, the Operations Center will engage in discussions (negotiations) with the site.
6. Final budget for the site is tailored to each site based upon these discussions.
7. Numbers of participants on a given protocol for a site is determined separately by the scientific operations group.
8. Total annual PIF budget for a site is determined as the sum of the per-participant costs for every protocol being performed at the site, multiplied by the number of participants expected to participate in each of these protocols for the year.
9. Once PIF budget is agreed upon with site, the site submits a PHS 2590 budget; cost-reimbursable sub-awards are issued based upon this.

IMPAACT

1. Uses the ACTG template in costing studies, albeit with a slight variation:
    - Uses just the "High-cost" non-U.S. template only for international sites.
2. Protocol budgets are reviewed by:

- Protocol Costing Working Group;
- Protocol Chair; Lab Group Representative; Clinical Trial Specialist; and Scientific Committee Chair.

3. Operations Staff incorporate changes; final review by fiscal Manager, and submitted to NEC.
4. As in ACTG, budgets are not tailored to site; all sites within a category (U.S. or International) enrolling the same number of people will receive the same PIF budget.

INSIGHT

1. Builds protocol budget using following steps:
    - Obtain time and events schedules for study and sub-study protocols.
    - Build study and sub-study visit payments using standardized labor, device or procedure, and lab (HHS CLAB) unit costs.
    - Determine per-capita payment amounts for coordinating centers.
    - Determine any coordinating center advance payments.
    - Develop accrual projections and visit schedules.
    - Prepare annual budget.
2. Support for studies come from multiple sources (US and Non-US Agencies).
3. Uses fee-for service model
    - Sites only paid if visit (i.e., service) occurs and data entry is complete.
    - Standardized fees results in same cost per participant at all sites.
    - No invoices required – if visit occurs, site is paid the proscribed amount (on quarterly basis).

MTN

1. Sites provide budgets to Operations Center in whichever format they prefer.
2. Budgets are reviewed in two Face-to-Face meetings during the year.
3. Budgets are translated into a cost/participant.
4. The Cost/ppt becomes a metric for comparing across sites.
5. Final budget is negotiated on a site-by-site basis, based upon the F-2-F meetings and on-going discussions.

Issues Discussed at the Meeting

HANC staff presented a list of issues to consider in protocol costing. These included taking into account:

1) … all phases of a trial, including planning, start-up, and post-close-out costs;
2) …the diversity of sites (geographically; institutional affiliation, etc.);
3) …deviations from plan (e.g., retention issues, under-enrollment, etc);
4) …the need to assure that all reasonable site costs are covered (i.e., when considering PIF funding, CTU Core award and other funds);

5) …staffing resources at site that are required to accomplish the site's mission (i.e., site capacity is in line with research requirements);
6) …the impact of new trial designs (e.g., Bayesian designs in which pre-defined changes in trial design based upon interim data analyses might have large cost implications);
7) …handling equipment maintenance and depreciation in budgets; and
8) …the need to minimize disruptions to Networks brought about by any changes in processes, as well as the need to anticipate impacts on Networks ahead of time and develop processes for minimizing them.

In addition to these issues, during the course of the meeting the participants identified a number of other issues deemed to be important. These included:

9) …the need for transparency in site budgets, so that Operations Centers can better understand the flow of revenues to sites;
10) …using budgets to ensure efficiencies at sites, such as use of resource sharing among the CRSs associated with a CTU;
11) …assuring accountability at sites for the use of funds;
12) …providing incentives for cost containment at sites, and;
13) …developing better methods for dealing with the complexities that arise with studies that are co-funded by several NIH Institutes/Centers, Agencies, etc.

Comparison Table

The table below represents an attempt to compare the approaches of the six networks on several key dimensions. Given how varied the networks are in terms of – among other things – their approaches to funding protocols, the size of network, the number of protocols that are active at any one time, and the role of the Operations Centers, identifying points of comparison is at best an inexact undertaking.

Table 1: DAIDS Networks Approaches to Protocol Costing

Point of Comparison / Network	ACTG	HPTN	HVTN	IMPAACT	INSIGHT	MTN
Use of a template to estimate protocol costs	Yes	Yes	Yes	Yes	Yes (the sum of time and events schedule and insertion of standardized costs associated with these represents a template)	No
Budgets determined based upon each Site's specific needs and input	No	In many instances	Yes	No	No	Yes
Uses a cost/participant as a key metric	No	For some, but not all protocol budgets.	Yes	Yes	Yes	Yes
Multiple funding sources for protocols need to be considered	Not Usually	Yes	No	Not Usually	Yes	No
Use of a capitation or fee-for-service model versus a cost-reimbursement model	Cost Reimbursement	Cost Reimbursement	Capitation model to develop budget; cost reimbursement to disperse funds to site	Cost Reimbursement	Fee-for-service	Capitation model to develop budget; cost reimbursement to disperse funds to site
PIF Includes funds other than specific protocol-related expenses?	Includes small amount for "scientific credit"	Includes some funds for pre-implementation and close-out activities	Includes small amount for community education supplement for each site	Includes amount for scientific credit	Includes Administration Costs for International and Site Coordinating Centers	Yes, based upon site-by-site needs

6.0 Post-meeting Reflections: Steps in Moving Forward

Subsequent to the September 13 meeting, participants were asked to share their thoughts about how best to deal with the issues identified in the meeting as we start developing specific recommendations that meet the objectives of the project. Most of the Networks represented at the meeting responded to this request. Below is listed a summary that attempts to consolidate the responses received by HANC.

- A common template across networks that delineates the activities involved in protocol visits is feasible;
- It may be possible to agree on a standard set of levels-of-effort required by a site to carry out each of the activities listed in the template;
- Having a separate stream of funds to the sites for protocol-specific planning and start-up costs (i.e., pre-IRB approval) from DAIDs will assist simplifying the process for PIF funding from the Networks;
- Agreement on a standard nomenclature for laboratory activities so that everyone will be using the same language when selecting assays, will be very helpful;
- Some flexibility will have to be retained by the Networks for dealing with protocol- and site-specific issues; i.e., a “one-size-fits-all” approach, taken to the extreme, will likely not work;
- The networks and OCSO must work toward increasing the transparency of site budgets; without greater transparency, the Networks will continue to be at least partially “blinded” in dealing with site budgets;
- A greater portion of revenues need to reflect actual performance and true costs at the sites.

Appendix C: Attendees at October 27, 2010 Meeting

Name	Network	Role/Title
Linda Berman	ACTG	Proj. Manager, Finance & Budg.
Linda Boone	ACTG	Senior Budget Analyst
Kathy Hinson	HPTN	CORE Assoc. Director
Gloria Pherribo	HPTN	Financial Associate
Banks Warden	HVTN	Director of Vaccine and Infectious Disease Division
Margaret Wecker	HVTN	Leader of Scientific Operations and Business Development
Kimberly Hitchcock	HVTN	Contracts Manager
Brandy Price	IMPAACT	Administrative Manager
Jill Utech	IMPAACT	Site Coordinator
Carol Vincent	IMPAACT	CRS Coordinator
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