Estimating site costs prior to conducting clinical trials

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Conducting clinical trials is costly and time consuming. Trial sites usually do not calculate site costs. Underestimating required resources slows enrollment and lowers data quality but it is currently unclear how to reliably estimate trial site costs. A group of trial staff designed and validated a tool for compiling trial tasks and calculating required expenditures prior to initiating a clinical trial. The tool was validated in two steps. Round-robin tests for accuracy compared case payments for the same trial calculated by different participants. A narrow CI was reached (22.95–715.69) demonstrating significantly similar estimates of the test participants (p = 0.039). To confirm the predictive value, the predicted and actual hours were compared and a correlation coefficient of 0.952 (p = 0.003) was found. A web-based tool, the Study Site Budgeting Tool, was developed, which allows trial sites to estimate staff costs at the site and determine the budget needed to conduct a clinical trial.

Keywords: calculation tool • case payments • pricing • site management • staff costs

Clinical trials represent the corner stone of evidence-based medicine [1]. While they are time-consuming and costly, they build the backbone of individual treatment decisions [2]. In 2005 a policy by the International Committee of Medical Journal Editors took effect requiring registration of clinical trials as a prerequisite for publication [3]. Since then a total number of 146,466 trials have been registered at Clinicaltrials.gov [4].

Conducting high-quality trials requires dedicated experts from a number of disciplines and takes place in a continuously monitored and regulated environment [5]. Individual steps of trial conduct have become highly time consuming and cost intensive, with staff being the main factor [6]. Activities at the trial site, that is, a hospital or private practice, are left to the discretion of the single investigator and may therefore vary significantly in quality. However, site performance determines trial quality. Sites are the primary data source, and the only direct link to the patient, putting them in a unique position for timely recruitment of trial participants. To carry these tasks into execution, sufficient work force is indispensable. Initiatives try to define minimum requirements of a clinical trial site to assure high-quality research and reduce inter-site variability [7,8]. Sites are supposed to establish standardized operating procedures and provide regular staff training both requiring sufficient resources [7,8]. Adequate reimbursement is a prerequisite to establish and manage a successful study site [6]. By enhancing site performance, for example, recruitment speed and data quality, sponsors will be able to reduce overall trial costs [9]. As site performance depends on adequate resources, reliable cost estimation is crucial for the site and sponsor alike.

The sponsor's calculation to determine trial fees is not always transparent to the clinical investigator. Pharmaceutical companies try to enhance transparency, for example, by voluntary self-regulation and codes of conduct concerning Dorothee Arenz^{*1,2}, Barbara Hero^{1,3,4}, Barbara F Eichhorst^{4,5}, Martin Langer^{1,5}, Lars Pester^{1,4,5}, Julia von Tresckow^{4,5}, Jörg J Vehreschild^{5,6}, Maria JGT Vehreschild^{5,6} & Oliver A Cornely^{1,2,4,5,6,7}

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collaboration with healthcare professionals [10]. To ensure that trial fees are proportionate to the service rendered, they recommend the physician's fee schedule as a reference guide. However, this schedule does not comprise all trial procedures, for example, assessment of adverse events (AE) or tasks performed by study coordinators. With that, calculations still include arbitrary assessments.

These problems may be reduced by determination of expedient and traceable trial fees by the site itself. However, for the site, the actual fee is hard to estimate with their prime task being medical expertise not cost and activity accounting. Calculations done at the clinical trial site usually consider patient-based tasks adequately but do not take into account administrative costs of the trial or allocate overhead expenses of the trial unit [9]. Efforts to estimate fees are currently limited by a general lack of reliable and transparent references for calculation [6,11]. To overcome this shortcoming, the 'STudy site bUDGEting Tool' (STUDGET) was developed, allowing calculation of trial related staff costs.

Methods

First, a task group was put together to develop STUDGET in two phases and five steps. The design phase consisted of:

- The itemization of trial tasks;
- The definition of hourly rates;
- The creation of STUDGET.
- The validation phase comprised:
- The testing for accuracy;
- The confirmation of the predictive value.

Design phase

Composition of the task group

The Clinical Trials Center at the University of Cologne (Cologne, Germany) conducts clinical research at the University Hospital. Besides offering centralized services it also supports decentralized clinical trial units (CTU) at various clinical departments. A task group of experienced investigators and study coordinators was formed from staff of the CTU. Participating CTU were highly active clinical trial sites in oncology, gynecology, hematology, infectious diseases and pediatrics. Four participating executive investigators had been registered in 18–107 trials (median: 24.5), and had received specialized training in clinical research (training courses for investigators and coordinating investigators, respectively). Six qualified study coordinators had been involved in the conduct of 10–46 trials (median: 20.5). Numbers are derived from the clinical trial management system of the Clinical Trials Center [12].

Itemization of trial tasks

Time expenditures of trial staff, that is, principal investigator, subinvestigators and study coordinators were considered to represent the genuine costs at the trial sites, while costs of specific consumables, external examinations and analyses are usually outsourced to external departments or companies. They can easily be identified via invoicing. In a first step, the task group reviewed and compiled all procedures associated with trials at their sites during a 3-month period. Potential procedures were broken down into single activities and grouped in order to be surveyed and calculated. To determine average expenditure per activity, the task group discussed and consented upon time intervals, taking into account possible variability determined by individual trial protocols or site structures.

Definition of hourly rates

To translate required hours of work into fees, hourly rates were defined for trial staff involved. For a university, noncommercial, mostly investigator-initiated trials are of major scientific interest. Therefore, a break-even calculation is deemed acceptable for these trials. When offering services to commercial sponsors, universities and other state-funded institutions need to procure these services at market price [13]. Therefore separate rates were determined for use in investigator-initiated and commercial trials.

Creation of STUDGET

Identified hours of work for a trial and hourly rates of the respective staff were conjoined in the calculation tool STUDGET. In a 3-month test phase within the task group, an alpha version of the software was used to verify functionality and practicality in various clinical trials. The draft list of activities was reviewed for completeness and complemented accordingly. Estimated time expenditures were verified in practice and adapted where needed.

Validation phase

Testing for accuracy

Though fees calculated may differ between sites, the aim was for a tool with low inter-user variability. Therefore round-robin tests were performed to evaluate the accuracy of STUDGET. Using STUDGET, the case payment of a trial formerly conducted at the University was calculated with the help of study coordinators and investigators involved in the trial to receive a comparison value. Then, participants from different CTU were given the corresponding trial protocol and case report forms and were asked to perform the same calculation based on STUDGET. Participants comprised members of the staff group but also staff not yet familiar with the tool. In a first round, no instructions were given to the participants. Discrepancies between resulting case payments and comparison value were reviewed and if needed basic entries were corrected to check for sensitivity of the respective data. Based on the results of the first round, data fields were adjusted to eliminate ambiguity. A second round was performed with the updated tool on the same trial. This time, participants received a detailed instruction prior to using STUDGET. Reproducibility of results was assessed using the Student's one-sample t-test.

Confirmation of predictive value

In a final step, the predictive value of the tool was evaluated by the difference between time calculated by STUDGET at baseline and the prospectively tracked time actually spent on the trial. Costs were calculated for all trials in advance of trial initiation. Study coordinators then tracked the time spent on these trials. From September 2010, all trials were evaluated for which cost calculation and enrolment of the first patient fell into a 12 month test period. Study coordinator times calculated by the tool were compared with the total hours spent on the trial by study coordinators. Correlation between groups was analyzed by the Pearson correlation coefficient.

Results

Design phase

STUDGET was developed as a web application that converts details on trial-specific activities into totals required as trial fees. To let the reader comprehend and test the functionality of the web-based tool, access is provided for a limited time frame of 3 months. Account details are: studget.clinicalsite.org; username: TestClinInvest; password: TestClinInvest.

The task force agreed on the following rules: instructions are kept to a minimum, if possible, entries are limited to a certain range or predefined values, and two types of input fields are distinguished: either data must be entered or data are pre-set but can be altered.

Itemization of trial tasks

Before listing the activities within the trial, basic information is needed about trial size, duration, study population and cost recovery. When documenting the trial course of a patient, a considerable amount of time is required for capturing information on AE and concomitant medication. It was assumed that the general condition of a study population correlates with the AE frequency and changes in concomitant medication. Thus, the level of care was chosen, for example, intensive care unit patient versus out-patient status as one parameter for the time spent on documentation. Respective times for documentation are given per week on trial for in-patients and per visit for outpatients. In-patients were grouped into 'intensive' care (patients in intensive care unit), 'high' care for patients receiving elaborate treatment, for example, chemotherapy or complex surgery and 'standard' care. For out-patients, two levels were given: 'high' care for patients receiving elaborate treatment and 'standard' care.

Activities within a trial were detailed and assigned to either principal investigator, subinvestigator or study coordinator. These were not limited to the obvious visit-specific procedures of the individual patient but also comprised 'hidden activities' for administering and running a trial. The activities were grouped as nonrepetitive, patient-based or continuous. Time expenditure was assigned to each activity. As required time can vary expenditures consented upon by the task group have been pre-set but can be adapted according to special conditions of the trial (e.g., additional preparation of sample tubes) or of the site (e.g., distance between patient unit and laboratory for sample preparation). A high variability was seen in blood sampling and electrocardiograph recording as these considerably depend on protocol specifications. Therefore, these activities were subdivided; for example, blood sampling comprises the drawing of blood, processing, storing and preparing shipment.

Time for assisting monitors and auditors and time for answering queries is calculated automatically correlating with the time for overall documentation.

Examples of activities compiled in the tool comprise the following: familiarization with protocol and informed consent form, preparation and collection of documents for sponsor and EC, and attendance at the investigator meeting are nonrepetitive activities to prepare trial start; clinical observation and assessment, blood sampling and delivery, and explanation of questionnaires or diaries represent patient visit-based activities; prescreening routines and contact with sponsor and monitor are occurring continuously during trial, independent of the number of patient included. In the list of activities, STUDGET requires entries of the number of times a certain activity has to be performed. In addition, the complexity of documenting AE and medication has to be given as a percentage of complete documentation. Two items require free estimation of time needed, as those are not based on any of the information given before. First, the time for documenting medical history and previous medication has to be estimated based on the complexity of trial documentation and the average prior treatment patients received. The second item is the principal investigator's assessment of adverse drug reaction reports according to the Council for International Organizations of Medical Sciences (CIOMS) and respective information of subinvestigators. Required time per month has to be estimated based on the expected overall number of serious AEs, the overall number of patients and the investigational state of the study drug.

Definition of hourly rates

Calculated hours are converted into costs by hourly rates derived from total labor costs. Rates are based on the time the staff actually spends on trial-specific activities, detracting time for general activities for sustaining the clinical trial unit, that is, quality management, training, IT maintenance. Thus, indirect costs of the unit are reflected in the hourly rates and distributed to trial-specific direct work hours. Each institution can enter the average annual labor costs for the roles of principal investigator, subinvestigator and study coordinator. An institutional overhead is added for commercial trials and can be adapted to the rate charged by the respective institution. An additional overhead can be individually entered; for example, for sites still in the start-up phase or large sites that require an internal administration.

Creation of STUDGET

The structure of STUDGET follows the workflow in a clinical trial. It is displayed in **Box 1**. Charges are

Box 1. Structure of the Study Site Budgeting Tool.

Basic information:

- Trial information
- Information about trial team
- Visit schedule
- Trial activities:
 - Nonrepetitive activities for preparation, initiation and close-out
 - Patient-based activities for visits per trial schedule
 - Visits during screening
 - Baseline visit
 - Visits during intervention phase with additional pharmacokinetic procedures
 - Visits during follow-up phase with additional telephone visits
 - Continuous activities
- Summation:
- Payments
- Required hours of work

calculated in two different ways: as payments per trial visit plus a start-up fee mainly applicable for commercial sponsors, or as a lump sum per patient, usually applicable for noncommercial trials. The latter sum includes the start-up fee on a *pro rata* basis.

For planning of staff assignment the required time to perform the trial is shown relative to trial duration. Time for preparation is given as a total, whereas all other time expenditures are given as the average time needed per month of trial duration.

Validation phase

Testing for accuracy

Case payments calculated in the round-robin tests are shown in Figure 1 and Table 1. In the first round robin test, results show a high deviation of calculated case payments from the comparison value (participant 1). To check for sensitivity of the result to basic information entered (e.g., number of patients, duration of trial, assessment of maintenance) input fields were corrected within the different calculations. The remaining range was mostly based on misinterpretation of the required information about study procedures. STUDGET was updated and entries were simplified.

In a second round, the deviation of results from comparison was considerably lower. However, a wide range between results could still be seen. When reviewing entries in detail, it was observed that some basic entries that are not subject to interpretation, for example, number of patients or duration of trial were not entered correctly, thus creating incorrect results.

Tests confirmed the initial tendency towards participants 2–13 calculating higher cost estimates than the authors (participant 1) did. After adjustment, a very narrow confidence interval was achieved in round robin test II, indicating excellent reproducibility of calculation results and demonstrating significantly similar estimates of the test participants 2-13 (p = 0.039).

Confirmation of predictive value

As time from first planning to first patient in usually takes at least 6 months, all 41 trials positively decided upon by the institutional review board in the first 6 months of the testing period were taken into account. Of these, 16 had already been initiated, and 11 of these were clinical trials with a patient- and visitbased schedule and had recruited at least one patient within the testing period. Two trials were excluded from analysis as the responsible study coordinators did not track time on trial. A further three trials had to be excluded from analysis because of the following deviations from planned trial execution. In one trial, procedures usually performed by study coordinators were done by subinvestigators, which was unforeseen upon calculation. In the second trial, the responsible study coordinator changed twice during the 4-month observation period of this trial resulting in a high amount of time spent on introduction and training of new staff. In the third trial, the study protocol was amended after calculation was done. The amendment substantially increased trial procedures, but no recalculation was performed. Details on the remaining sample of six trials are shown in Figure 2 and Table 2. A high degree of correlation between calculated and counted hours on study was found (Pearson's correlation coefficient of 0.952; p = 0.003).

In the six trials investigated the overall amount of time required of study coordinators had a ratio of 76.6% of all hours required including those of the investigators. With that, the results of the study coordinator hours were considered representative of STUDGET.

Discussion

A cost calculation tool for clinical trial sites was developed. STUDGET estimates staff costs at the site to evaluate adequacy of visit fees and/or case payments offered by a sponsor. It is also used by investigators initiating their own trials to calculate case payments for participating sites. It provides clinical trial units with reference values for adequate trial payments, given that detailed instructions and careful investigation of basic information about the trial and the expected study population is correctly entered.

A transparent and detailed estimation of costs to occur during the course of the trial enables a reasonable payment schedule. This should not only reflect the total amount required but also the distribution of costs over time. Paying up-front lump sums per patient at time of inclusion is common in noncommercial trials. However, it does not correspond to actual cost accruement for trials with patients who continue in a trial over a long period of time [14].

An important aspect of trial payments from private industry is that any cash flow to investigators has the potential to arouse suspicion and may be associated with the unlawful acceptance of benefits [15,16]. As a consequence, sponsors and sites alike have a tendency to underestimate the site workload [6]. This underfunding causes a lack in site staff impacting on recruitment efforts and data quality [16]. With a transparent calculation of costs sites are able to justify adequate fees.

For proper usage of the tool, its potential limitations should, however, be taken into account. When testing the tool in round-robin tests, a noticeable inter-user variability became apparent. This could be





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Table 1. Sequential round-robin tests comparing case payments calculated for the same trial by different participants.					
	Round-robin test 1		Round-robin test 2		
	Original data	Adjusted data	Original data	Adjusted data	
Participant 1	1827.27	1827.27	1671.97	1671.97	
Participant 2	2276.99	1495.74	1715.55	1715.55	
Participant 3	-	-	1373.71	1569.55	
Participant 4	Invalid entries	1880.11	-	-	
Participant 5	2949.53	2396.03	1872.25	2043.56	
Participant 6	44,893.75	4447.25	2419.00	2228.03	
Participant 7	5526.50	1509.92	1440.81	1768.47	
Participant 8	3265.34	1265.34	-	-	
Participant 9	941.76	1116.76	1209.22	1457.44	
Participant 10	46,362.50	4469.51	28,703.41	2824.05	
Participant 11	75,512.34	21,593.59	-	-	
Participant 12	76,437.31	15,332.31	2071.03	2384.00	
Participant 13	6313.83	2322.54	2559.98	2380.97	
Student's t-test for one sample					
Mean difference from participant 1	24,575.72	3384.92	3146.36	369.32	
95% CI of difference	2193.45-46,957.98	-1167.22–7937.06	-3747.63-10,040.35	22.95–715.69	
p-value	0.035	0.129	0.323	0.039	

All costs are presented in Euros. Calculated case payments for the chosen trial are taken from the Study Site Budgeting Tool. For each of both tests, original data are the values from the Study Site Budgeting Tool as received from the participants. Adjusted data are taken from the tool after correction of wrong basic entries, thus identifying sensitive fields.

attributed to the fact that users from varying medical backgrounds differed in their classification of procedures as trial-specific or as routine procedures. For example, blood samples for hematology testing were considered to be routine diagnostic tests in a hematooncological department but were calculated as studyspecific procedures at a psychiatry unit. Moreover experience in performing clinical trials as well as using STUDGET has a significant input on variability.



Figure 2. Comparison of calculated and prospectively tracked times. The scatter plot compares calculated hours and prospectively tracked hours for six clinical trials investigated.

STUDGET is based on hourly rates and total annual labor costs at the time of contract negotiations. As clinical trials may run over a long period of time, additional costs due to amendments as well as inflation rates and changes in labor cost need to be considered.

Future perspective

In the future, the use of STUDGET may be expanded to further aspects. First, trials may fall behind the original calculation, either due to amendments or to conditions within the trial unit. Combining STUDGET with tracking of time spent on a trial could detect such deviations from the original plan while the trial is being executed.

STUDGET was made available to other noncommercial institutions, mainly other academic medical centers. Its practical application is taught in training courses for study coordinators and investigators. It was also offered to funding institutions to help establish feasible lump-sums. For the future this might promote participation of investigators in noncommercial trials, where underfunding has been identified as a problem [17], lowering clinician acceptance [18,19]. Third, it has been proposed to make trial fees transparent to the patient during informed consent process [5,20]. A mere naming of an amount of compensation would probably be misleading for a patient usually not involved in these issues [21]. STUDGET provides a schedule of efforts by the investigator and his team. Attached to the informed consent this might help patients to better understand the framework in which a clinical trial is conducted.

Calculations done by STUDGET are already used to negotiate trial budgets with the sponsor. However, the flexibility to adapt a pre-fixed budget varies as well as the discrepancy between calculated and proposed budget. A review of efforts and success of budget negotiations would be helpful to further assess the benefit of the calculation.

Financial & competing interests disclosure

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	Total of SC hours tracked	Total of SC hours calculated [†]		
Trial 1	139.5	73.9		
Trial 2	19.0	18.5		
Trial 3	118.0	132.6		
Trial 4	371.5	294.6		
Trial 5	387.5	442.0		
Trial 6	53.0	59.3		
Mean	170.15	181.42		
SD	164.53	159.53		
Pearson correlation = 0.952 p-value = 0.003				

^tSC hours calculated comprise: hours spent on preparation and initiation; hours on patient visits multiplied by the number of respective visits actually performed; and hours for continuous tasks multiplied by number of months from initiation to end of testing period. SC: Study coordinator.

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Executive summary

Background

- Conducting clinical trials is costly and time-consuming. Adequate reimbursement is a prerequisite to establish and manage a successful study site. Underestimating required resources slows enrollment and lowers data quality.
- Efforts to determine costs are limited by a lack of reliable references for calculation.
- A tool for calculating trial fees prior to initiating a clinical trial was developed.
- Methods
- A task group was formed from highly active clinical trial sites at the University of Cologne, Germany.
- The group developed the tool in two phases and five steps: design phase with itemization of trial tasks, definition of hourly rates and creation of the tool; and the validation phase with testing for accuracy and confirmation of the predictive value.
- In the design phase, activities in clinical trials were compiled and basic time expenditures and hourly rates assigned. With the results, the 'STudy site bUDGEting Tool' (STUDGET) was designed.
- In the validation phase, calculations for the same trial performed by different users were compared. To assess the predictive value of the tool, calculated and tracked study coordinator hours were compared in a sample of six trials.
 Particle

Results

- The web-based tool STUDGET determines hours of work and calculates the hourly rates of staff, totalizing them to required fees.
- In round-robin tests a narrow confidence interval was achieved, indicating excellent reproducibility of calculation results.
- Comparing predicted and actual hours in a sample of six trials, a high degree of correlation was found.
- Discussion
- Inter-user variability can be attributed to differences in classifications of procedures as trial specific or routine, trial experience and knowledge of STUDGET.
- Calculations in STUDGET are based on a fixed time point. Flexible conditions due to amendments and changes in labor cost need to be considered.
- STUDGET allows trial sites to determine the case fee needed to conduct a clinical trial and provides a transparent calculation of costs.

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