Cost Methodology of COMBINE

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Abstract:

Objective: This article describes the methodology used in estimating the mean cost per patient of the interventions delivered in COMBINE, a randomized controlled trial (RCT) comparing pharmacotherapies and behavioral interventions for outpatient treatment of alcohol dependence. **Method:** Our methodology identifies a broad list of nonresearch activities necessary to implement the COMBINE interventions in standard clinical practice. For each activity, we include the time costs of clinical assessments and interventions by staff, the cost of space, laboratory charges and the cost of medical supplies. We also estimate the patients' time used for each of these activities. **Results:** We present the estimated cost per activity for 15 intake assessments plus the Medical Management (MM) and Combined Behavioral Intervention (CBI) sessions for 9 of the 11 COMBINE sites. Labor costs represent the bulk of the total cost for all activities. The Form 90 AIR/ED is the most expensive intake activity both in terms of labor and space costs. The CBI session is more expensive than the MM session. **Conclusions:** Our methodology estimates the cost to treatment providers and to patients of implementing the COMBINE intervention in standard practice. Compared with previous methods, the prospective design of our methodology allows for higher quality data, and the detailed activity costing helps identify key cost drivers. Future analyses will present actual COMBINE intervention cost estimates based on trial data. Although this cost study is specific to the COMBINE interventions, the concepts, instruments and methods used here can be applied to any RCT.

Keywords: COMBINE Study | randomized controlled trial (RCT) | Form 90 AIR/ED | cost | alcohol dependence | alcohol intervention

Article:

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Cost Methodology of COMBINE*

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ABSTRACT. Objective: This article describes the methodology used in estimating the mean cost per patient of the interventions delivered in COMBINE, a randomized controlled trial (RCT) comparing pharmacotherapies and behavioral interventions for outpatient treatment of alcohol dependence. **Method:** Our methodology identifies a broad list of nonresearch activities necessary to implement the COMBINE interventions in standard clinical practice. For each activity, we include the time costs of clinical assessments and interventions by staff, the cost of space, laboratory charges and the cost of medical supplies. We also estimate the patients' time used for each of these activities. **Results:** We present the estimated cost per activity for 15 intake assessments plus the Medical Management (MM) and Combined Behavioral Intervention (CBI) sessions for 9 of the 11 COMBINE sites. Labor costs represent the bulk of the total cost for all activities. The Form 90 AIR/ED is the most expensive intake activity both in terms of labor and space costs. The CBI session is more expensive than the MM session. **Conclusions:** Our methodology estimates the cost to treatment providers and to patients of implementing the COMBINE intervention in standard practice. Compared with previous methods, the prospective design of our methodology allows for higher quality data, and the detailed activity costing helps identify key cost drivers. Future analyses will present actual COMBINE intervention cost estimates based on trial data. Although this cost study is specific to the COMBINE interventions, the concepts, instruments and methods used here can be applied to any RCT. (*J. Stud. Alcohol,* Supplement No. 15: 50-55, 2005)

ALCOHOL AND DRUG abuse impose significant costs on society. In 1992, the economic cost of alcohol and drug abuse was estimated to be $246 billion (Harwood et al., 1998). The majority of these costs arise from alcohol abuse ($148 billion). The significant social costs of alcohol abuse have prompted considerable interest in cost and cost-effectiveness studies on alcoholism treatment (Subcommittee on Health Services Research, 1997), and pressure has increased to identify therapies that are not only efficacious but also cost-effective. Much of this pressure has been driven by managed care, which has placed a premium on economic studies that assess whether the clinical and economic outcomes of new pharmacotherapies and behavioral interventions justify their costs.

In light of the increased need for cost-effectiveness studies, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) funded a study to examine the costs and cost-effectiveness of the pharmacotherapies and behavioral interventions included in the COMBINE trial. COMBINE is a multisite, randomized controlled trial (RCT) that is assessing the efficacy of two pharmacotherapies (naltrexone and acamprosate) and psychotherapy, individually and in combination, in the treatment of alcohol dependence. COMBINE is one of the most ambitious clinical trials ever undertaken for the treatment of alcoholism, and its ancillary cost-effectiveness study should yield invaluable information on the costs and cost-effectiveness of combining pharmacotherapies and behavioral interventions for the treatment of alcohol dependence.

In this article, we describe the methodology used to estimate the cost of the various therapies in COMBINE. Although COMBINE is an RCT design, the perspectives of our cost methodology are the treatment provider and patient in standard clinical practice rather than the cost of the COMBINE intervention as implemented in the trial. Our perspective increases the usefulness of the cost estimates outside of a research setting and allows policy makers to apply the results to real-world settings. As a practical matter, our methodology excludes research costs from the intervention cost estimates. Because the COMBINE trial is ongoing, this article presents only the costs of the individual nonresearch activities that comprise the COMBINE intervention and not the actual patient-level COMBINE intervention costs. Once the trial is completed, we will use patient-level data on the frequency of each activity to estimate the cost of COMBINE for each person in the trial as well as the mean cost for participants in each of the treatment conditions (COMBINE Study Research Group, 2003).

A cost analysis is a first step in a full economic evaluation of a treatment intervention and provides critical infor-

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mation beyond its contribution to a cost-effectiveness analysis. In an ideal situation, cost studies provide not only dollar estimates but also the amount of resources used so that the results can be applied to different circumstances and prices. Cost studies also identify the key drivers of cost. This information allows policy makers to identify critical cost components and facilitates sensitivity analyses.

Despite their importance, cost analyses are a relatively new addition to RCTs. Typically, cost studies have been an "add-on" to an existing clinical trial, and often much of the economic data have been collected retrospectively (e.g., Jofre-Bonet et al., 2004; Lave et al., 1998; Schädlich and Brecht, 1998). RCTs are typically performed on pharmacological agents, and there is a cost and cost-effectiveness literature related to psychotropic medications (e.g., Doran et al., 2003; Essock et al., 2000). However, there appears to be no cost or cost-effectiveness studies performed prospectively in RCTs for alcohol interventions. Several studies have examined the costs of providing substance abuse treatment services in a naturalistic setting and have developed cost estimation tools for doing so (French et al., 1997; Zarkin et al., 2004). Zarkin et al. (2003) describe a prospective methodology for estimating the cost of an alcohol intervention but not in the context of an RCT. However, similar methodologies have apparently not been developed for costing RCTs in general and in the alcohol and drug fields specifically.

In an early attempt to examine the cost of alcoholism treatment, Holder et al. (1991) relied on findings from clinical trials to determine the effectiveness of various alcoholism treatments. They combined clinical trial effectiveness data with estimates of the cost of treatment obtained from health care providers, health insurance carriers, state alcohol and drug abuse authorities and self-insured employers. Importantly, they did not have estimates of the resources used in treatment from clinical trial data, and so they did not perform a detailed cost study. Recognizing the limitations of their study, Holder et al. concluded that their study should serve as a stimulus for future clinical trial research into the cost-effectiveness of alcoholism treatments.

Schädlich and Brecht (1998) conducted a retrospective analysis of clinical trial data to estimate the cost and cost-effectiveness of acamprosate in treating alcoholism in Germany. Schädlich and Brecht performed their analysis from the perspective of the German health care system and therefore considered only the direct medical costs of inpatient care and rehabilitation treatment. Although Schädlich and Brecht represent an advance over observational studies, several features limit their cost study. First, resource use data were not collected in the clinical trial, and therefore they relied on expert opinion and other external sources for resource use data. Second, they provide little detail on the methodology used in their cost study and so provide little guidance to other researchers attempting to conduct similar cost studies.

Cisler et al. (1998) estimated the costs to replicate Project MATCH interventions, a multisite RCT, in a real-world clinical setting. They obtained detailed resource costs for the MATCH treatment modalities for two of the nine MATCH sites. These included salary costs, supervision costs, cost of materials and administrative overhead costs. They assumed a standard wage for a therapist with the minimum necessary qualifications. They did not identify the activities for treatment intervention. They also did not collect patient time costs that are an important component of time-intensive interventions nor did they estimate the cost of space. Although Cisler et al. provide more detail on their methods than previous studies, because their cost study did not estimate patient time or attempt to cost out the separate activities of each therapy, more methodological guidance for researchers attempting to conduct a cost study is needed.

The cost study methodology we present in this article prospectively collects resource use data at the activity level as part of the overall clinical trial protocol at 9 of the 11 COMBINE sites. Our methodology allows detailed estimates of labor costs from the treatment provider perspective for nonresearch activities required to implement COMBINE in standard practice. We also include detailed costs of other resources, such as space, laboratory activities and medications. In addition, our methodology estimates the costs incurred by patients, including travel and waiting time and the time spent on intervention activities.

Method

Our cost study methodology follows the microcosting approach as recommended by Drummond et al. (1987) and Gold et al. (1996). Our method has two steps: develop a taxonomy of relevant activities and gather data. Many activities performed in COMBINE are prompted by the research needs of the study. The taxonomy distinguishes between research activities that should not be included in the cost of the therapy and activities that would need to be conducted to implement the therapy in real-world clinical practice. For example, certain questionnaires are required for research purposes but not required in standard practice. There are also activities associated with managing data for the research study. Because we are interested in estimating the cost of COMBINE when the interventions are delivered in standard practice, we excluded these research activities from our cost estimates.

To identify the relevant activities, we obtained a list of tests and questionnaires that were administered to patients as part of the COMBINE protocol. We then identified those that would most likely be used if the interventions were delivered in standard clinical practice. This identification involved some judgment, and we implemented a consensus approach with the cost-effectiveness study principal investigators (PIs). Sometimes a particular intake assessment was

identified as essential for the intervention, but not all assessment time points for that assessment were judged clinically relevant in standard practice. For example, the Profile of Mood States and the Important People Instrument were identified as instruments that would be used in standard practice at intake, but their use at subsequent weeks (e.g., 4, 8, 16) was identified as research related.

Once we identified the relevant activities, we gathered data on both the time spent by clinical staff and patients and the space associated with each activity. To gather these data, we designed the Project Coordinator's Resource Allocation Worksheet (PC-RAW). The PC-RAW collected data on the total labor hours spent on each activity, both by the person conducting the assessment or intervention and by the patient; the space used in conducting that activity, including the room and building name and room size; and all supplies and materials used. We computed the median and mean labor hours and room size. Because of the small sample ($N = 9$ sites), our preferred estimate is the median, although the two estimates were generally very similar.

The labor costs of each activity are equal to the product of the amount of time spent by each person on the activity and their wage. Salary data for each staff member involved in delivering the COMBINE interventions were provided by the site PIs. For salaried staff, salary included the actual wage plus a fringe rate that covered all benefits. For contract staff, the hourly contract rate was used. All salary data were adjusted to 2003 dollars using the Bureau of Labor Statistics Consumer Price Index. From the Coordinating Center's Data Management System (DMS), we were able to obtain a list of staff IDs for each site and the number of times staff conducted each activity. This information was used to calculate a weighted average hourly rate for all activities at each site. Because of differences in staffing mix across sites, the average hourly wage rate for an activity varied across sites. The average hourly wage rate for the 15 intake activities at each site was multiplied by the median number of minutes spent on that activity across all sites as reported on the PC-RAW. The median time spent on the Medical Management (MM) and Combined Behavioral Intervention (CBI) sessions for each site was obtained from the DMS. The median time was calculated from the start and stop times recorded by the clinicians on the session record forms. Finally, the median labor cost for each activity was calculated across all sites.

Although the labor costs of the persons delivering the intervention are of primary importance from the perspective of treatment providers, patient time is also an important cost. In addition, because a large number of evaluations in the COMBINE intervention are self-assessed, patient time is a significant component of the total cost. At this point, we do not have estimates for patient time costs, but they will be added when we have access to the patients' wage data that are being collected in the trial. Reported wage data represent the opportunity cost of patients' time. From the economic viewpoint, they represent the value of the foregone use of patients' time. For patients who are not employed, we will estimate their wages using their demographic characteristics and the results of human capital wage models (Willis, 1986) estimated on a database such as the National Longitudinal Alcohol Epidemiological Study. Patient travel time to the clinic and waiting room time are recorded on a revised version of the Form 90 (Form 90 At Intake, Revised/Economic Data [AIR/ED]; Miller and Del Boca, 1994), which records information on alcohol consumption and economic outcomes, such as health care utilization, crime and incarceration, labor market behaviors and motor vehicle accidents.

To estimate space costs, the median size of the room used for each activity across the nine sites was calculated. The median space was multiplied by the annual rent per square foot prorated by the median time for which the room was used for each activity as reported in the PC-RAW to derive the space cost at each site. The market rent per square foot for a commercial Class B space inclusive of maintenance fees and utilities was obtained from the CB Richard Ellis (www.cbre.com/research) Market Index Briefs for the second quarter of 2003 and the CB Richard Ellis Global Market Rents report for January 2003. For the two sites that did not have a published CB Richard Ellis report, we obtained an average market rent by calling real estate agents in those areas. The median space cost for each activity was calculated across all sites. Space costs for patients' waiting room time will be estimated by using the price per square foot estimate described above and by assuming a standardized space allocation per person (Zarkin et al., 2003). To avoid double counting costs, we have not included the costs of institutional overheads because those rates usually include space costs provided by the university.

The average wholesale price for naltrexone 50 mg was obtained from the RED BOOK (Thomson Micromedex, Greenwood Village, Colorado; www.micromedex.com/products/redbook/windows). However, because acamprosate is not available for sale in the United States, we obtained its price from the British National Formulary (Joint Formulary Committee, 2003). A ratio of the dollar price to pound price of naltrexone was calculated using the two data sources. Assuming that the same ratio holds for acamprosate, the dollar price of acamprosate was calculated by multiplying the dollar-pound ratio by the pound price of acamprosate. The unit price for both acamprosate and naltrexone will be multiplied by the daily dosage to obtain the daily cost for each of these medications. Per the COMBINE protocol, the dosage for acamprosate was 3 g per day. The dosage for naltrexone was titrated as 25 mg for days 1-4, 50 mg for days 4-7 and 100 mg thereafter. We ignored the cost of the placebo because placebo would not be given in standard clinical practice. Unit costs for laboratory tests that were

deemed essential for standard clinical practice were obtained from ACM Medical Laboratories (Rochester, NY; www.acmlab.com). These costs included the cost of collecting, processing and testing biological samples and providing written laboratory reports.

Cost estimation

The clinic cost of each activity is the sum of the labor, space, laboratory and medication costs noted above. To estimate the per patient costs of the therapies in COMBINE, these activity costs will be multiplied by the number of times a patient receives each activity, which will be obtained from the trial data. These cost products will then be summed over all activities to obtain the cost for each patient, and these costs will be aggregated within each treatment condition to obtain the mean cost per patient.

The estimated cost of each activity is reported below. The cost per patient in each COMBINE arm will be calculated when data collection for the COMBINE trial is completed. The total per patient cost of COMBINE is equal to the sum of the clinic costs per patient plus the patients' travel time costs, patients' waiting costs and patients' time cost spent on all activities. Individuals who miss some intervention sessions will receive a lower dose of the intervention and will have lower intervention costs.

After costs per patient are estimated, a sensitivity analysis will be performed. This analysis will assess the impact of changing various cost parameters on intervention costs. These parameters include wages, costs of other inputs and activity time estimates.

Results

Results of the activity-level cost analysis are reported in Table 1. This table presents the median total clinic costs of conducting the COMBINE activities that would be used in standard clinical practice. These costs depend on clinic staff time, staff wages and clinic space costs. Patient time for each activity, as reported by clinic staff, is also shown. However, since patient-level data on wages, travel time and waiting room time are not available until the end of the trial, we are unable to compute patient time costs at this time.

Staff labor costs represent the bulk of the total cost for all activities. The Form 90 AIR/ED is the most expensive intake activity both in terms of labor and space costs. The form takes longer to complete than other intake instruments.

TABLE 1. Patient time and clinic labor and space costs per activity, 2003($)

	Time (minutes)		Clinic costs ($)		
Activity	Median patient time	Median staff time	Total labor cost	Total space cost	Total cost of activity
Intake assessments					
Vitals and BAC	7	7	3.67	0.15	3.82
Medical history	15	20	15.43	0.49	15.92
Physical examination	20	25	19.34	0.51	19.85
Form 90 AIR/ED	60	60	18.80	1.27	20.07
SCID-IV	18	20	7.13	0.38	7.51
Other SCID modules	30	28	13.57	0.58	14.15
Demographic form	5	5	1.58	0.11	1.69
Drinker Inventory of Consequences	10	1	0.31	0.02	0.33
Important People Instrument	15	15	4.69	0.32	5.01
Profile of Mood States	5	1	0.29	0.02	0.31
Alcohol Abstinence Self-Efficacy Scales	7	1	0.30	0.02	0.32
Alcohol Dependence Scale	10	1	0.31	0.02	0.33
University of Rhode Island Change Assessment Scale	7	1	0.31	0.02	0.33
Concurrent medications[a]	5	5	2.76	0.13	2.89
Menstrual calendar[a]	3	3	2.25	0.08	2.33
MM activities					
MM session	20	20	15.28	0.45	15.73
CBI activities					
CBI session	55	55	28.79	1.16	29.95
Personal feedback report	0	40	12.51	1.03	13.54

Notes: BAC = blood alcohol concentration; Form 90 AIR/ED = Form 90 At Intake, Revised/Economic Data; SCID = Structured Clinical Interview for DSM; MM = Medical Management; CBI = Combined Behavioral Intervention. [a]These activities and costs are included as part of the MM sessions in addition to being included in the intake assessment.

TABLE 2. Cost of medication and laboratory activities, 2003($)

	Unit price (US$)
Medications	
Naltrexone 50 mg tablet[a]	4.5683
Acamprosate 333 mg tablet[b]	0.5178
Laboratory activities[c]	
Chemistry panel with 18 constituents	39.66
Chemistry panel with 8 constituents	37.86
Hematology with differential and platelet count	24.00
Urine drug screen	66.88
Beta human chorionic gonadotropin	24.00

Sources: [a]RED BOOK; [b]British National Formulary and calculations discussed in the text; [c]ACM Medical Laboratories.

The physical examination has approximately the same staff labor cost as the Form 90 AIR/ED, even though it takes less than half the time to complete as the Form 90 AIR/ED, because the physical examination is performed by medical professionals who have higher wages than those administering the Form 90 AIR/ED. Some intake activities involve self-administered instruments, such as the Drinker Inventory of Consequences, Profile of Mood States and the Alcohol Dependence Scale. Because they require very little nonpatient time, the clinic costs associated with these activities are low. However, these activities involve higher patient costs, which will be added to the clinic costs in the calculation of total COMBINE costs. Although the median hourly wage for a CBI therapist is lower than that of an MM therapist ($31.68 vs $45.83), the CBI session is more expensive than the MM session because the average time spent on a CBI session is 55 minutes versus an average of 20 minutes for an MM session. Table 2 presents the unit price of the two medications used in COMBINE and the unit price of all laboratory activities that are necessary for initiating and monitoring the COMBINE pharmacotherapy intervention.

Discussion

Alcohol and drug abuse impose significant costs on society, with the majority of these costs arising from alcohol abuse (Harwood et al., 1998). Given the significant social costs of alcohol abuse, there is considerable interest in cost and cost-effectiveness studies on alcoholism treatment (Subcommittee on Health Services Research, 1997). Yet, despite this interest, researchers have little guidance on how to conduct a cost analysis within the context of an RCT.

This article describes the cost estimation methodology we will use in estimating the costs of the COMBINE interventions. Our ultimate goal is to estimate the cost of COMBINE interventions if these interventions were delivered in standard care rather than in a research setting. Our methodology entails identifying nonresearch-related activities required to implement COMBINE, developing a cost for each activity and then multiplying this cost per activity by the number of units of the activity that each person receives. In this article, we present costs of the COMBINE activities, which are determined by labor and space costs as well as the cost of medication and laboratory tests. To estimate the costs of the COMBINE interventions, the next step is to use results from the COMBINE trial to multiply these activity costs by the number of units of each activity that patients receive.

Our methodology has several limitations. Because the study was implemented in the context of a research-based RCT, our methodology relies on the judgment of the cost-effectiveness study PIs as to which activities are primarily research related and which would likely be used in standard clinical practice. To minimize this issue, we implemented a consensus approach to achieve agreement on these nonresearch activities. Another limitation is that, although we have plausibly identified activities that would likely be implemented in standard clinical practice, the treatment regimen we cost out follows the COMBINE protocol. Because patients may be seen more frequently in an RCT than in standard practice, costs may be artificially inflated. We have tried to minimize this concern by including only activities that are likely to be used in standard clinical practice. However, the fact remains that the inflexibility of a standardized RCT protocol that mandates activities at fixed time points suggests that our cost estimates provide an upper bound on the costs of implementing the COMBINE regimen in standard clinical practice.

Our cost data collection methodology relies on estimates of time spent on various COMBINE activities as estimated by each site's project coordinator. Alternatively, time estimates could have been collected by surveying each staff member individually about their time spent on each activity or by performing a time-in-motion study for each staff person. These alternatives may have produced more accurate estimates, but they were judged too burdensome and too expensive. Finally, we have not estimated the cost of training staff or the cost of supervising staff to ensure adherence to the COMBINE clinical trial protocol.

One of the biggest advantages of our cost methodology is that it is a prospective design. Thus we will obtain more timely and higher quality data than if we were to collect these data retrospectively. Also, we disaggregate each COMBINE intervention into various activities and estimate costs for each activity. The level of detail of our activity costing approach distinguishes our costing method from previous efforts in the literature. This detail allows for more accurate cost estimates and identifies key drivers of cost. Also, by separating costs into resources and prices, we can apply different prices to different circumstances and estimate costs under alternate treatment protocols.

Another noteworthy feature of our cost methodology is the ability to estimate patients' travel and waiting time costs plus their costs of performing nonresearch intervention

activities. Because the COMBINE interventions include time-intensive behavioral components, estimates of patients' costs are important in estimating the total cost of the COMBINE interventions. Finally, although this cost study is specific to the COMBINE interventions, the concept, instruments and methods used here can be applied to any RCT. We hope that future studies will adopt our methodology and further refine these estimates.

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