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Memorandum

To: Trialists

Fr: Curt Meinert

Re: The first design question: Should the trial be multicenter?

The empirical evidence is that the question is usually answered "no", if indeed it is considered at all. Of the 19,000 randomized controlled trials published in 2010 (PubMed counts; 22 September 2011), only 20% (3,800) were multicenter. Of the 93,000 trials listed in clinicaltrials.gov (19 September 2011), only 17% were multicenter.

Not all trials should be multicenter, but the science of trials would be better if more were.

Most people, faced with the option of doing a trial in one clinic or multiple clinics, will opt for one clinic unless it is obvious that the sample size cannot be achieved with just one clinic.

Why? Primarily because, all other things being equal, doing a trial in a single clinic is easier, costs less, and has less variance than one done in multiple clinics.

Of these reasons, the only one unquestionably true is that it is easier.

Also, no doubt, if it is possible to meet the recruitment goal and timetable with a single clinic, the cost will be less than with multiple clinics. But the chance of achieving the specified enrollment goal in the time specified is less with one clinic than with multiple clinics. Hence, the cost per unit of information generated may be less with multiple clinics, even if the total cost is more.

Consider a randomized placebo-controlled trial with a five year timetable to enroll 100 people (1:1 assignment ratio) and to treat and follow them for a year.

Timetable

Event	Time (mos)
Funding.	minus 3 - 0
Start of funding.	0
Protocol development.	0 - 3
IRB submissions and approvals.	3 - 6
Forms development.	3 - 6
Data system development.	7 - 9
Start of enrollment..	9
End of enrollment.	36
End of followup..	48
End of data entry..	51
End of data editing.	54
Data freeze..	54
Final analysis and publication..	54 - 60

The trial is sponsored by Acme Drugs and figures heavily its licensure plans for its serum rhubarb lowering drug. The trial is designed to treat people with blab blab with elevated serum rhubarb levels. Blab blab (poenalethargyinsomina) is a chronic debilitating condition with onset in the middle years of life characterized by muscle pain and weakness, lethargy, and difficulty sleeping. Acme Drugs is a start-up company with its only product being its hypo-rhubarb drug. The timetable above is dictated by the company's time-to-cliff analysis (total cash reserves divided by monthly expenditure burn rate); 14 months beyond the completion date for the trial outlined above.

Much of the work establishing serum rhubarb as a risk factor for blab blab has been done by Dr X in Minneapolis. He has a large referral practice for people with the condition. Drs Y and Z, from Boston and Los Angeles, respectively, are also recognized experts in blab blab and head referral clinics for people with the condition.

Investigator X is confident he can recruit the 100 people needed in the time required.

If you are responsible for calling the shots do you go with X or do you also involve investigators Y and Z and their clinics for enrollment?

The answer depends on whether you go boating without a life jacket. If you do, you are likely to go with X alone because it is seen as faster, easier, and cheaper than having three study clinics.

But if you always strap on a life jacket before leaving the dock you will go multiclinic, even if the cost is higher.

You could, of course, start with X and if recruitment lags then bring on Y and Z. But the chance of catching up on enrollment once you recognize things are lagging is slim. It will be at least six months into enrollment before you realize you are in trouble. Add 6 to 9 months to

bring the clinics online and get IRB approvals and there will be only about a year left for enrollment.

The mind set of the trialist is to minimize the number of clinical centers as a variance conserving strategy. Even if the entry criteria are the same across clinics, clinic-to-clinic populations will differ and hence variation will be larger with multiple clinics. Hence, the sample size for multicenter trials should be larger to compensate for added variance. The amount depends on assumptions, but realistically is probably around 10 - 15%.

The belief is that single center trials are less expensive than multicenter trials. Indeed, the absolute cost may be less, but the cost per unit of information may be more.

Suppose two options for the trial outlined above: Option 1: Enrollment and followup done by Clinic X, and Option 2: Three clinics, X, Y, and Z for enrollment and followup. The enrollment goal under option 2 is increased by 10% to compensate for added variability with multiple clinics. The budget for the coordinating center is increased by 30% to cover the costs in managing and monitoring three clinics instead of one.

Option 1: Clinic X and coordinating center
(direct costs)

Clinic	
Start up costs (including IRB submission)	$20,000
Patient enrollment @ $2,500 per person; 100 persons	$250,000
Treatment and followup @ $7,500 per person; 100 persons	$750,000
Total	**$1,020,000**
Coordinating center	
yr 1	$100,000
yr 2	$100,000
yr 3	$100,000
yr 4	$100,000
yr 5	$100,000
Total	**$500,000**
Total	**$1,520,000**

Option 2: Clinics X, Y, and Z and coordinating center
(direct costs)

Clinics	
Startup costs ($20,000 per clinic)	$60,000
Patient enrollment @ $2,500 per person; 110 persons	$275,000
Treatment and followup @ $7,500 per person; 110 persons	$825,000
Total	**$1,160,000**
Coordinating center	
yr 1	$130,000
yr 2	$130,000
yr 3	$130,000
yr 4	$130,000
yr 5	$130,000
Total	**$650,000**
Total	**$1,810,000**

The cost per person year of followup under option 1, assuming the enrollment goal and timetable is achieved, is $15,200. But what if only 50 people are enrolled? Then the cost is $30,400.

The per unit cost is $18,100 under option 2 if the sample size and timetable goals are met. If 90 people are enrolled under option 1 and 110 under option 2, the absolute costs are $1,420,000 and $1,810,000 and $15,778 and $16,454 per person year of followup, respectively. The per unit cost is higher with option 1 if enrollment is 20% short of the goal and option 2 is at goal.

Since I always wear a life jacket when boating, I am, therefore a multicenter trialist. Reasons below.

On reasons to favor multiclinic to single clinic trials

Reason 1: Organizational structure

Comment: A virtue of multicenter is that investigators have to have formal organizational structures to operate. Technically, the need for organizational structure is just as great in single clinic trials, but less likely to be formalized because of the geographic proximity of people. The need is easier to overlook than in multicenter trials.

Reason 2: Lines of communication and separation of responsibilities

Comment: The lines of communications and divisions of responsibilities have to be formalized in multicenter trials where activities are vested in people at different centers. The need for crisp lines of communication and explicit channels of communications is as important in single center trials but more likely to be overlooked because of familiarity when everyone is under one roof.

Reason 3: Leadership

Comment: The PI in a single center trial is usually also a person who plays a key role in enrolling and treating people in the trial. Typically, the study chair in multicenter trials

has only a marginal role in operation of the clinic of which he/she is part, if indeed the person is associated with any study clinic. The separation makes for more balanced approaches to issues of enrollment, treatment, and protocol compliance.

Reason 4: Independent coordinating center
Comment: The typical multicenter has a coordinating center that is funded independently of all other study centers and apart from all other centers. The separation and independence allows the center to function without fear of interdiction by other center heads or study leaders. That independence and standing is generally not possible in single center trials where people charged with monitoring report to the study PI.

Reason 5: Compartmentalized data
Comment: The fact that multicenter trials involve multiple clinics means that clinic-related problems and deficiencies are isolated to the clinics where the problems occur. If the problems are serious enough to lead to data purges, the only clinics affected are where the purges are made. The trial still goes on because data are partitioned by clinic. Contrast that with the situation if performance is bad in a single clinic trial. The entire trial goes down.

Reason 6: Probability of achieving sample size and time goals
Comment: There is no guarantee of any trial meeting its goals, but the chances are better with multiple clinics than with a single clinic.

Reason 7: Protocol compliance and monitoring
Comment: The reality that there will be clinic-to-clinic differences in study populations and in the way the study protocol is interpreted means that more energy is devoted to ensuring compliance to the study protocol than when people are enrolled and followed in a single clinic. Hence, it is possible that compliance and monitoring will be better than in the typical single center trial.

Reason 8: Publication
Comment: There is no guarantee that results will be published when a trial is finished, but the chances are probably better in multicenter trials than in single center trials because of more robust organizational structures and divisions of labor.