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Memorandum

To: Center for Clinical Trials faculty and staff

Fr: Curt Meinert

Re: On quotafication in trials

Definitions

quota *n* - [ML, fr L *quota pars* how great a part] 1. A proportional part or share. 2. The number or amount representing or constituting a proportional share or limit, as in a **recruitment quota**.

quota requirement *n* - [**trials**] A **requirement** imposed to ensure a specified mix in the **study population** with regard to one or more **demographic variables**, disease state variables, enrollment site, or other variables observed at or prior to **enrollment**; stated in numbers required, proportions required, or as minimums required; eg, in regard to **gender**, 50 males and 50 females, 50% female, or at least 50% female. rt: recruitment quota, **sample size requirement** ***Usage note***: See **quotification**.

quotification *n* - The act or process of imposing a **quota requirement** on the mix of persons **enrolled** into a **trial**. rt: **quota requirement**, **stratification** ***Usage note***: Not to be confused with **stratification**. The purpose of stratification is to ensure that the different **treatment groups** all have the same proportionate mix of people with regard to the **stratification variable**(s). The purpose of quotification is to ensure a **study population** having a specified mix with regard to the variables used for quotification.

stratification *n* - 1. Broadly, the act or process of **stratifying** (defn 2 or 3). 2. An active ongoing process of **stratifying**, as in the sense of defn 2, as in placing **patients** into **strata** as they arrive at a **clinic** as a prelude to **enrollment** and **randomization** to **treatment** in a **trial**. 3. The act or process of classifying **treatment units** or **observations** into strata after **enrollment** for a **subgroup analysis**; **post-stratification**. rt: **classification**, **quotification** ***Usage note***: Stratification is done as a means of **controlling** sources of **variation** related to or assumed to be related to the **outcome**. Stratification (defn 2) and **blocking** in the **treatment assignment** process serve different purposes. Blocking is imposed as a means of ensuring that the **assignment ratio** will be satisfied or nearly satisfied; stratification is done to ensure the comparability of the treatment groups with regard to the variable(s) used in stratification. There is confusion regarding the meaning and impact of stratification on the design and operation of a trial. Often the act of stratification is taken as evidence of the need to perform **treatment comparisons** within the various strata represented in the stratification. Although

that may be desirable, such comparisons are not necessary. Valid comparisons of the **treatment groups** can be performed by pooling across strata. As a rule, the mix of persons enrolled into a trial is determined by the mix of persons seen and ultimately judged eligible for **enrollment**. Hence, the numbers to be represented in the various strata will be **variables** having values known only after completion of enrollment. The imposition of a **sample size requirement** for one or more of the strata (see **recruitment quota**), in addition to one for the trial, extends the time required for **recruitment** and should not be imposed unless there are valid scientific or practical reasons for doing so. Confusion also arises from use of the term **stratification** in two distinctly different contexts, as suggested in defns 2 and 3 above. Use **post-stratification** for uses in the sense of defn 3, especially when in settings, such as trials, where both forms of stratification are used.

stratification variable *n* - 1. A **variable** used to classify **treatment units** into **strata** in relation to **treatment assignment**. 2. A variable used to classify **observation units** into strata in relation to **data analysis**.

Introduction

A quota, in the context of a trial, is a requirement imposed on the sample size for the purpose of ensuring a specified mix of persons in regard to some characteristic. The characteristic may be clinic (in multicenter trials), one or more demographic characteristics (such as, gender, ethnic origin, or age), or one or more baseline characteristics.

Quotification is not to be confused with stratification. The later is done to ensure that the distribution of the stratification variable is the same across treatment groups, whereas quotification is done to ensure that that variable has a specified distribution in the finished sample size. The mix with regard to the variable floats with stratification and is fixed or constrained with quotification.

Examples

The RFP leading to creation of what subsequently came to be known as the Childhood Asthma Management Program (CAMP) had both a clinic and gender quota. It specified that each of 8 clinics would be required to enroll 132 children and that:

Each clinical center shall recruit males and females, and must specifically include at least 44 children from minority groups, such as Blacks, Hispanics, and Native Americans. (RFP-NIH-NHLBI-HR-90-12; issue date 1 November 1990)

The RFP giving rise to what became known as the National Treatment Emphysema Trial (NETT) specified that one of the selection criteria for clinics would be based on a study-wide minority and gender requirement:

This information will be used to make the final funding decision for the Clinical Centers which will be made with the objective of obtaining a study-wide patient mix which includes 6 percent minorities and 30 percent women. (RFP-NIH-NHLBI-HR-97-02; issue date 3 June 1996)

Reasons for quotification

Scientific

The foremost scientific reason for imposing a quota requirement on top of the sample size requirement is when there is reason to believe that treatment effect will differ by subgroup. The requirement is imposed to ensure adequate numbers for estimating effect differentials.

However, to justify quotification on scientific grounds, the trialist needs evidence supporting the notion of a treatment by subgroup quantitative interaction. The reality is that such evidence is hard to come by (usually because it does not exist).

Another reason for quotification on scientific grounds is simply as a means of ensuring a finished sample size with some minimum number of persons in a designated subgroup so that trialists will be able to estimate treatments effects by subgroup, even if only at a marginal level of precision. The requirements in CAMP and NETT are motivated in part by this desire.

Political

The tendency toward quotafication on demographic grounds is largely political in nature. The requirements in CAMP and NETT are, in part, of this nature.

The push for apportionment of research effort based on gender, and to a lesser extent on ethnic origin, came from Congress with enactment of the 1993 NIH Revitalization Act. It specifies that the Director of the National Institutes of Health (NIH) must ensure (for a trial involving diseases or conditions common to men and women) that the trial is

> *designed and carried out in a manner sufficient to provide for a valid analysis of whether the variables being studied in the trial affect women or members of minority groups, as the case may be, differently than other subjects in the trial.* (NIH Revitalization Act of 1993)

Broadly interpreted, the Act was a mandate to require NIH-funded trialists to design to have sufficient numbers of women and minorities to determine whether there are gender or ethnic origin by treatment interactions. (The requirement has been implemented to apply only to phase III trials; see National Institutes of Health: *NIH guidelines on the inclusion of women and minorities as subjects in clinical research*; Federal Register 59 (28 March), 1994:14,508-14,513; see also Freedman et al Controlled Clinical Trials 16, 1995;277-285: *Inclusion of women and minorities in clinical trials and the NIH revitalization act of 1993 – The perspective of NIH clinical trialists*).

Operational

Sometimes quotas are imposed simply to ensure a manageable mix of people at a clinic. For example, if a clinic requires separate facilities to screen and examine women and men, the clinic may set limits on the number of women and men that can be enrolled to ensure optimal use of its facilities.

Usually clinics in multicenter trials have target enrollment goals. Typically, that goal, when all clinics are enrolled at the same time, is N/r where N is the total sample size and r is the number of clinics in the trial. The goal becomes a quota when a clinic is required to stop enrolling when its goal is reached. For example, the RFP leading to creation of CAMP specified clinics capable of

enrolling 132 children.

Clinic sample size quotas in multicenter trials

Investigators have the option of fixing enrollment by clinic or letting it float. To assess the impact of fixing enrollment consider a trial involving 3 clinics and a sample size of 300; consider for different clinic scenarios as listed in Table 1. The combined enrollment rate is given by r_s (column E). The ranges of rates is given in column F.

Assuming constant enrollment rates over time and that clinics start enrollment at the same time, then the contributions of individual clinics is as listed in Table 2. The difference in the contribution of clinics to the finished sample size of 300 ranges from 0 (scenario 1) to near 6-fold (scenario 6).

One option, if investigators want to protect against marked difference in the numbers enrolled, is to cap enrollment. Capping comes into play when investigators want to "standardize" workloads across clinics. Indeed, funding itself imposes a crude form of capping when clinics are provided with the same basic level of funding.

The effect of capping is to reduce variation. For example, the range for clinics, with unconstrained enrollment for scenario 5, is 162 (column F; Table 2), compared to 120 with capping at 150 and 60 with capping at 120 (columns F and K, respectively; Table 3). But the reduction comes at a cost – increased time for enrollment. The times required to complete enrollment with capping at 150, 120, and 100 are given in Table 4. The reduction in enrollment efficiency (relative to unconstrained enrollment) is given in columns F, G, and H for capping at 150, 120, and 100, respectively.

Table 1: Clinic enrollment rates

A	B	C	D	E	F
	Enrollment rate/week				Rate
Scenario	Cl_1	Cl_2	Cl_3	r_s	range
1	1.00	1.00	1.00	3.00	0.00
2	1.20	0.90	0.90	3.00	0.30
3	1.00	1.00	0.75	2.75	0.25
4	2.00	1.00	0.50	3.50	1.50
5	2.00	1.00	0.25	3.25	1.75
6	3.00	1.00	0.50	4.50	2.50

Table 2: Numbers enrolled by clinic when enrollment is unconstrained

A	B	C	D	E	F
Scenario	Cl_1	Cl_2	Cl_3	Tot	Range
1	100	100	100	300	0
2	120	90	90	300	30
3	109	109	82	300	27
4	171	86	43	300	128
5	185	92	23	300	162
6	200	67	33	300	167

Table 3: Numbers enrolled by clinic when enrollment is capped

A	B	C	D	E	F	G	H	I	J	K
	150 cap / clinic					120 cap / clinic				
Scenario	Cl_1	Cl_2	Cl_3	Tot	Range	Cl_1	Cl_2	Cl_3	Tot	Range
1	100	100	100	300	0	100	100	100	300	0
2	120	90	90	300	30	120	90	90	300	30
3	109	109	82	300	27	109	109	82	300	27
4	150	100	50	300	100	120	120	60	300	60
5	150	120	30	300	120	120	120	60	300	60
6	150	100	50	300	100	120	120	60	300	60

Table 4: Enrollment times (weeks) under different cap restrictions and efficiencies relative to uncapped enrollment

A	B	C	D	E	F	G	H
	Cap restriction				Efficiency		
Scenario	None	150	120	100	150	120	100
1	100	100	100	100	1.00	1.00	1.00
2	100	100	100	111	1.00	1.00	0.90
3	109	109	109	133	1.00	1.00	0.82
4	86	100	120	200	0.86	0.72	0.43
5	92	120	240	400	0.77	0.38	0.23
6	67	100	120	200	0.67	0.56	0.34

Demographic mix quotas

A demographic-based quota is one involving gender, ethnic origin, age, or some other demographic characteristic of persons enrolled into a trial.

Gender mix quota

To illustrate the effect of mix quotas on time required for enrollment, consider the multicenter trial discussed above with a gender quota requirement as expressed below.

Option 1: The finished sample size for the trial shall consist of exactly 150 males and 150 females

Option 2: The finished sample size for the trial shall consist of 150 members of the lesser gender group and as many of the greater gender group as can be enrolled during enrollment of the lesser gender group

Option 3: The finished sample size of each clinic shall consist of exactly 50 males and 50 females

Option 4: The finished sample size of each clinic shall consist of 50 members of the lesser gender group and as many of the greater gender group as can be enrolled during enrollment of the lesser gender group

Note that the requirement is imposed at the level of clinic with options 3 and 4 and at the level of the study with options 1 and 2. The finished sample size will be 300 under options 1 and 3, whereas, for options 2 and 4 it will be in excess of 300.

Note also, that options 3 and 4 involve a defacto clinic sample size quota in addition to a gender mix quota.

To assess the effect on enrollment, suppose the gender flows of eligibles persons in clinics are as specified in Table 5. Note that the specifications are in terms of eligible persons. The mixes for persons screened may be different than those for eligibles if the yield of eligibles differs depending on gender.

Table 5: Gender mix fractions by clinic

A	B	C	D	E	F	G	H	I	J	K	L
	Gender mix (eligibles)									Overall gender mix	
	Cl_1			Cl_2			Cl_3				
Scenario	M	F	Rate	M	F	Rate	M	F	Rate	M	F
1	50	50	1.00	50	50	1.00	50	50	1.00	50.00	50.00
2	55	45	1.20	55	45	0.90	55	45	0.90	55.00	45.00
3	60	40	1.00	55	45	1.00	50	50	0.75	55.45	44.55
4	40	60	2.00	50	50	1.00	50	50	0.50	44.29	55.71
5	60	40	2.00	60	40	1.00	25	75	0.25	57.31	42.69
6	25	75	3.00	75	25	1.00	50	50	0.50	38.89	61.11

The unconstrained gender mix for clinics combined is as given in columns K and L of Table 5 (assuming as indicated above). The times (in weeks) required to enroll 300 people, in the absence of a mix constraint, for the different scenarios are as listed in column B of Table 4.

The enrollment times under options 1 and 2 are given in Table 6 (time denoted by T'; column D).

Table 6: Enrollment times (weeks) for gender mix options 1 and 2

A	B	C	D
Scenario	Males	Females	T'
1	100	100	100
2	91	111	111
3	98	122	122
4	97	77	97
5	81	108	108
6	86	55	86

The corresponding times under options 3 and 4 are given in Table 7. The time required to finish enrollment for the trial (column M) is given by the maximum of t', where t' is the longest period of time required by a clinic to enroll the lesser gender group (columns D, G, and J).

Table 7: Enrollment times (weeks) by gender and clinic for gender mix options 3 and 4

A	B	C	D	E	F	G	H	I	J	K	L	M
	Clinic 1			Clinic 2			Clinic 3			Total		
Scenario	M	F	t'	M	F	t'	M	F	t'	M	F	T'
1	100	100	100	100	100	100	100	100	100	100	100	100
2	76	93	93	101	123	123	101	123	123	101	123	123
3	83	125	125	91	111	111	133	133	133	133	133	133
4	63	42	63	100	100	100	200	200	200	200	200	200
5	42	63	63	83	125	125	800	267	800	800	267	800
6	67	22	67	67	200	200	200	200	200	200	200	200

The observed clinic male:female mixes with unconstrained enrollment and under options 1, 2, and 4 are given in Table 8.

Table 9 provides times required for achieving mix requirements under the different mix options. The times are the same for options 1 and 2 and for options 3 and 4 (columns B and H, respectively). The finished samples sizes under options 2 and 4 are given in columns E and K, respectively. Columns D and J give efficiencies relative to the time required in the absence of gender mix requirements. Columns G and M give observed sample sizes for options 2 and 4, respectively.

The time required under options 1 and 2 is the time it takes clinics to enroll the lesser gender group. The time needed is given by the gender-specific enrollment rate for that group divided into the number required. For example, for scenario 5 (Table 9), for females: 150/(0.4269)3.25/week = 150/1.39/week = 108 weeks; compared to 150/1.86/week = 81 weeks for males.

As noted, the time is the same for option 2 as for option 1. The difference is in the finished sample size. Under option 2 enrollment of both gender groups continues until the minimums are met for both gender groups. It is fixed at 300 under option 1. For example, the finished sample size for scenario 5 is 349 (150 females and 199 males) with option 2 compared to 300 for option 1.

Table 8: Clinic enrollment by gender under different mix options

A	B	C	D	E	F	G	H	I	J	K	L	M
	Clinic 1			Clinic 2			Clinic 3			Total		
Scenario	M	F	Tot	M	F	Tot	M	F	Tot	M	F	Tot
Unconstrained gender mix												
1	50	50	100	50	50	100	50	50	100	150	150	300
2	66	54	120	50	40	90	50	40	90	166	134	300
3	65	44	109	60	49	109	41	41	82	166	134	300
4	68	102	170	43	43	86	22	22	44	133	167	300
5	111	74	185	55	37	92	6	17	23	172	128	300
6	50	150	200	49	17	66	17	17	34	116	184	300
Option 1 mix requirement: 150 males and 150 females												
1	50	50	100	50	50	100	50	50	100	150	150	300
2	60	60	120	45	45	90	45	45	90	150	150	300
3	59	49	108	54	55	109	37	46	83	150	150	300
4	77	92	169	49	39	88	24	19	43	150	150	300
5	96	87	183	49	43	92	5	20	25	150	150	300
6	64	122	186	64	14	78	22	14	36	150	150	300
Option 2 mix requirement: At least 150 males and 150 females												
1	50	50	100	50	50	100	50	50	100	150	150	300
2	73	60	133	55	45	100	55	45	100	183	150	333
3	73	49	122	67	55	122	45	46	91	185	150	335
4	77	116	193	49	49	98	24	24	48	150	189	339
5	128	87	215	64	43	107	7	20	27	199	150	349
6	64	194	258	64	22	86	22	22	44	150	238	388
Option 4 mix requirement: at least 50 males and 50 females per clinic												
1	50	50	100	50	50	100	50	50	100	150	150	300
2	61	50	111	61	50	111	61	50	111	183	150	333
3	75	50	125	61	50	111	50	50	100	186	150	336
4	50	76	126	50	50	100	50	50	100	150	176	326
5	76	50	126	75	50	125	50	150	200	201	250	451
6	50	151	201	150	50	200	50	50	100	250	251	501

Table 9: Times to completion of enrollment by option and sample sizes with options 2 and 4

A	B	C	D	E	F	G	H	I	J	K	L	M
	Options 1 and 2						Options 3 and 4					
	Time			Option 2 SS			Time			Option 4 SS		
Scenario	T'	T	E	N'	N	N'/N	T'	T	E	N'	N	N'/N
1	100	100	1.00	300	300	1.00	100	100	1.00	300	300	1.00
2	111	100	0.90	333	300	1.11	123	100	0.81	333	300	1.11
3	122	109	0.89	335	300	1.12	133	109	0.82	336	300	1.12
4	97	86	0.89	339	300	1.13	200	86	0.43	326	300	1.09
5	108	92	0.85	349	300	1.16	800	92	0.12	451	300	1.50
6	86	67	0.78	388	300	1.29	200	67	0.34	501	300	1.67

Multiple demographic mix quotas

A multiple-mix quota is one involving specification for two or more demographic characteristics, eg, as represented for quota requirements in CAMP and NETT.

To illustrate consider scenario 5 under option 1 where, in addition to the 50:50 gender mix, suppose there is also a requirement for an 80:20 majority:minority mix. The quotas are: 120 majority males, 120 majority females, 30 majority males, and 30 minority females. To determine the effect of the added restriction on enrollment it is necessary first to specify the underlying gender-ethnic mix of eligible persons flowing to clinics (Table 10).

Table 10: Gender and ethnic origin marginals by clinic; per 100 persons

A	B	C	D	E	F	G	H	I	J	K	L	M
	Clinic 1				Clinic 2				Clinic 3			
	Gender		Ethnic		Gender		Ethnic		Gender		Ethnic	
	M	F	Maj	Min	M	F	Maj	Min	M	F	Maj	Min
5 a	60	40	70	30	60	40	80	20	25	75	90	10
5 b	60	40	80	20	60	40	85	15	25	75	90	10
5 c	60	40	90	10	60	40	90	10	25	75	95	5

The gender and ethnic mixes. if clinics enroll unconstrained, are 57:43 for gender and the respective majority:minority ethnic mixes are 75:25, 82:18, and 90:17, for scenarios 5 a, b, and, c, respectively. If we assume that the ethnic mix of eligibles is the same across gender groups, then the flow of eligibles by clinic is given by the products of marginals for gender and ethnic mix. For example, for Scenario 5 a the underlying mix fractions in Table 11 are 0.42 (0.60x0.70; Table 10) for majority males, 0.28 (0.40x0.70) for majority females, 0.18 (0.60x0.30) for minority males, and 0.12 (0.40x0.30) for minority females for clinic 1.

Table 11: Gender and ethnic flows of eligibles persons to clinics; per 100 persons

A	B	C	D	E	F	G	H	I	J	K	L	M
	Clinic 1				Clinic 2				Clinic 3			
	Males		Females		Males		Females		Males		Females	
	Maj	Min	Maj	Min	Maj	Min	Maj	Min	Maj	Min	Maj	Min
5 a	42	18	28	12	48	12	32	8	22.5	2.5	67.5	7.5
5 b	48	12	32	8	51	9	34	6	22.5	2.5	67.5	7.5
5 c	54	6	36	4	54	6	36	4	23.75	1.25	71.25	3.75

To achieve the two requirements under the constraints of option 1, the enrollment process has to be one involving stops when the indicated quota is met. The times in Table 12 are the times it takes the clinics to enroll 120 majority males, 120 majority females, 30 minority males, and 30 minority females. For example, the time of 86 weeks for enrollment of majority males for scenario 5 a is the rate at which clinics enroll majority males, ie, (3.25x0.57x0.75 =) 1.3894/week, divided into 120.

Table 12: Enrollment times (weeks) for gender-ethnic mix options 1 and 2

A	B	C	D	E
	Males		Females	
Scenario	Maj	Min	Maj	Min
5 a	86	63	116	85
5 b	78	91	105	121
5 c	71	168	96	225

The effect of imposing both a gender and ethnic mix requirement on time needed for enrollment be seen in Table 13. The time needed for satisfying options 1 or 2, scenario 5 a, is 116 weeks compared to 92 weeks with unconstrained enrollment. The corresponding times for an ethnic mix requirement alone and for a gender mix requirement alone are 99 and 108 weeks, respectively.

The enrollment times under option 3 are as listed in Table 14. The requirement under that option is for each clinic to enroll 50 males and 50 females and to have an 80:20 split in majority versus minority people in the two gender groups. The times required to achieve the quota requirements in this example are driven by the ethnic requirement for clinic 3 because eligible minority people are in shortest supply at that clinic. For example, under scenario 5 c it would take that clinic 3,200 weeks to enroll the required number of minority males.

Table 13: Enrollment times (weeks) and efficiencies under options 1 and 2 for different quota requirements

A	B	C	D	E	F	G	H
	Times (wks)				Time efficiency		
Scenario	None	Gender	Ethnic	Both	B/C	B/D	B/E
5 a	92	108	99	116	0.85	0.93	0.79
5 b	92	108	104	121	0.85	0.88	0.76
5 c	92	108	192	225	0.85	0.48	0.41

Table 14: Times (weeks) to complete enrollment under option 3 with a gender and ethnic origin quota

A	B	C	D	E	F	G	H	I	J	K	L	M
	Clinic 1				Clinic 2				Clinic 3			
	Males		Females		Males		Females		Males		Females	
	Maj	Min	Maj	Min	Maj	Min	Maj	Min	Maj	Min	Maj	Min
5 a	48	28	71	42	83	83	125	125	711	1,600	237	533
5 b	42	42	63	63	78	111	118	167	711	1,600	237	533
5 c	37	83	56	125	74	167	111	250	674	3,200	225	1,067

The impact of quota requirements on cost and precision

The total time, T_T, needed for conduct of a trial can be depicted as:

$$T_T = T_E + T_F$$

where T_E is the time needed for enrollment and T_F is the time needed for treatment and followup after completion of enrollment. The impact of mix requirements is to increase T_T and thereby increase cost, or, when T_T is fixed (often the case), reduce precision because of reduced followup.

For example, suppose for the multicenter trial described above that persons are to be treated and followed for 100 weeks following enrollment. In that case, for scenario 5, T_T is 192 weeks (92 weeks (Table 4) + 100 weeks) with unrestricted enrollment. The corresponding times with a gender mix requirement are 208 weeks (108 weeks (Table 9) + 100 weeks) under mix options 1 or 2, and 900 weeks (800 weeks (Table 9) + 100 weeks) under mix options 3 and 4. The costs (assuming a constant per unit cost over time) are 1.083 and 4.688, respectively, relative to the cost of unrestricted enrollment.

If the period of the trial is fixed, then the impact of a gender mix requirement is to reduce the amount of followup time for estimating treatment effects. For example, suppose T_T is fixed at 192 weeks. The table below gives the person weeks of followup generated for scenario 5 when all persons are treated and followed to the end of week 192 (Panel A: Common closing date) and when each person is treated and followed 100 weeks or to week 192, which ever comes first, and then separated from the trial (Panel B: Anniversary closing date).

Table 15: Weeks of person followup times for a 192 week trial with a gender mix requirement; scenario 5 clinic population

A	B	C	D
	Followup person weeks		
Gender constraint	Males	Females	Total
A: Common closing date			
None	24,966	18,834	43,800
Option 1	22,725	20,700	43,425
Option 3			
Clinic 1	8,550	8,025	16,575
Clinic 2	7,525	6,475	14,000
Clinic 3	1,152	3,456	4,608
	17,227	17,956	35,183
B: Anniversary closing date			
None	17,100	12,900	30,000
Option 1	15,000	14,824	29,824
Option 3			
Clinic 1	5,000	5,000	10,000
Clinic 2	5,000	4,792	9,792
Clinic 3	900	2,650	3,550
	10,900	12,442	23,342

Followup time with no mix requirement

Panel A: Males: 0.57[(92/2)300 + (100)300]; Females: 0.43[(92/2)x300 + (100)300]

Panel B: Males: (0.57)30,000; Females: (0.43)30,000

Option 1 followup time

Panel A: 150(192 - t/2), where t is the time required to achieve the quota requirement (Table 6)

Panel B: (150)100 if n_{92} is 150; otherwise $n_{92}(100) + (150 - n_{92})(146 - t/2)$, where t is the time required to achieve the quota requirement; eg, for females: 128(100) + (22)(92) = 12,800 + 2,024 = 14,824

Option 3 followup time

Panel A: If quota achieved by week 192 (see Table 7 for clinic times): 50(192 - t/2); if quota not achieved by week 192: $n_{192}(192/2)$, where t is the time required to achieve the quota requirement and n_{192} is the number enrolled by the end of week 192

Panel B: If quota achieved by week 92 (see Table 7 for times): (100)x50; if quota achieved after week 92 but by week 192: $100n_{92} + (100 - (t - 92)/2)(50 - n_{92}) = 100n_{92} + (146 - t/2)(50 - n_{92})$; if quota not achieved by week 192: $100n_{92} + (100 - 100/2)(n_{192} - n_{92})$

On ethical issues with demographic-based quotas in treatment trials

IRBs adherent to the concept of demographic neutrality are likely to object to mix requirements, if by imposition of the requirements, patients are rejected merely because of those characteristics. Investigators in CAMP struggled with this dilemma. The RFP specified that each clinic was to enroll at least 44 minority children. Since the RFP also specified that clinics were to enroll 132 children, the requirement meant that at least 1/3rd of the population enrolled at each clinic was to be from minority groups. Hence, as written, any clinic having an unregulated flow of eligibles of less than the required mix would have been required to reject eligible majority children in favor minority children.

Ultimately, the requirement was elevated to the study-level. The requirement of 44 minority children per clinic, translated to the level of the study, called for a finished sample size involving of at least 352 (8x44) minority children. To avoid clinics having to select on the basis of ethnic origin, clinics were allowed to enroll without regard to ethnic origin until the minimum number was achieved.

On the practical limits of demographic mix requirements and coping strategies

The desire of sponsors and investigators to be "politically correct" in regard to who gets studied inexorably drives them toward quotas to ensure "properly representative" study populations. The task of the trialist is to "talk" investigators out of quotas for reasons outlined above, but that is not easy in the early dawn of trials when all things are still possible. Suggested strategies are as follows:

Strategy 1: Challenge on ethical, scientific, and practical grounds

Comment

Ideally, challenge based on sound argument alone should be sufficient to negate most quota requirements proposed were it not for the "yes but" rebuttals. Invariably, the underlying basis for the "but" has to do with perceived political requirements to ensure a "properly representative" study population.

Strategy 2: Rewrite the requirement to minimize impact

Comment

The less restrictive a requirement the less its impact on performance. Hence, the trialist should work to elevate requirements specified at the level of clinic to the level of study (eg, as discussed above for CAMP) and to rewrite as minimums rather than as absolutes.

Strategy 3: Work to ensure a selection process for clinics consistent with the imposed quota requirements

Comment

The ability of the trialist to impact on clinic selection is limited, at best. That opportunity is nonexistent in RFA and RFP sponsor-initiated trials and limited in investigator-initiated trials, to the extent that selection is subject to peer-review performed by a group independent of the trial.

However, even if that opportunity exists, the ability to make selections consistent with the requirement is limited because investigators are notoriously unreliable when it comes to predicting mix flows in their clinics, to say nothing about innate tendencies to slant what they report in favor of selection.

Strategy 4: Urge the sponsor to fund additional clinics to facilitate meeting the quota requirements
Comment

This option is viable only if the sponsor has funding to allow such expansion and is practical only if exercised early in the course of the trial. Generally, there comes a point when the cost and effort of bring new clinics online is prohibitively expensive relative to the expected return.

Strategy 5: Resist quota requirements markedly at odds with expected clinic flows
Comment

The more divergent the requirement from the underlying flows of clinics, the more difficult it will be to meet.

Strategy 6: Challenge post-facto quota requirements
Comment

Quotas, if imposed at all, should be specified before clinics are selected and before the protocol is written and approved by IRBs.

Strategy 7: Work to modify the flow of eligible persons to clinics consistent with imposed quota requirements
Comment

This option is intuitively appealing but largely unrealistic and always time consuming and expensive.

The ability to modify flows in treatment trials involving tertiary care clinics is logistically and practically difficult. Changing the flow requires efforts to modify the behavior of referring physicians – no mean task. An option is for such clinics to take on the role of primary care clinics and to attempt to recruit directly. However, such efforts are likely to be considerable and not likely to yield sizable numbers of patients, to say nothing of the "town and gown" problems such approaches may create.

Basically, the option for flow management is limited to prevention trials involving "healthy" people not under the care of anyone for the condition targeted for treatment. However, in such settings there are reasons to be parsimonious in regard to imposed quota requirements. Graphic evidence of the likely cost of opening a trial such as MRFIT to females is provided in a paper entitled *Redesign of Trials Under Different Enrolment Mixes* (CL Meinert: Statist Med 1999;18, 241-251). The cost of the trial, had it been designed to include females in numbers sufficient to provide the same power as for men in MRFIT, was estimated to be 4.5 times the actual cost of MRFIT ($115 million). The increase would have been 16-fold if the trial had been designed to provide that level of power for gender and ethnic origin (majority or minority origin).

Strategy 8: Resist quota requirements likely to increase cost or to reduce precision without additional funding

Comment

A useful strategy, but do not expect it to be regarded as the pièce de résistance because such arguments are likely to fall on deaf ears. The deafness has to do with naivety regarding the actual cost of quota requirements, especially early on when the case is argued.

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