Medical Statistics (MATH38071) Solution Exercise Sheet 5
(Treatment Allocation)

1. A randomised controlled trial is planned to compare two treatments using simple randomisation with an equal allocation ratio. Randomisation will use computer generated pseudo-random numbers drawn from a uniform distribution U[0,1]. A sequence of numbers generated from this distribution is given in the table below.

a) Define a rule to convert these numbers into an allocation procedure for two treatments using simple randomisation and apply this to the sequence of numbers below to generate a treatment allocation list for 15 patients.

Fifteen Pseudo-Random Numbers

1.	0.563686	2.	0.677324	3.	0.709757	4.	0.864386	5.	0.871244
6.	0.179610	7.	0.101589	8.	0.496910	9.	0.543064	10.	0.875666
11.	0.961947	12.	0.603230	13.	0.210339	14.	0.475509	15.	0.189905

Solution

a) A simple rule would be to allocate to treatment B if the number is greater than 0.5.

b) Base on this the allocations would be

1.	B	2.	B	3.	B	4.	B	5.	B
6.	A	7.	A	8.	A	9.	B	10.	B
11.	B	12.	B	13.	A	14.	A	15.	A

Alternatively one might divide the digits for a particular decimal place into two equal size groups. For example one could choose the last decimal place with digits 0 to 4 being A and digits 5 to 9 as B.

2. Suppose instead that the trial in question 1 had three treatments and again requires an equal allocation ratio. Define a new rule to allocate three treatments A, B & C, and apply this using the pseudo-random numbers above to generate a treatment allocation list for the first 15 patients assuming simple randomisation.

Solution

A simple rule would be to divide the digits for a particular decimal place to each treatment. For example with three treatments allocate to treatment A if the first decimal place was 1, 2, 3, to B if for the numbers 4,5,6 and to C for 7,8,9. Any zero would then be ignored. Base on this the allocations would be

1.	B	2.	B	3.	C	4.	C	5.	C
6.	A	7.	A	8.	B	9.	B	10.	C
11.	C	12.	B	13.	A	14.	B	15.	A

3. A randomised trial plans to use *block* randomisation with a block size L with N treatments and an equal number of patients M allocated to each treatment so that $L=M \times N$. Show that the number of possible unique blocks equals $\frac{L!}{(M!)^N}$.

Solution

Suppose the patients in each block are numbered in sequence from 1 to L. Considering the first treatment the number for ways in which the M patients can be selected from L is the number of combinations

$$C(L,M)=\frac{L!}{M!(L-M)!}$$

Considering now the second treatment the number of ways of selecting these patients from the remaining L-N is

$$C(L-M,M)=\frac{(L-M)!}{M!(L-2M)!}$$

The total number of blocks is therefore

$$\begin{aligned}&C(L,M)\times C(L-M,M)\times\ldots\times C(2M,M)\\&=\frac{L!}{M!(L-M)!}\times\frac{(L-M)!}{M!(L-2M)!}\times\ldots\times\frac{(2M)!}{M!M!}\\&=\frac{L!}{(M!)^N}\end{aligned}$$

as required.

4.

a) Draw up a treatment allocation list for the first 15 patients for a trial comparing three interventions using block randomisation with a block size of three using the first digit of the random numbers listed above in sequence.

Solution

The number of unique blocks, $P=\frac{L!}{(M!)^N}$ with L=3, N=3 and M =1. Therefore $P=3!=6$

For treatments A, B and C these are

(1) ABC (2) ACB (3) BAC (4) BCA (5) CAB (6) CBA

For 15 patients one requires 5 random numbers with a block size of 3. If the sequence of random numbers chosen was 5, 6 , 1, 1, 4, 5 , the first 15 patients would be randomised in sequence to
CAB CBA ABC ABC BCA

b) How many unique blocks are there if the block size was 6 instead of 3?

Solution

The number of unique blocks $P=\frac{L!}{(M!)^N}$ with L=6, N=3 and M =2.

Therefore $P=\frac{6!}{(2!)^3}=6\times5\times3=90$.

There are 90 unique blocks if the block size is 6 an the number of treatments is 3

5. A trial with two treatments uses *block randomisation* with a block size of 6 with an equal allocation ratio. The trial is stopped after 63 patients are recruited. Determine the probability distribution of the difference in treatment group sizes at this stopping point.

Solution

For a block size L and N treatments the number of blocks is $\frac{L!}{(M!)^N}$ where M=L/N.

For a block size of 6 and two treatments the number of blocks is $\frac{6!}{(3!)^2}=\frac{6.5.4}{3.2.1}=20$.

With a block size of 6 the difference in treatment groups is either 0, 1, 2 or 3. Let p_n be the probability of a difference of n.

If the total number of patient is odd, the number of patients in one arm must be even and the other odd and the difference in groups is therefore odd.

Hence, after 63 patients are recruited, the difference must be either 1 or 3. Hence $p_0 = p_2 = 0$.

There are just two of the 20 unique blocks for which the imbalance is 3, AAABBB and BBBAAA.

Since all blocks are equally likely the probability of a difference of 3 is therefore 2/20 giving $p_1 = 0.1$

Since $p_0 = p_2 = 0$, and $p_1 = 0.1$, $p_3 = 1 - p_0 - p_1 - p_2 = 0.9$.

6. In a trial comparing two treatments for adolescent depression, cognitive behavioural therapy (CBT) is compared with drug therapy(SSRI). Patients are to allocated treatment by deterministic minimisation, using *gender* and *severity* classified as *moderate* or *severe*. After the first ten patients have been recruited and assign a treatment, the number of patients allocate to each treatment for each characteristic is given in the table below.

Male		Female		Moderate		Severe	
CBT	SSRI	CBT	SSRI	CBT	SSRI	CBT	SSRI
4	2	1	3	3	2	2	3

a. How many patients have been allocated CBT?

Solution

After the first ten patients have been recruited five have been allocated CBT.

b. The next 5 patients entering the trial, listed in order of entry, have the following characteristics

Patient Number	Gender	Severity
11	male	moderate
12	female	moderate
13	male	moderate
14	male	severe
15	female	severe

Solution

The table below give the totals and allocation after each patient is entered into the trial. Totals that have increased have been emboldened.

After patient	*Pat. Characteristics*	***Male***		***Female***		***Mod.***		***Sev.***		*Total**		*Treatment Allocation*
		CBT	*SSRI*	*CBT*	*SSRI*	*CBT*	*SSRI*	*CBT*	*SSRI*	*CBT*	*SSRI*	
10		*4*	*2*	*1*	*3*	*3*	*2*	*2*	*3*	*-*	*-*	
11	(male, mod.)	*4*	***3***	*1*	*3*	*3*	***3***	*2*	*3*	*7*	*4*	*SSRI*
12	(female, mod.)	*4*	*3*	***2***	*3*	***4***	*3*	*2*	*3*	*4*	*6*	*CBT*
13	(male, mod.)	*4*	***4***	*2*	*3*	*4*	***4***	*2*	*3*	*8*	*6*	*SSRI*
14	(male, sev.)	***5***	*4*	*2*	*3*	*4*	*4*	***3***	*3*	*6*	*7*	*CBT*
15	(female, sev.)	*5*	*4*	***3***	*3*	*4*	*4*	***4***	*3*	*5*	*6*	*CBT*

Scores for each treatment are calculated from the row above for the previous allocation, then in deterministic minimization allocation is to the treatment with the lower score. The totals for each allocation are shown for each patient below

Patient Number	Gender	Severity	CBT Total	SSRI Total	Allocation
11	male	moderate	4+3=7	2+2=4	SSRI
12	female	moderate	1+3=4	3+3=6	CBT
13	male	moderate	4+4=8	3+3=6	SSRI
14	male	severe	4+2=6	4+3=7	CBT
15	female	severe	2+3=5	3+3=6	CBT

7. In early clinical trials alternate allocation was sometimes used to assign treatment rather than randomisation. Why is this poor method of allocating treatment to patients in a clinical trial?

Solution This a poor method of allocation as it is predictable, because the person recruiting patients may be aware of the previous allocation and will therefore know the next treatment allocation , which may affect their willingness to recruit a patient, thereby causing *Allocation Bias*.