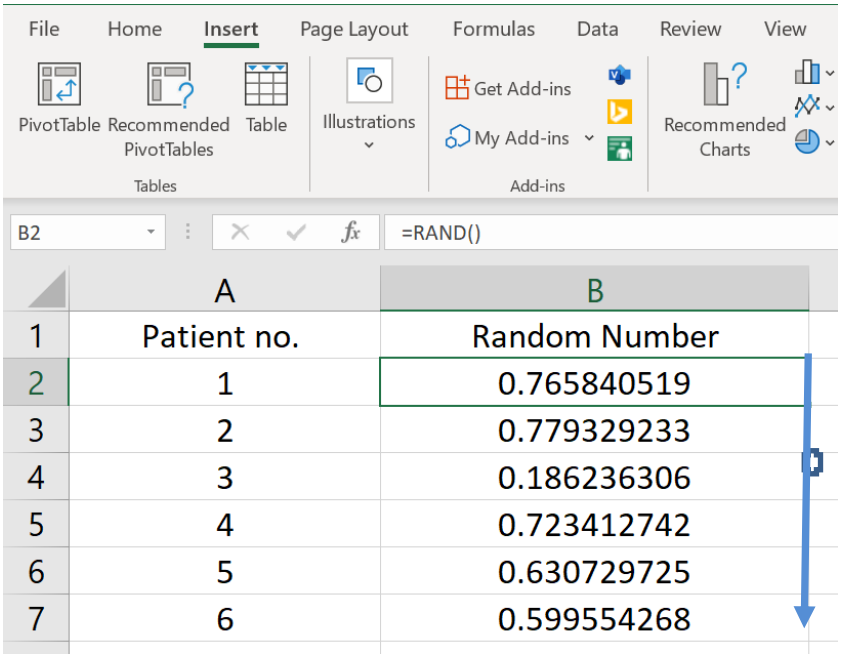
Supplementary file 2. Details of randomisation and allocation concealment

The simplest method of randomisation is by using computer generated random numbers. This may be performed in the Microsoft excel program by using the function =RAND() which has been entered in a cell e.g. B2 in the Figure 1(SF 2). This function generates random numbers greater than 0 but less than 1. In the figure the numbers may be seen in column B. Once a value is obtained for the function =RAND(), students can pull the right lower corner of the cell (highlighted as a blue square) to include as many random numbers as desired. The total number of random numbers desired would be equal to the sample size of the study. All cells in the column B from the 2nd row will thus have some number between 0 and 1.

Step 1.

Figure 1(SF 2): Function: =RAND()



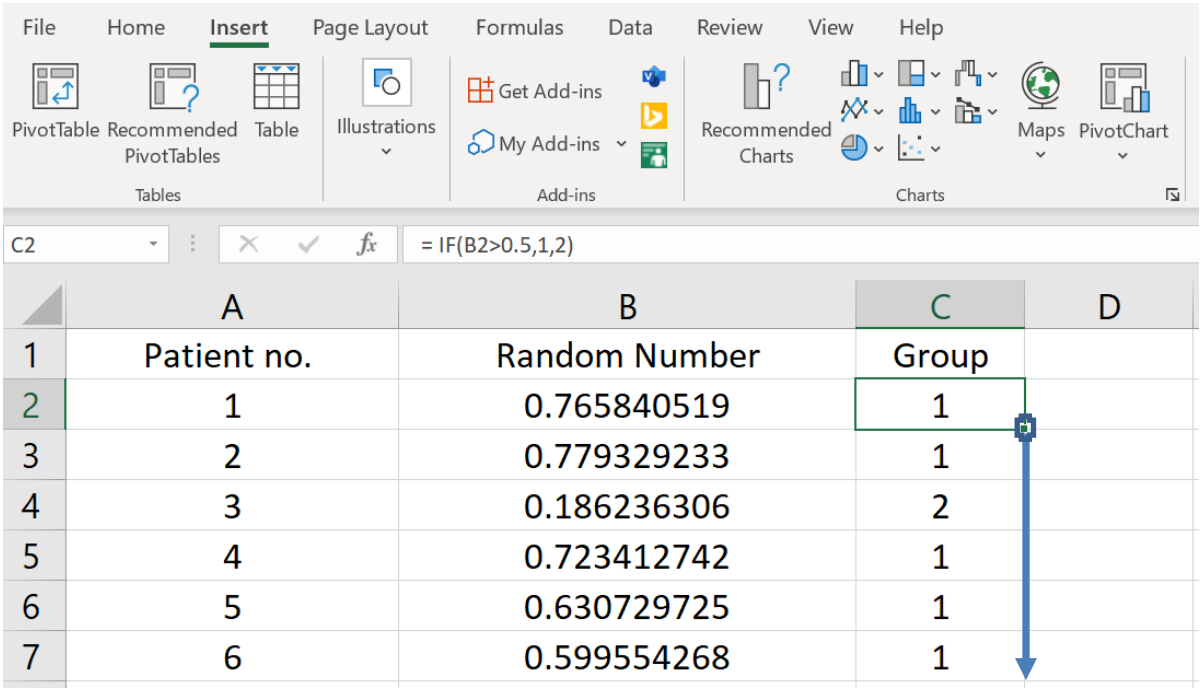
	A	B
1	Patient no.	Random Number
2	1	0.765840519
3	2	0.779329233
4	3	0.186236306
5	4	0.723412742
6	5	0.630729725
7	6	0.599554268

Once the random numbers have been generated, we need to allocate groups based upon these randomly generated numbers. We can decide that all numbers greater than 0.5 will be allocated group 1 and those below 0.5 will be given group 2. To segregate on this basis, we need to put in another formula in Step 2.

Step 2

By entering formula function: =IF(B2>0.5,1,2) in the cell C2, we may allot number 1 if the value of the random number in B2 is greater than 0.5, else the number allotted is 2 [Figure 2 (SF2)]. This may serve as groups 1 and 2 which can later be labelled as per the study name eg Lignocaine group and Bupivacaine group.

Figure 2(SF 2): Function =IF(B2>0.5,1,2)



	A	B	C	D
1	Patient no.	Random Number	Group	
2	1	0.765840519	1	
3	2	0.779329233	1	
4	3	0.186236306	2	
5	4	0.723412742	1	
6	5	0.630729725	1	
7	6	0.599554268	1	

There are drawbacks to this technique as chances of allocation to the two treatment arms are likely to be significantly different when the sample size is small (less than 100). It is thus preferable to use block randomisation.

Block Randomisation: This method allocates subjects into groups or blocks that result in a probability that each arm will contain an equal number of individuals by sequencing participant assignments by block. The block size must be divisible by the number of study groups. A disadvantage of block randomisation is that the allocation of participants may be predictable and result in selection bias when the study groups are unmasked.

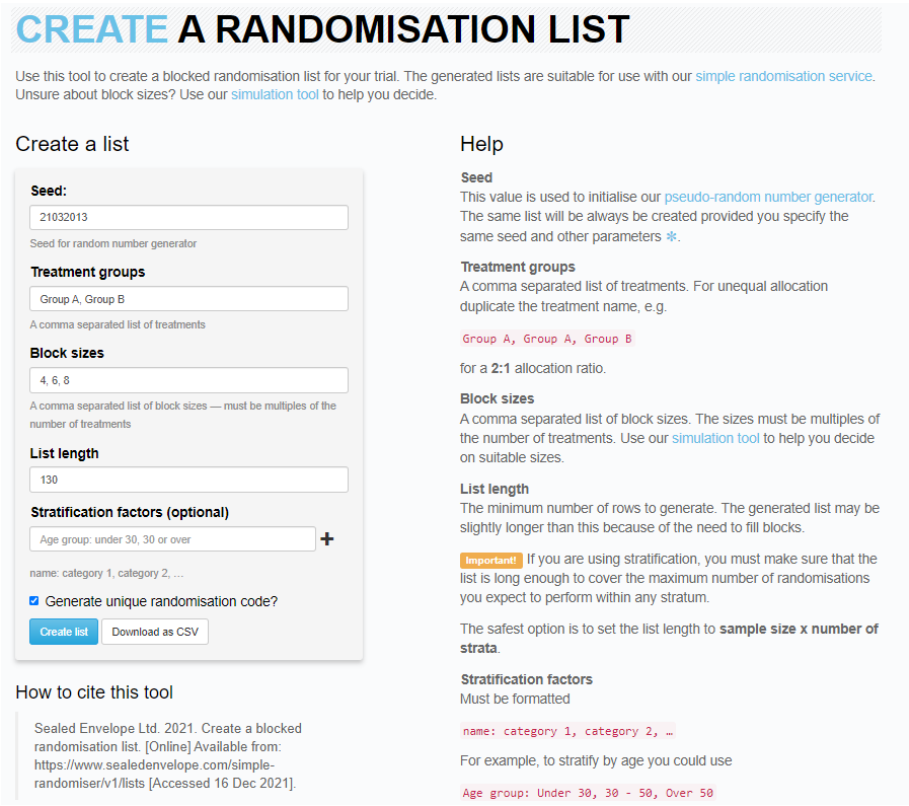
Stratified Randomisation: Tries to address the need to control and balance the influence of covariates. Stratified randomisation is achieved by generating a separate block for each combination of covariates, and subjects are assigned to the appropriate block of covariates.

An example of a source which can serve most of the purposes of randomisation, is a website www.sealedenvelope.com. Although there are many sources of randomisation and treatment allocation online, authors have chosen this website solely as an example and it is not to endorse that this is the best available resource.

Once the website is reached, there is a drop-down tab for “RANDOMISATION” on the top panel. From this drop-down menu, “CREATE A LIST” tab has to be clicked where all details need to be filled as may be noted from Figure 3(SF2).

As an example of a study enroling 130 subjects, to utilise the service to block randomise them into two treatment groups with varying block sizes of 4,6 and 8, all the values can be fed at the desired place as may be seen in the Figure 3(SF2). There is an optional feature of stratification of the randomisation based upon factors such as age if it is likely to cause confounding. Certain surgeries like a laparoscopic cholecystectomy are more likely in females around forty. Guidance for entry of values is also provided alongside the tabs. All entire are made as may be seen with a unique Seed number which will help generate the similar sequence if re-entered.

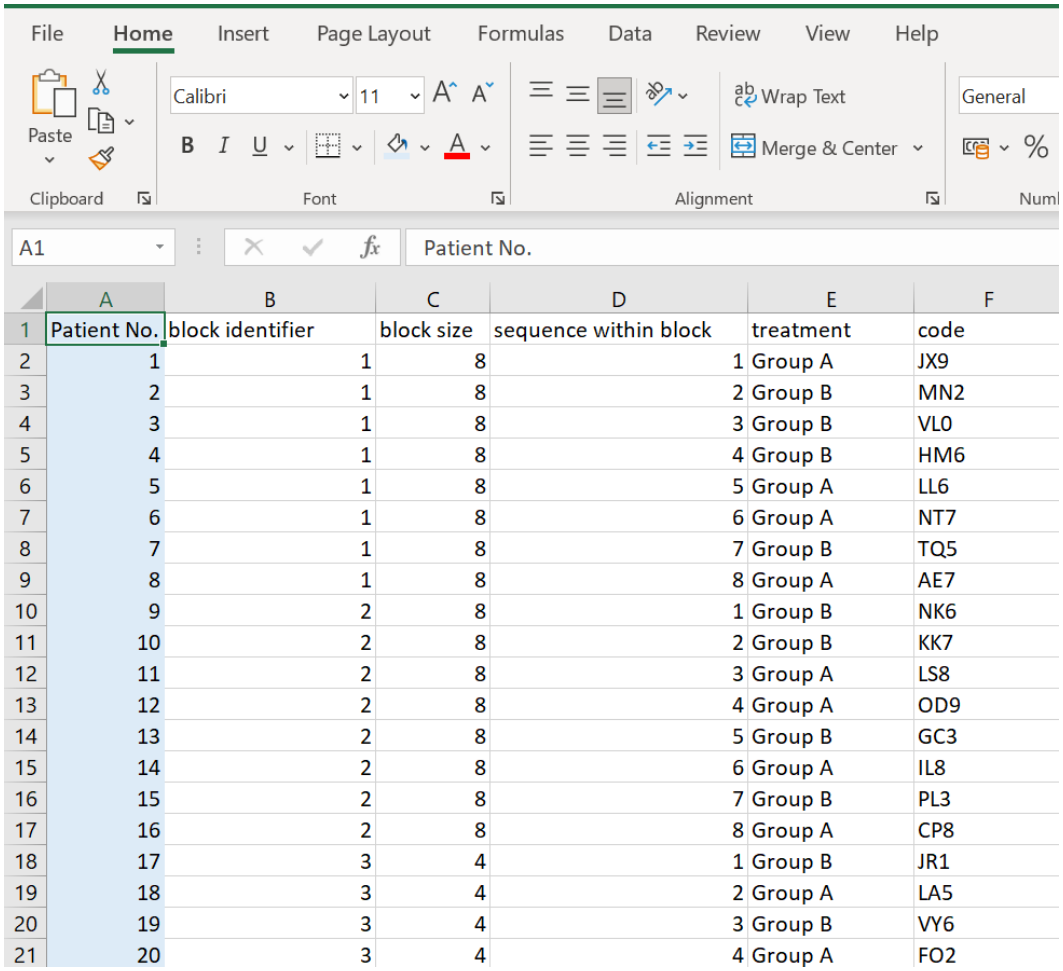
Figure 3(SF 2). Details to be entered for creation of a block randomisation list.



Once the values have been fed as shown, the list has to be downloaded as an Excel style **CSV** format. A snapshot of the downloaded file may be seen as Figure 4(SF2). The excel sheet has columns for block identifier, block size, sequence within the block, treatment group allocated and unique randomisation code. It should be noted that patient number column is not generated by the website and the column containing patient number has been added in this [Figure 4(SF2)]. This unique list shall be available with a statistician or any other person not involved with the study. Even the statistician may be shielded from knowing the identity of treatment group.

Figure 4(SF2)

Output Excel sheet for block randomisation using online web site sealedenvelope.com



Patient No.	block identifier	block size	sequence within block	treatment	code
1	1	8	1	Group A	JX9
2	1	8	2	Group B	MN2
3	1	8	3	Group B	VL0
4	1	8	4	Group B	HM6
5	1	8	5	Group A	LL6
6	1	8	6	Group A	NT7
7	1	8	7	Group B	TQ5
8	1	8	8	Group A	AE7
9	2	8	1	Group B	NK6
10	2	8	2	Group B	KK7
11	2	8	3	Group A	LS8
12	2	8	4	Group A	OD9
13	2	8	5	Group B	GC3
14	2	8	6	Group A	IL8
15	2	8	7	Group B	PL3
16	2	8	8	Group A	CP8
17	3	4	1	Group B	JR1
18	3	4	2	Group A	LA5
19	3	4	3	Group B	VY6
20	3	4	4	Group A	FO2

Allocation concealment

The interventions (even medicines) are sometimes sealed in sequentially numbered identical envelopes/containers according to the allocation sequence.

Thus, in this case, 130 envelopes with have to be made. The paper should be reasonably thick to ensure that nothing can be read through them even after flashing light behind it. Aluminium foil inside the envelope has been used to render the envelope impermeable to light. The treatment group allocated i.e. Group A/ Group B, needs to be placed inside the envelope and the paper containing the treatment allocation group should be folded to prevent being read through the envelope. Some authors may put the unique randomisation code along with the treatment allocation e.g. Group A, JX9 inside the envelope. This envelope needs to be sealed with only the enroled patient number mentioned on the front of the envelope. The envelopes are then sequentially placed as per the enroled patient number. As and when the patients are recruited, top-most sealed envelope goes to the researcher who allots the treatment and ensures blinding. e.g. person preparing the identical drug infusions. To ensure sanctity of the process of the allocation sequence, the name and unique detail e.g. inpatient ID or birth date of the participant may be written on the envelope. Though a video tape may also be made of the sealed envelope with participant details visible, it is almost never practised for post graduate thesis work. Some authors place a carbon paper inside the envelope such that patient information is transferred onto the allocation card placed inside the envelope. An independent second researcher may later verify the sanctity of process by viewing the video tapes to ensure the envelopes were still sealed at the time of participants' names being entered on them. To ensure a fair distribution, containers should be opened sequentially and only after the subject’s identification and other details are documented at all the appropriate proformas and places.

Some other methods used are: numbered or coded containers; pharmacy controlled; on-site computer systems, secure computer-assisted method where allocations are held in a locked unreadable electronic file. These criteria establish minimum methodological standards, yet they are met by only about a quarter of trials.

It is important to document who generated the allocation sequence, who enroled the participants, and who assigned participants to the interventions. This will vary with all studies, however an example of how this may be entered into the thesis is: “Simple randomisation was performed using computer generated random number list prepared using

Microsoft Excel 365 (2019) by a researcher not involved in this study. After generating the random numbers and allotment of the treatments, chits with group allocations, were sequentially placed inside an opaque envelope, sealed by the researcher and numbered. These envelopes were kept with him. After a post graduate student obtained an enroled patient's consent, he telephoned this researcher who noted all details and opened the sealed envelope. As per sequence, he directed another anaesthesiologist involved in the study but independent of the recruitment process, for allocation consignment."