Chapter A2: Randomization

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Summer 2017

Structure

1. **Simple randomization**
2. Random permuted blocks
3. Biased coin designs and urn schemes
4. Stratification
5. Minimization
6. Unequal randomization

Naive randomization

Doctor flips a coin: this is a natural procedure, but...

1. coin might be biased;

2. doctor knows what treatment is allocated, so double blindness is impossible;

3. overemphasizes the aspect of uncertainty in front of the patient;

4. creates groups of different sizes, problematic in small trials.

Problem 1 can be avoided through the use of a reliable random number generator; problems 2 and 3 if this is done by another person (so that the doctor remains blind).

Groups of different sizes in small trials

Suppose $2n$ patients are allocated to two treatment groups 1 and 2 independently with equal probability. For the number in group 1, N_1, we have

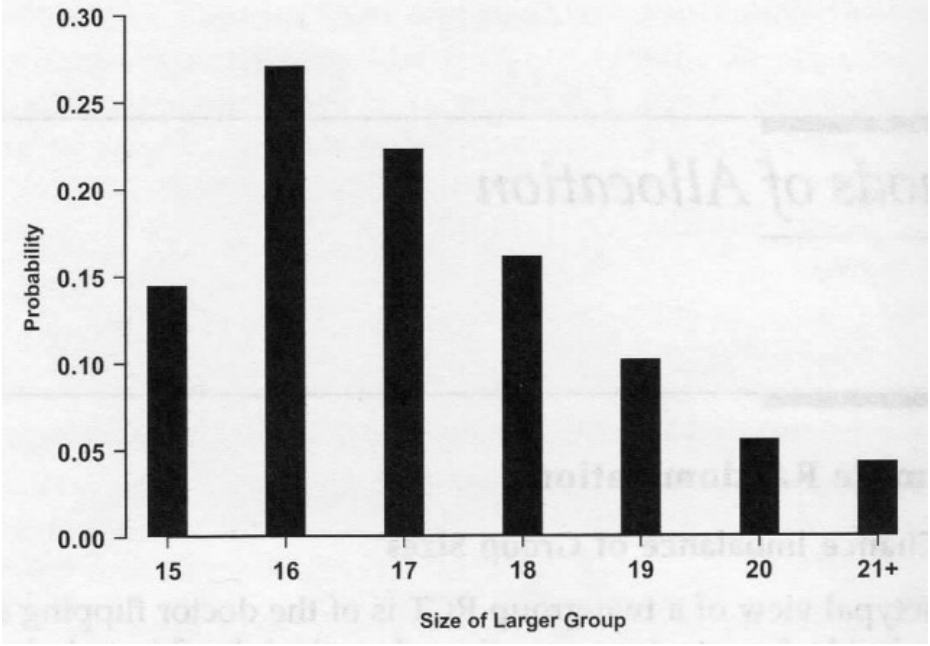
$$N_1 \sim Bin(2n, \frac{1}{2}).$$

The size N_{max} of the larger group takes values in the set $\{n, n+1, \ldots, 2n\}$ with probabilities

$$\begin{aligned} Pr(N_{max} = n) &= \binom{2n}{n}\left(\frac{1}{2}\right)^{2n} \\ Pr(N_{max} = r) &= 2\binom{2n}{r}\left(\frac{1}{2}\right)^{2n}, \quad r = n+1, \ldots, 2n. \end{aligned}$$

Example

Distribution of larger group size in a trial of 30 patients with two treatment groups formed by simple randomization:



Loss of power

Suppose we are designing an RCT to detect a clinically important difference equal to a standard deviation at the 5% significance level. If 30 patients are recruited then the power $1-\beta$ can be found as

$$1-\beta \;=\; \Phi\left(\sqrt{\frac{n_1 n_2}{30}}-1.96\right).$$

If $n_1 = n_2 = 15$, $1-\beta = 78\%$.

If $n_1 = 20$ and $n_2 = 10$, $1-\beta = 73\%$.

If $n_1 = 24$ and $n_2 = 6$, $1-\beta = 59\%$.

Loss of power is not tolerable.

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Random permuted blocks

The problem of unbalanced group sizes can be solved by a form of restricted randomization known as *random permuted blocks* (RPB):

- RPBs of fixed block length
- RPBs with random block length

Random permuted blocks of fixed length

Consider the sequences of length 4 that comprise two 1s and two 2s:

1. **1 1 2 2** 2. **1 2 2 1** 3. **1 2 1 2**
4. **2 2 1 1** 5. **2 1 1 2** 6. **2 1 2 1**

A list of independent identically distributed random numbers is then generated, each element being chosen from $\{1, 2, 3, 4, 5, 6\}$ with equal probability.

Random permuted blocks of fixed length (ctd.)

- This results in a sequence in which each patient is equally likely to receive treatment 1 or treatment 2 but the randomization has been restricted to allow only sequences of 1s and 2s such that at no stage along that sequence does the foregoing number of 1s and 2s differ by more than 2.

- 4 is a good compromise between blocks of length 2 (too great restriction) and longer blocks (too large differences between group sizes, too many candidate blocks).

Random permuted blocks of fixed length: drawback

- If the trial is organized in such a way that the doctors involved in the study know which treatments patients already in the study have received, then after 3 patients (modulo 4) have been admitted, knowledge of previous treatment allocations and the block length allows the next treatment to be predicted with certainty.

- This means that **selection bias** may be a problem (and subsequently also **assessment bias**, as in all cases where the doctor is not blinded).

Solution to this problem: RPBs with random block length

For example blocks of sizes 4 (6 possible blocks) and 6 (20 possible blocks)

1. Generate a random number X from the set $\{4, 6\}$ where $Pr(X = 4) = \frac{1}{2}$.

2. If $X = 4$, generate a random number Y from the set $\{1, 2, 3, 4, 5, 6\}$ (each number equally likely) and set S_i to be the block of length 4 corresponding to Y (see slide 8).

3. If $X = 6$, generate a random number Y from the set $\{1, 2, \ldots, 20\}$ (each number equally likely) and set S_i to be the block of length 6 corresponding to Y.

RPBs with random block length: properties and remarks

- Each patient is equally likely to receive treatment 1 or treatment 2.
- The number of patients allocated to the two groups can never differ by more than 3.
- The possibility of selection bias is negligible.

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Biased coin designs and urn schemes

- With RPBs with random block length, prediction of allocation is very unlikely but not impossible.
- Alternative: stochastic methods based on the adjustment of the probability of treatment allocation as the trial proceeds in such a way that the probability of assignment to overrepresented treatments is reduced.
- Many variants, for example biased coin designs and urn schemes.

Biased coin designs and urn schemes (ctd.)

- Denote as $N_1(n)$ (resp. $N_2(n)$) the number allocated to treatments 1 and 2, respectively, after n patients have entered the study.
- Let the imbalance in treatment numbers be $D(n) = N_1(n) - N_2(n)$.
- In biased coin designs and urn schemes, the probability of allocation of the $(n+1)th$ patient to treatments 1 and 2 depends on $D(n)$.

Principle of biased coin designs (Efron, 1971)

The biased coin design changes the allocation probability according to the value of $D(n)$:

If $D(n) = 0$, allocate patient $n+1$ to treatment 1 with probability $1/2$.

If $D(n) < 0$, allocate patient $n+1$ to treatment 1 with probability P.

If $D(n) > 0$, allocate patient $n+1$ to treatment 1 with probability $1-P$.

with $\frac{1}{2} < P \leq 1$.

Principle of biased coin designs (Efron, 1971)

We can easily show:

$$\begin{aligned} Pr(|D(n+1)| = j+1 \mid |D(n)| = j) &= 1-P \\ Pr(|D(n+1)| = j-1 \mid |D(n)| = j) &= P \end{aligned}$$

- Some properties of this method can be discerned from known properties of random walks.
- In the long run, the probability of exact balance is $2 - P^{-1}$.
- With $P = 1$ exact balance is ensured, but the sequence is deterministic. $P = 2/3$ or $P = 3/4$ may be more appropriate.

Principle of urn schemes

- Patients are allocated by randomly choosing a ball from the urn and assigning the patient to the treatment written on the selected ball.
- Initially the urn contains $(2r)$ balls: r labeled 1 and r labeled 2.
- The selected ball is returned to the urn and s balls labeled with the treatment which was not chosen, are added to the urn.

Principle of urn schemes (ctd.)

It can be shown:

$$\begin{aligned} Pr(|D(n+1)| = j+1 \mid |D(n)| = j) &= \frac{1}{2} - \frac{|D(n)|s}{2(2r+ns)} \\ Pr(|D(n+1)| = j-1 \mid |D(n)| = j) &= \frac{1}{2} + \frac{|D(n)|s}{2(2r+ns)}. \end{aligned}$$

Interpretation? Choice of r and s?

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Stratification

- RPBs are often used in practice in combination with *stratification*.
- Stratification is used to control the imbalance between the groups not with respect to their size but with respect to their composition: although randomization will, in principle, produce groups that are balanced with respect to any prognostic factor, in practice, treatment groups that are not alike with respect to important prognostic factors can and do occur.
- **Example:** We want to compare a new method of treatment (D) with an existing method (U) to see if it improves the glycemic control of patients under 16 years of age who suffer from type I diabetes. The outcome is a normally distributed variable known as Hb1A1c (high value $=$ poorer control).

Stratification: example (ctd.)

- Suppose the RCT will recruit $2n$ patients and within the patient population being recruited a porportion θ are children (< 12 years) and remaining patients adolescents.

- Suppose we form two groups of size n (e.g. using RPBs).

- Then the number of children in the group receiving D (resp. U), M_D (resp. M_U), will have the distribution $Bin(n, \theta)$.

- On average, we expect θn children in each group. This is essentially what we mean when we say that, in principle, randomization will produce balanced groups.

Stratification: example (ctd.)

- Suppose that the treatment has no effect.
- Suppose that the expected value of Hb1A1c is μ_C in children and μ_A in adolescents with $\mu_A > \mu_C$.
- The expected value of Hb1A1c in groups D resp. U is

$$\frac{M_D\mu_C + (n - M_D)\mu_A}{n} \quad \text{resp.} \quad \frac{M_U\mu_C + (n - M_U)\mu_A}{n}.$$

- The expected difference in treatments would then be $\frac{M_D - M_U}{n}(\mu_C - \mu_A)$ $\rightarrow$ biased trial.

Solution: using stratification

- Rather than allocate all patients in one process, we allocate patients of different types separately.

- Example children/adolescents: we would prepare, using RPBs, not one allocation but two: one for children and one for adolescents.

- Within each stratum one should not use simple randomization, otherwise allocation is not affected by whether or not patients are grouped into strata $\rightarrow$ use RPBs.

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Principle of minimization

- Suppose we have 4 prognostic factors with I, J, K, L levels, for example in breast cancer: age (≤ 50 or > 50), stage of disease (I-II vs. III-IV), time between diagnosis and effusion (≤ 30 months vs. > 30 months), and pre- vs. post-menopausal. So $I = J = K = L = 2$.

- RPB within strata would ensure $|n^A_{ijkl} - n^B_{ijkl}| \leq \frac{1}{2}b$ for each quadruplet (i, j, k, l), where b is the maximum block size used in the RPB.

- This is often not necessary. Often it is sufficient that $|n^A_{i+++} - n^B_{i+++}|$, $|n^A_{+j++} - n^B_{+j++}|$, $|n^A_{++k+} - n^B_{++k+}|$, and $|n^A_{+++l} - n^B_{+++l}|$ are small.

Principle of minimization (ctd.)

1. The 1st patient is allocated by simple randomization.
2. Denote as n^A_{ijkl} and n^B_{ijkl} the number of patients with prognostic factors i, j, k, l allocated to treatment A and B at some stage of the trial.
3. A new patient is entered to the trial who has prognostic factors w, x, y, z.
4. Form the sum $(n^A_{w+++} - n^B_{w+++}) + (n^A_{+x++} - n^B_{+x++}) + (n^A_{++y+} - n^B_{++y+}) + (n^A_{+++z} - n^B_{+++z})$.
5. If the sum is negative (resp. positive) then the new patient is allocated to A (resp. B) with probability $P > 0.5$.

$P < 1$ protects against selection bias, but selection bias is very unlikely in this setting anyway.

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Unequal randomization

- In some cases, it makes sense to gain extra experience in the use of the (new) treatment by unequal randomization, i.e. one of the groups is supposed to be larger than the other one.

- A side-effect is that it may even encourage recruitment in certain trials.

- The main inconvenience is that unequal group sizes lead to a lower power. We will come back to this issue in Chapter A3.

Unequal randomization: loss of power

- On slide 16 of Chapter A3, we will see that

$$1 - \beta \approx 1 - \Phi(z_{1-\alpha/2} - \frac{\tau}{\sigma\lambda})$$

  where $1 - \beta$ is the power and $\lambda = \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}$.

- For groups of equal size n, n is obtained as $2\lambda^{-2}$.

- For a fixed total size, λ increases and the power $1 - \beta$ decreases with increasing class imbalance.

- However, this decrease is almost negligible for imbalance no greater than 2:1.

Unequal randomization: loss of power

Power $1-\beta$ plotted against ratio of group sizes (for $n_1+n_2 = 168$, $\tau/\sigma = \frac{1}{2}$, $\alpha = 0.05$, $1-\beta = 0.9$ at ratio$= 1$):