Random allocation

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Marcia H. Varella, MD, PhD, MHS
Define random allocation, and why it is important.

Describe three methods of random allocation:
  - Simple.
  - Stratified.
  - Block.

Define concealed allocation, and why it is important.

Assess the randomization and concealment allocation methods used in a paper.

Demonstrate interactive teaching strategies and tools.
Most challenging concepts / issues

• Stratified and blocked randomization
• Concealment of allocation vs blinding
Randomized controlled trial

“A clinical trial that involves at least one test treatment and one control treatment, concurrent enrollment and follow-up of the test- and control-treated groups, and in which the treatments to be administered are selected by a random process.”

National Library of Medicine
Randomization depends on two interrelated but different processes

- **Sequence generation:**
  - An **unpredictable** allocation sequence **generated through a random process.**

- **Allocation concealment:**
  - Rigorous implementation of the random sequence through a **mechanism that prevents foreknowledge** of treatment assignment.
Random allocation

- Allocates subjects to the interventions (experimental or control) through *chance*.
- Each subject has a *known probability* (usually equal) of receiving any of the interventions.
- *Random allocation ≠ random sampling.*
Random allocation
Random selection
Random allocation vs random selection

Most RCTs use convenience rather than random sampling methods
Why?

- Creates study groups with *similar prognosis* = it controls bias and confounding by making the *groups homogeneous at baseline*.

- *Equal distribution* of the benefits and risks of the interventions (which are usually unknown).
Simple randomization:

- Coin toss, throwing a dice
- Random number table:
  - Textbook
  - Computer generated
- Random allocation software
OpenEpi provides statistics for counts and measurements in descriptive and analytic studies, stratified analysis with exact confidence limits, matched pair and person-time analysis, sample size and power calculations, random numbers, sensitivity, specificity and other evaluation statistics, R x C tables, chi-square for dose-response, and links to other useful sites.

OpenEpi is free and open source software for epidemiologic statistics. It can be run from a web server or downloaded and run without a web connection. A server is not required. The programs are written in JavaScript and HTML, and should be compatible with recent Linux, Mac, and PC browsers, regardless of operating system. (If you are seeing this, your browser settings are allowing JavaScript.) The programs can be run in the browsers of many iPhone and Android cellphones.

Test results are provided for each module so that you can judge reliability, although it is always a good idea to check important results with software from more than one source. Links to hundreds of Internet calculators are provided.
1 = 20 participants
2 = 30 participants

Probability of 20 heads in 50 flips of a coin: 6%
Non-random allocation:
- Order of entry into the clinic/hospital
- Day of the week, month
- Last digit of document (ID, clinical record, etc.)
Using your smart phone, please:

- Enter “flip a coin” in your web browser.
- Flip a coin once to get “Heads” or “Tails”.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Heads (N = )</th>
<th>Tails (N = )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td></td>
<td></td>
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<tr>
<td>Pediatrician</td>
<td></td>
<td></td>
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<tr>
<td>Follow the NBA</td>
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</tbody>
</table>
Additional safeguards

- Stratified randomization
- Block randomization
Stratified randomization
Stratified randomization

- Increases balance between groups in terms of *selected participants’ prognostic characteristics* at baseline.
- Participants are randomized *within each stratum*.
- The total number of strata is the *product* of all categories within each stratum:
  - Center: 4 (A, B, C, D)
  - Gender: 2 (M, F)
  - Obesity: 2 (Y, N)

\[ \text{16 strata} \]
Block randomization

- Keeps the *number* of participants in each treatment group within a desired ratio (usually 1:1 or “equal”)
- Participants are randomized *within each block*
A. Block size of 4

B. Possible permutations with repetition (i.e., 2 to control group, 2 to treatment group)

C. Random selection of blocks (i.e., 1, 3, 4, 4, 3, 6, 1, 2, 5, 2 – 40 participants)
IMPORTANCE  In the intensive care unit (ICU), orotracheal intubation can be associated with increased risk of complications because the patient may be acutely unstable, requiring prompt intervention, often by a practitioner with nonexpert skills. Video laryngoscopy may decrease this risk by improving glottis visualization.

OBJECTIVE  To determine whether video laryngoscopy increases the frequency of successful first-pass orotracheal intubation compared with direct laryngoscopy in ICU patients.

DESIGN, SETTING, AND PARTICIPANTS  Randomized clinical trial of 371 adults requiring intubation while being treated at 7 ICUs in France between May 2015 and January 2016; there was 28 days of follow-up.

INTERVENTIONS  Intubation using a video laryngoscope (n = 186) or direct laryngoscopy (n = 185). All patients received general anesthesia.
1. Please go to kahoot.it
2. When provided, enter the Game PIN
3. Get ready to play!
System test. Which of these countries has won the most world champion titles at the FIFA World Cup?

1. Argentina
2. Brazil
3. Germany
4. Italia
1. Researchers stratified by center (7 ICUs) and expert / nonexpert status of the physician; which of the following is correct about such stratification?

A. Stratification made equal the number of patients randomized to each treatment.

B. Before randomizing it was needed to know who was going to intubate each patient.

C. This stratification intended to ensure baseline balance between the treatments on gender.

D. The trial had 9 strata (7 sites plus 2 levels of expertise).
2. The trial also used “blocks of 4”; which one of the following is correct about this block randomization?

A. Participants had 4-times higher chance of being allocated to video than to direct laryngoscopy.

B. All patients within each block of four were randomized together to video or to direct laryngoscopy.

C. The largest difference between the number of patients per treatment group will be 2.

D. Block randomization contributed to achieve good baseline balance regarding gender.
A. Block size of 4

B. Possible permutations with repetition (i.e., 2 to control group, 2 to treatment group)

C. Random selection of blocks (i.e., 1, 3, 4, 4, 3, 6, 1, 2, 5, 2 – 40 participants)
- Define random allocation, and why it is important.
- Describe three methods of random allocation:
  - Simple.
  - Stratified.
  - Block.
- Define concealed allocation, and why it is important.
- Assess the randomization and concealment allocation methods used in a paper.
- Demonstrate interactive teaching strategies and tools.
Randomization depends on two interrelated but different processes

- **Sequence generation:**
  - An unpredictable allocation sequence *generated* through a random process.

- **Allocation concealment:**
  - Rigorous implementation of the random sequence through an *assignment mechanism that prevents foreknowledge* of treatment assignment.
“When those enrolling patients are unaware and cannot control the arm to which the patient is allocated.”

“Preventing the next assignment in the trial from being known.”

Refers to the technique used to implement the random sequence, not to generate it.
To speed up the next session, I am going to randomize participants to two groups generating random numbers:

1. **Yes**, may ask questions
2. **No**, no questions allowed

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**Concealment of allocation vs blinding**

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>2</th>
<th>2</th>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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</tbody>
</table>

50 Random Numbers from 1 to 2

Generated by the OpenEpi Random Program

www.openepi.com
Concealment of allocation vs blinding

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>Yes, may ask questions</td>
</tr>
<tr>
<td>2.</td>
<td>No, no questions allowed</td>
</tr>
<tr>
<td>3.</td>
<td>No, no questions allowed</td>
</tr>
<tr>
<td>4.</td>
<td>Yes, may ask questions</td>
</tr>
<tr>
<td>5.</td>
<td>Yes, may ask questions</td>
</tr>
<tr>
<td>6.</td>
<td>Yes, may ask questions</td>
</tr>
<tr>
<td>7.</td>
<td>Etc.</td>
</tr>
</tbody>
</table>
Concealment of allocation vs blinding

1. Yes, may ask questions
2. No, no questions allowed
3. No, no questions allowed
4. Yes, may ask questions
5. Yes, may ask questions
6. Yes, may ask questions
7. Etc.
Concealing the allocation

Adequate

1. Remote randomization:
   • Phone call to a methods/randomization center.
   • Website system.
   • Pharmacy of the hospital.
2. Consecutively numbered, opaque and sealed envelopes or packages.

Not adequate

1. Random sequence **known in advance** (paper board)
2. Envelopes or packages **without the three safeguards**.
3. Non-random, predictable sequence (order of arrival, day of week, etc.)
<table>
<thead>
<tr>
<th></th>
<th>Allocation concealment</th>
<th>Blinding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Purpose</strong></td>
<td>Conceals / preserves randomization</td>
<td>Keeps participants &amp; trial personnel unaware of treatment received</td>
</tr>
<tr>
<td><strong>Bias prevented</strong></td>
<td>Allocation (selection)</td>
<td>Measurement and cointervention</td>
</tr>
<tr>
<td><strong>When in the trial</strong></td>
<td>When participants enter the trial (during recruitment)</td>
<td>After participants enter the trial (after recruitment)</td>
</tr>
<tr>
<td><strong>Feasibility</strong></td>
<td>Always possible</td>
<td>Not always possible</td>
</tr>
</tbody>
</table>
Video Laryngoscopy vs Direct Laryngoscopy on Successful First-Pass Orotracheal Intubation Among ICU Patients
A Randomized Clinical Trial

IMPORTANCE In the intensive care unit (ICU), orotracheal intubation can be associated with increased risk of complications because the patient may be acutely unstable, requiring prompt intervention, often by a practitioner with nonexpert skills. Video laryngoscopy may decrease this risk by improving glottis visualization.

OBJECTIVE To determine whether video laryngoscopy increases the frequency of successful first-pass orotracheal intubation compared with direct laryngoscopy in ICU patients.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial of 371 adults requiring intubation while being treated at 7 ICUs in France between May 2015 and January 2016; there was 28 days of follow-up.

INTERVENTIONS Intubation using a video laryngoscope (n = 186) or direct laryngoscopy (n = 185). All patients received general anesthesia.
3. Which of the following statements re allocation concealment is correct for Lascarrou’s trial?

A. Given the interventions (video vs direct laryngoscopy) it was impossible to conceal the allocation.
B. The use of stratified randomization ensured that the allocation was concealed.
C. The use of blocks during the randomization ensured that the allocation was concealed.
D. The software used to collect the entry data automatically allocated the patients.
Q & A
Did the randomization process produce groups similar with respect to known prognostic factors?

<table>
<thead>
<tr>
<th></th>
<th>Video Laryngoscopy (n = 186)</th>
<th>Direct Laryngoscopy (n = 185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>62.7 (15.3)</td>
<td>62.8 (16.3)</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>122 (65.6)</td>
<td>113 (61.1)</td>
</tr>
<tr>
<td>BMI, mean (SD)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>26.2 (6.7)</td>
<td>26.6 (7.2)</td>
</tr>
<tr>
<td>Simplified Acute Physiologic II, mean (SD)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>58.0 (21.0)</td>
<td>57.7 (21.8)</td>
</tr>
<tr>
<td>Activity level (Knaus chronic health status score), No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal health status</td>
<td>24 (12.9)</td>
<td>22 (11.9)</td>
</tr>
<tr>
<td>Moderate activity limitation</td>
<td>90 (48.3)</td>
<td>103 (55.7)</td>
</tr>
<tr>
<td>Severe activity limitation due to chronic disease</td>
<td>70 (37.6)</td>
<td>56 (30.3)</td>
</tr>
<tr>
<td>Bedridden</td>
<td>2 (1.1)</td>
<td>4 (2.2)</td>
</tr>
<tr>
<td>Charlson comorbidity index, mean (SD)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2.9 (2.1)</td>
<td>3.0 (2.1)</td>
</tr>
<tr>
<td>Diagnosis at admission to the intensive care unit, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute circulatory failure</td>
<td>32 (17.2)</td>
<td>22 (11.9)</td>
</tr>
<tr>
<td>Acute neurological failure</td>
<td>46 (24.7)</td>
<td>40 (21.6)</td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>73 (39.2)</td>
<td>86 (46.5)</td>
</tr>
<tr>
<td>Trauma</td>
<td>35 (18.8)</td>
<td>37 (20.0)</td>
</tr>
<tr>
<td>Other*</td>
<td>45 (24.2)</td>
<td>44 (23.8)</td>
</tr>
<tr>
<td>Reason for intubation, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological failure</td>
<td>71 (38.2)</td>
<td>76 (41.1)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>52 (28.0)</td>
<td>51 (27.6)</td>
</tr>
<tr>
<td>Circulatory failure</td>
<td>3 (1.6)</td>
<td>4 (2.2)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (7.0)</td>
<td>9 (4.9)</td>
</tr>
</tbody>
</table>
Take home messages II

- **Concealed allocation:** It is not possible to predict / control the assignment of participants entering the trial.

- **Methods:**
  - Remote randomization.
  - Consecutively numbered, opaque and sealed envelopes or packages.

- Unlike blinding, **it is always possible** to conceal the allocation.