Some Random(ized) Thoughts

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In this EBM Hub edition, we use the interesting, prospective, randomized, double-blinded study of Min et al from this current issue of Aesthetic Surgery Journal as a springboard to address a key methodological issue that is important in the proper execution and reporting of a randomized, controlled trial: the method of randomization. Randomization is among our most powerful protective mechanisms for removing bias from a study. A well-performed randomization makes it more likely that the study conclusions will be valid. Randomization works by reducing the chance that our pre-knowledge of certain factors will influence how the study is performed, specifically that our pre-knowledge of patient factors does not influence which patients get which treatments, or that we might perform the treatments differently based on such knowledge. Investigators, reviewers, and journal editors put a lot of emphasis on the method of randomization, and as a reader, so should you. Why? How much difference can it make? With trials, a small error at one point (eg, randomization) multiplies another error at another point, and so on, therefore, several small errors can lead to a totally wrong, backwards result. (Two other tools, blinding and allocation concealment, also prevent pre-knowledge from influencing how trials are performed and assessed. Click on the following link to learn more about how blinding and allocation concealment work alongside randomization: http://youtu.be/znBuDyMjhTM)

When performing a randomized trial, it is important that the authors describe how the randomization process was performed, and the more detail provided the better the reader is assured of the integrity of the process. If you are planning a study or just reading and assessing one, be sure to think about the how, when, and who of your randomization process.

- **How?** Although historically considered adequate, we now know that alternate chart numbers, sealed envelopes, or odd or even days or birthday days are not optimal randomization methods as these are not random events. The best approach is to use a remote-site 24-hours telephone system that randomizes patients using a computer-generated sequence. Acceptable alternate methods include a random number table found in statistics books or computer-generated random numbers. In the present article, it appears that the authors selected a computer-generated random number generation system. “After giving informed consent, patients were randomly allocated (Microsoft Windows, NET Framework 3.5®, Seattle, Washington) to one of the following groups before injection: Group I included 21 patients who received intramuscular injections with 2 units of toxin at each point and Group II included 21 patients who received intramuscular injections with 4 units of toxin at each point.”

- **When?** Ideally, randomization should take place just before the actual intervention (here a Botox injection), reducing the risk of some randomized patients subsequently being dropped from the study. All patients who are randomized should be accounted for and reported in
the published article, which Min et al do by describing the only patient who did not complete the study and why. (This patient dropped out of the study for an unrelated reason after receiving the allocated treatment but before the assessment was complete). However, the addition of a flowchart (Figure 1) that illustrates how many patients were randomized, how many received the allocated treatment, and how many were finally assessed is an ideal way for authors to communicate this information.

- **Who?** We also need to know who performed the randomization. To keep the process as “clean” as possible, randomization should ideally be left to an independent person not involved directly in care of the patient, and preferably a biostatistician. Biostatisticians are experts in understanding the randomization process and the pitfalls of inadequate randomization. Investigators are urged to consult a biostatistician at the inception of the study and definitely not at the conclusion of the study, for even a biostatistician cannot rescue flawed methodology (unless you bribe him with a lot of dollars which would guarantee his early retirement!).

When assessing any article, it is important to keep an eye out for hints that an issue may have occurred in the randomization process. For example, if each individual patient appropriately has an independent 50:50 chance of being randomized into either treatment arm, it is statistically unlikely that an exactly equal number of patients will be.

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**Figure 1.** An example of a potential flowchart (that might have been included in this RCT). Question marks indicate where additional data points could have been included in the text of the article; for example, how many screened individuals were excluded because they did not meet specific inclusion criteria, how many declined to participate and why, how many received the treatment in each group, and how many were lost to follow up in each group. Such a flowchart helps the reader understand how the study was executed and in particular, who exactly was randomized.
randomized to each treatment group, a situation that occurred commonly in the past when alternating envelope systems of randomization were used. Although it is certainly possible that computer-generated random number generation can lead to equal numbers in each treatment arm, especially in a smaller study like this one, on average it is statistically more likely that an asymmetric assignment into the treatment groups will occur; for example, 23 patients in the 2 unit dose arm and 19 patients in the 4 unit dose arm, or vice-versa. (Note: In this instance the authors provide us reassurance by stating “every patient got a 50% probability to be allocated to either treatment group.” However, think about a different scenario: If you were reading a larger study with 500 patients who were independently randomized and you saw exactly 250 in each treatment arm, wouldn’t you be a bit suspicious?)

For investigators, being clear and detailed about how randomization was performed can provide the reader significant reassurance as to the “tightness” of the RCT. This additional information can potentially be relayed in a single sentence, for example: “Randomization was completed by a biostatistician using a call-in computer randomization service [Acme Randomization, Inc., Anytown USA] with an independent 50% chance of allocation into either treatment arm after study informed consent was obtained and immediately prior to treatment.” The inclusion of a randomization-allocation-completion flowchart pulls all of this information together.

So the next time you are reading an article detailing a randomized trial, pay attention to the how, when, and who of randomization so that you can figure out for yourself what was done well and what might have been improved or communicated better (Table 1). Thinking about randomization will help you determine for yourself whether the conclusions are valid or, on the other hand, might be inaccurate due to suboptimal randomization.

Disclosures
The authors have no conflict of interests to disclose related to the content of this article.

REFERENCES