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Designing Inclusion and Exclusion Criteria

Designing Inclusion and Exclusion Criteria

Brianna Hornberger and Sneha Rangu

Summary

- Effective inclusion and exclusion criteria create the ideal pool of participants to get the most beneficial data for the study.
- An inclusion/exclusion list is a balance of broad yet specific criteria.
- The narrowness of inclusion/exclusion criteria has a direct impact on the study's recruitment and feasibility, while the broadness of criteria can affect the data's integrity.
- Including a general medical exclusion statement can prevent needing to go to the Institutional Review Board (IRB) for special requests and instead places the decision power in the hands of the research team.
- Referring to studies with similar goals in your literature review will help ensure your criteria are feasible to incorporate into your study's purpose and aims.
- Training research staff on criteria is crucial to certify high-quality data from each participant.

Introduction

There are several challenges when determining the inclusion and exclusion criteria for your study. This list of criteria sets the stage for the potential participant pool and plays a direct role in the feasibility of your study. Too narrow of a criterion can lead to a sample size that produces insignificant amounts of data, while too broad of a criterion can lead to data that is clouded by external factors. You can find the perfect balance of specificity through understanding the purpose of your criteria, reading key studies with similar goals to yours, and measuring the impact on study feasibility. It is important to consider potential problems that could arise and the reality of how many participants you will be able to screen. Remaining focused on the purpose of your study will allow you to create effective inclusion/exclusion criteria for collecting the most significant data.

What are Inclusion/Exclusion Criteria?

The inclusion/exclusion criteria set the stage for who can participate in your study. Your total list of criteria should amount to three to ten sentences describing the exact type of participant you are looking for. Once a study is approved, the criteria are held to a high standard. This means that if any participant screened meets all the criteria, they must be included in the study unless the research team requests an exclusion from the Institutional Review Board (IRB). Similarly, any major deviations to the exclusion criteria must be conveyed to the IRB.

The inclusion criteria will explain the different requirements someone must meet in order to participate in your study. Depending on your study's aims and procedures, this could include a participant's:

- Certain age group,
- Specific medical diagnosis, or
- Brand of phone.

It is your responsibility to determine which criteria are crucial for your participants to meet in order to help the study collect the most significant results. The exclusion criteria, on the other hand, should list features of a person that, if met, immediately deems that person ineligible to participate in the study. The exclusion criteria consist of qualities about a person or the external factors around them that would go against the goal of your study or interfere with it. This could include items from the list below:

- Current medication use,
- Participation in another study with similar study interventions or procedures at the same time, or
- Diagnosis of a condition that might interfere with the integrity of data collected.

One exclusion criterion that is very valuable to any study is a general medical exclusion statement. This prevents the study team from needing to go through the IRB to request a special case exclusion or modify the study protocol. An example of this type of exclusion criterion is the following statement, "Subjects who have active medical or psychiatric conditions which, in the opinion of the research/investigative team, would compromise (or interfere with) their ability to participate in the study." This broad statement is important because it:

- Places the power of decision for excluding a subject in the hands of the research team,
- Is more feasible than listing every diagnosable psychiatric or medical condition, and
- Covers any conditions you may not have explicitly stated in your criteria.

You want to have a safeguard so the researchers can decide if something is hindering a participant from providing correct data without needing to go through the IRB for approval. An

example of how this can benefit the research team is if a subject came into a screening meeting clearly smelling of recent alcohol consumption. If your exclusion criteria did not include drug or alcohol abuse, the IRB would require you to allow this subject to participate in the study unless you contacted them for an exclusion. If your exclusion criteria includes a broad statement about medical or psychiatric conditions, however, the members of the research team would have the power to decide whether or not the subject can participate. This eliminates the burden of contacting the IRB or modifying your protocol if you did not include a general term for drug or alcohol abuse in the exclusion criteria. Having a broad statement for such conditions allows you to cover a much bigger umbrella of people than having to list every single one and risk missing any key conditions.

Important Aspects of Inclusion/Exclusion Criteria

There are a few important aspects that you should be sure to consider when developing your inclusion/exclusion criteria. First, your criteria should be narrow, yet broad. Your criteria should be specific because the more narrow they are, the less heterogeneity there will be across all your participants. This requires you to be very specific in describing how to determine whether or not a participant meets a certain criterion. After reading through your criteria, there should be no gray areas on whether or not you can include a potential participant in your study. With that being said, your criteria have a direct influence on the recruitment and feasibility of the study. If your inclusion/exclusion criteria are too narrow, it will make it very difficult to identify subjects. Criteria that are too narrow or specific cause two problems:

- Not enough participants, and
- Not enough data.

The more participants, the higher chance of obtaining significant results. If your pool of participants is too small, you will have less data and therefore the results will be less significant when running statistical analyses such as t-tests. In each specific criterion, you must make sure it is very clear and specific for many reasons. One reason to be specific is to control external or other factors. Your criteria need to account for any possible interference with your study that could come from outside the participant's involvement. For example, if you have developed an application that only works for Android users and not Apple users, be sure to state as an inclusion criterion: "Participant must have an Android phone" instead of "Participant must have a cell phone." This would guarantee participants are able to use the application during your study.

Another reason to be specific in your criteria is for replication purposes. Research continually builds off of past research, and you should write your study protocol with that in mind. It is imperative to be as clear as possible in order to:

- Ease replication of the study for other researchers. Having other researchers replicate your study further validates your results and adds more significance to your findings.
- Increase the reliability of the results. The description of who can and cannot participate guides the composition of the patient pool. If unclear criteria allow the wrong subject to participate, the data can easily lose its reliability.

Lastly, it is also important to be clear so that every member of the research team understands the criteria required of each potential participant. This is to make sure that researchers are aware before and during the study in case at any point they notice something that could be of concern to violating any criteria. The research team must be aware of the criteria because they are the eyes and ears taking in the data and the participant experiences. This is especially important during the time of recruitment to ensure only participants who are qualified for the study comprise the subject pool.

Steps for Determining Effective Criteria

1. **Brainstorm as a team.** What criteria do you and your research team believe should be included? Look at your project goal statement and baseline measures. What are you starting at, and what do you hope to find? Do your criteria support your goal? Having more than one person develop the criteria is necessary, as everyone has a unique perspective.
2. **Carefully look through key studies from your literature review.** The inclusion/exclusion criteria from other studies similar to yours may be relevant to your study. They provide insight you may have overlooked or not thought of. Those studies, since they are most reflective of your study goal, are also great resources for the specificities required of your criteria. It is important to always compare any inspiration for criteria taken from other studies to your project goal to determine if anything needs to be altered to better fit your study in particular.
3. **Refer to valid sources for medical conditions to include/exclude.** This is important because in your criteria you must properly and specifically describe each medical condition you are referring to so there is no confusion. If there is confusion on whether a participant fits a certain criterion, one could potentially join the study and then halfway through the team or the participant could question their eligibility. It is important to avoid wasting the time of both the researchers and the participant, collecting inaccurate data, and potentially angering the participant. Valid sources are credible and accurate to current medical research. For example, mayoclinic.org and uptodate.org. Keep in mind that some sources, such as uptodate.org, may require a fee to access information.
4. **Consider the arms of your study.** If more than one group is being analyzed (for example, having a control group and an intervention group), consider the different criteria

that you need to include for both of them. You will have one list of inclusion/exclusion criteria total, so ensure that both group's needs are considered when making that list.

5. **Look at past protocols.** If you have access to protocols from other studies at your institution or through your literature review, look at examples of inclusion/exclusion criteria from studies that have already been completed. They can help assure you if you are heading in the right direction with your criteria and inform you of any other potential criteria that need to be considered.
6. **Justify the reasoning behind each criterion.** Once you have decided on your criteria, go back through each statement and justify the specific reason it has a place on your list of inclusion/exclusion criteria. The investigator must be able to provide the rationale behind each criterion in case one or more gets questioned during the approval process. This is not only important during the approval process, but for the duration of the study. The IRB can audit a study at any moment, and if they suspect you have enrolled a subject that you should have excluded, they can refer back to your list of criteria and question you. Having justification for the reasoning behind each of your criteria will quickly clarify any questions brought up during an audit from the IRB.

Assess Impact of Inclusion/Exclusion Criteria on Recruitment Feasibility

As stated above, the inclusion/exclusion criteria have a direct impact on the recruitment feasibility of your study. To calculate how feasible your recruitment is with the current criteria you have created, you might consider filling out an Attrition Table (Figure 1). This is a spreadsheet or table in which the prevalence of each criterion is listed to show the impact each one has. You fill it out by working backward (refer to Figure 1):

1. Start with the number of participants needed to complete the study (i.e., 10).
2. Divide by the prevalence of the first criterion (in this case, insomnia), working from the bottom of the table up (i.e., $10 \div .25$). In Figure 1, follow the bottom green arrow.
3. Then, write the quotient of that equation in the "Number of Subjects" column (i.e., 40). In Figure 1, follow the red arrow.
4. Continue dividing the number of subjects by each prevalence until there are no criteria left. This will then leave you with the number of subjects you must screen in order to find the number of participants required for your study (i.e., 320).

At this point, you can use the number of subjects needed to screen to evaluate the amount of time you will need to screen participants. In the example shown in Figure 1, because of all the different inclusion/exclusion criteria, this sample study must screen 320 subjects. If needed, removing the inclusion criterion of the female gender reduces the number from 320 to 160. If it takes ten minutes to screen a record, this change of inclusion criterion would save the researchers over 25

hours of work. The important trade-off is the quality of your study since having rigorous inclusion/exclusion criteria can enhance study rigor and reproducibility. In Practical Guides/Worksheets, there is an excel document that you can use to begin your Attrition Table. Another approach is to start with several inclusion/exclusion criteria, then remove exclusion or inclusion criteria if recruitment becomes difficult (this will require an IRB modification).

Figure 1. Attrition Table.

Criteria	Prevalence	Number of Subjects
Number needed to screen		320
Female	.5	320
Age >55 years	.5	160
Willing to be in a research study	.5	80
Insomnia	.25	40
Number needed for study		10

Examples of Criterion Topics

The goal of your study will direct the specifics of your criteria, but here are some examples of topics to consider when creating your list of criteria. There are many more topics to consider depending on the focus of your study, but this can provide you some insight into what kind of topics are covered in the criteria.

Symptoms/diagnosis

If you are studying a population with a certain diagnosis, you may have an inclusion criterion that the participant must have that medical condition diagnosed by a healthcare provider. In another case, you might be evaluating certain symptoms of a diagnosis and you could have an inclusion criterion stating that the participant must have been dealing with those symptoms for a specific amount of time. An example of this would be for a study involving insomnia patients, you might say participants must show symptoms of insomnia (name specific symptoms like difficulty falling and staying asleep, tiredness during the day, etc.) for at least four weeks prior to the date of contact.

Technology requirements

If your study includes an application that requires the participant to have a certain type of technology, you must put that as an inclusion criterion. For example, if you are having patients use an application that is only available on Apple and Android phones, you must state that participants must be Apple or Android users. If you are having patients do anything that requires internet access by phone, tablet, or computer, you want to include that as a criterion as well. You might need to consider the time and place that the participant will access these devices, and if that has any impact on your participant requirements.

Medication

If the participants in your study are taking medications, you might include that their health must be stable for a certain number of weeks. Consider if you need to exclude participants that are taking any medications that may interfere with study procedures. This will heavily depend on the nature and focus of your study. If the population you are studying is likely to be taking a medication (related or unrelated to the condition being studied), ensure you include how long they must be stable on it to lessen the effect of external factors on your study.

Education/Language Requirements

Consider the level of education needed to participate in your study, especially if it is a cognitive study. For example, you can state as an inclusion criterion that, “participants must have at least 7 years of education.” Another consideration is if there are any language requirements for participants. This will mostly rely on the available surveys or measures being used with the participants as well as the abilities of the research team. If you are only able to collect data with surveys in English, you must include this in your inclusion criteria.

Demographics

When deciding on your inclusion/exclusion criteria, consider the demographic you are studying. Think about the age, ethnicity, population, etc. that you are researching. If you are looking into pediatric patients, what requirements must there be for parents who will help the child participate? An example might be that one parent must have a reading level of fourth grade.

Symptom contamination/comorbidities

If you are studying a certain condition or symptom, consider other conditions or symptoms that are often comorbid or causing them. You want to exclude conditions or similar symptoms that may interfere with the topic of your study. An example of this would be: if you are studying the effect of a relaxation therapy on women with insomnia, you may need to consider excluding women who are pregnant or likely to become pregnant. A pregnant woman or a new mother will have external factors that impact their sleep schedule that will skew your study data.

Enrollment in other research studies

Another exclusion criterion to be considered, especially if conducting a neurological, clinical, or behavioral study, is participation in other neurological, clinical, or behavioral studies. This is important to include to avoid the impact of other research studies on the results of your study.

Table 1. Sample Criterion Topics.

1. Not Recommended: “Subjects will be included in the study if they have insomnia.”
This example is too vague in terms of diagnosis. How will your research team guarantee the participants have insomnia?
2. Recommended: “Subjects will be included in the study if they have insomnia diagnosed by a physician and have had symptoms (trouble falling and/or staying asleep) for at least eight weeks.”
This example clarifies the requirements of diagnosis as well as the symptoms the subject must be experiencing. The specific symptom time frame ensures that the subject has been dealing with the condition and therefore their symptoms are more likely to be stable throughout the study.
3. Not Recommended: “Subjects will be excluded from the study if they are taking medications.”
This is a very broad exclusion criterion which will make recruitment very difficult. There are many different types of medication that subjects may be taking that will not interfere with your study whatsoever. For example, this criterion would exclude all people who are taking birth control, acne medication, antidepressants, blood thinners, etc. It will greatly decrease the feasibility of your study to include this criterion.
4. Recommended: “Subjects will be excluded from the study if they are currently on any medications in which the effects are not stable or, in the opinion of the research team, the treatment might interfere with the results of the study.”
This statement is more specific in excluding subjects who are not stable on their medication in order to limit external factors on the data. It also excludes subjects on medication that might interfere with the results of the study in case the subject is being treated for the condition that is being studied. This is to prevent skewed data results.

Training Staff on Inclusion/Exclusion Criteria

Once the inclusion/exclusion criteria for your study are established, it is imperative to train all members of the research staff on what each of them are and why they are important. This, again,

is to ensure there is no confusion and each statement is clear to all members involved in the study. This is important to maintain the integrity of the data collected. Researchers must be fully informed and familiar with the criteria so they are able to adhere to them when screening and speaking with potential subjects. If researchers are not adhering to the criteria when recruiting participants, it could skew the results. If ineligible participants are included in the selected participant pool, they will add inaccurate data to the study results and it can lead to false conclusions.

The following list contains steps you can take to guarantee your research staff is well versed with the inclusion/exclusion criteria.

1. **Quiz Staff Members on Key Criteria.** You can start by defining each criterion and then quizzing staff on each of the meanings. You may also consider providing scenarios of potential patients who are on the edge of eligibility or ineligibility so you can talk through the thought process as a team.
2. **Require Staff to Have a Copy of Criteria When Screening.** It is important for staff to have a copy of the list of criteria so they can efficiently screen patients. This will prevent ineligible patients from getting through to the next stage of screening.
3. **Include Inclusion/Exclusion Criteria on Screening Script.** This will help your staff as they speak with potential subjects by allowing them to refer back to the list at any point. This will also help staff explain to patients why they are ineligible for the study. In some cases, patients would like to know exactly why they cannot participate in a research study, and referring to the inclusion/exclusion list can increase transparency with patients.
4. **Direct Questions to the Private Investigator.** If any questions arise among your staff regarding a subject's eligibility based on the inclusion/exclusion criteria, inform them to direct their questions to the study's Principal Investigator (PI).

Potential Updates to Inclusion/Exclusion Criteria

As the study progresses in time, participants, and complexity, you may need to update the original inclusion/exclusion criteria. Specific edge cases may arise or patterns may occur that bring different potential criteria to your attention. In order to update your criteria, you must prepare a modification to submit to the IRB. This will include adding items or taking out items in your inclusion/exclusion list that are currently approved by the IRB. With every IRB modification, you must provide evidence and reasoning to your protocol changes. For example, if you choose to add Spanish speaking patients to your study, you must provide an explanation and ensure that study procedures will allow for this (i.e. translating surveys). This may involve additional literature review and further investigation of medical conditions.

After submitting to the IRB and receiving approval, you must update study documents to reflect any changes to the inclusion/exclusion criteria. This may include the script, database and other study documents that are referenced by staff. Presenting your inclusion/exclusion criteria in an organized manner throughout all study documents will help to avoid confusion among both staff and patients.

Practical Guides/Worksheets

Supplement 1: Attrition Table, provided by Brianna Hornberger and meant to function for your specific study.

<https://docs.google.com/spreadsheets/d/1afJ94FAFIYUVDHFczLYh2DzkGOVYTw5QPedWrYvAs84/edit?usp=sharing>

Conclusion

Effective inclusion/exclusion criteria streamline the recruitment process and determine the subjects who will provide your study's data. It is a very important step in the development of your protocol and you should develop it with careful attention to the goals of your study and the type of data you hope to find. As you brainstorm with your team, there are a plethora of sources to help you create the ideal inclusion/exclusion list. Look through key studies/past protocols and assess the feasibility of recruitment in regards to your study's aims. You can achieve finding the perfect balance of narrow and broad criteria and use it to train the research staff in recruiting the best fit participants for your specific study. When inclusion/exclusion criteria are thoroughly explained and carefully selected, they play a major role in the reliability and replicability of recruitment and data.

Resources

A Google Sheet checklist to assist with preparing your research proposal is available and includes a section with specific checklist items related to this chapter:

https://docs.google.com/spreadsheets/d/1Z5-AvaQwQPaWz6OTEPmK0_QF6PAvhHICwwyjmlbdvzI/edit#gid=0 (a copy is also available at the end of this book). We encourage you to copy this master Google Sheet checklist to your Google Drive and edit it.

1. "Inclusion and Exclusion Criteria in Research Studies: Definitions and Why They Matter"
 - This resource provides further explanation for what inclusion/exclusion criteria should be.
 - <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6044655/>

2. “Methodology for Research I”
 - This resource explains the importance of remaining objective and replicative and how it can benefit your study.
 - <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5037944/>
3. “Protocol Design - Inclusion and Exclusion Criteria”
 - This source explains in greater detail the importance of being able to justify each criterion.
 - <https://assessment-module.yale.edu/human-subjects-protection/protocol-design-inclusion-and-exclusion-criteria>
4. “Inclusion and Exclusion Criteria”
 - This source has many different examples of good inclusion/exclusion criteria.
 - <http://biostat.mc.vanderbilt.edu/TPT/SOURCE/Checklist/StudyPop/Inclusion%20and%20Exclusion.html>
5. Mayo Clinic
 - This source has valid medical information for clarifying criteria.
 - <https://www.mayoclinic.org/>
6. Up-To-Date
 - This source has current, clinical information that you can use to narrow down or clarify criteria.
 - <https://www.uptodate.com/home>

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