# The Research Question Part III: Hypotheses

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Welcome this video is entitled The Research Question Part III: Hypotheses. I will remind you to please refrain from distributing or copying this video lecture.

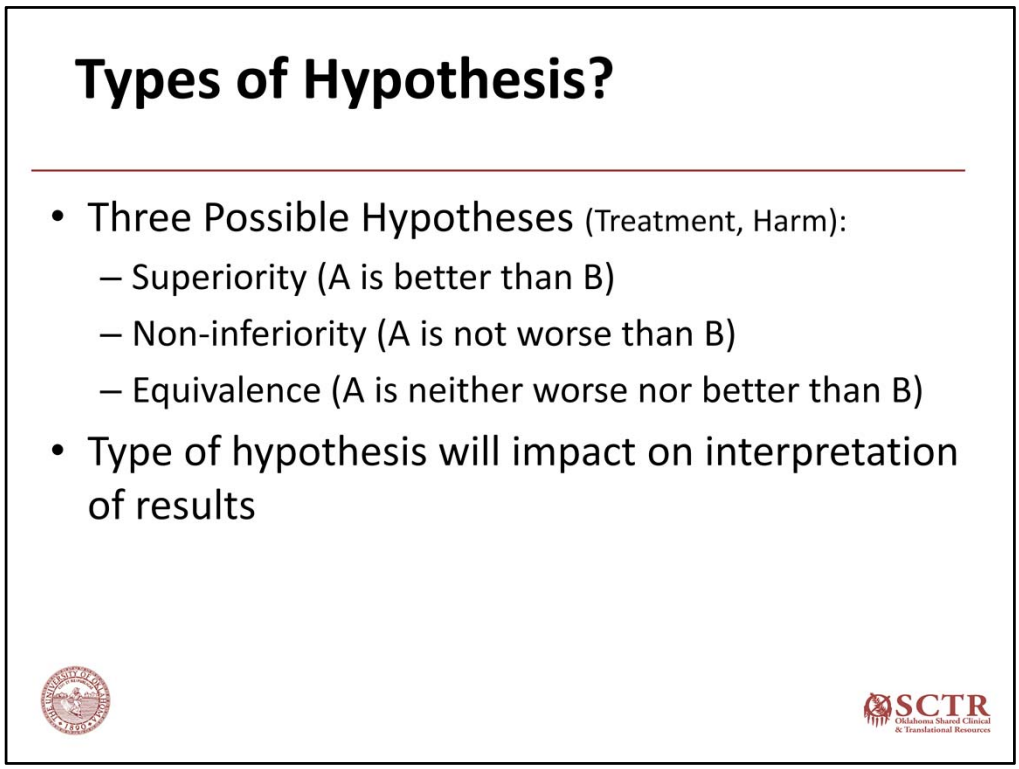
# Outline

- Types of Hypotheses
  - Superiority
  - Non-inferiority
  - Equivalence
- Ethics of Non-inferiority
- Importance of stating the hypothesis *a priori*

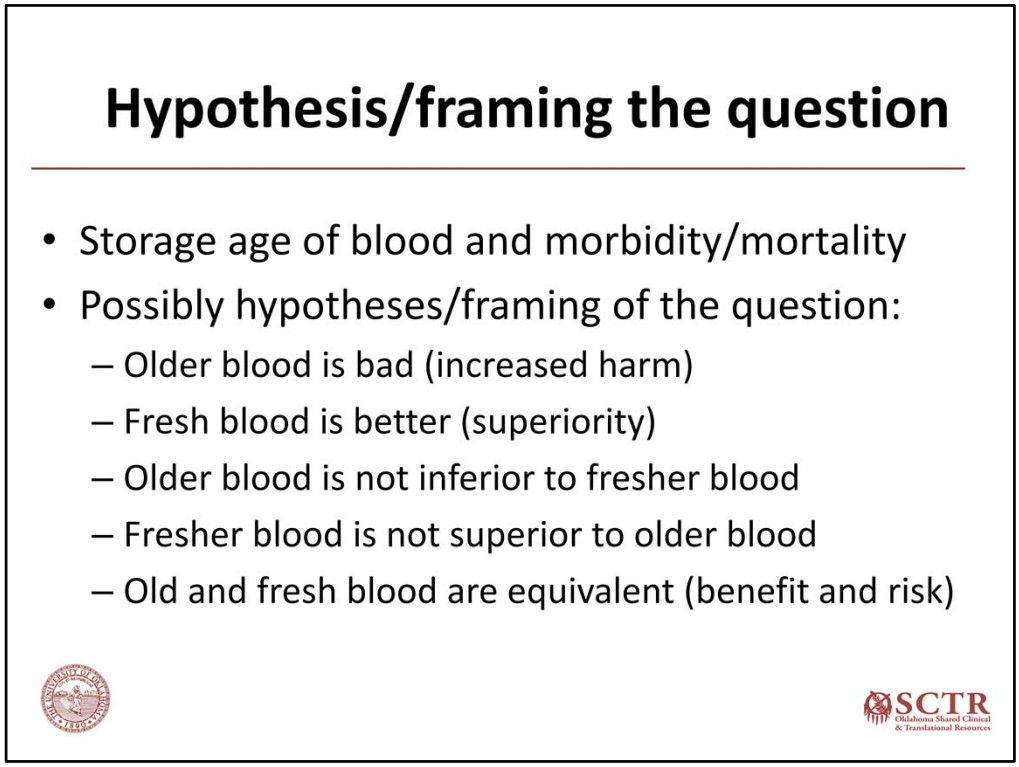
In this part of the module will cover different types of hypotheses including superiority, noninferiority, and equivalence hypotheses. Discuss the ethics noninferiority questions as well as to discuss the importance of stating your hypothesis a priori.

# Hypothesis

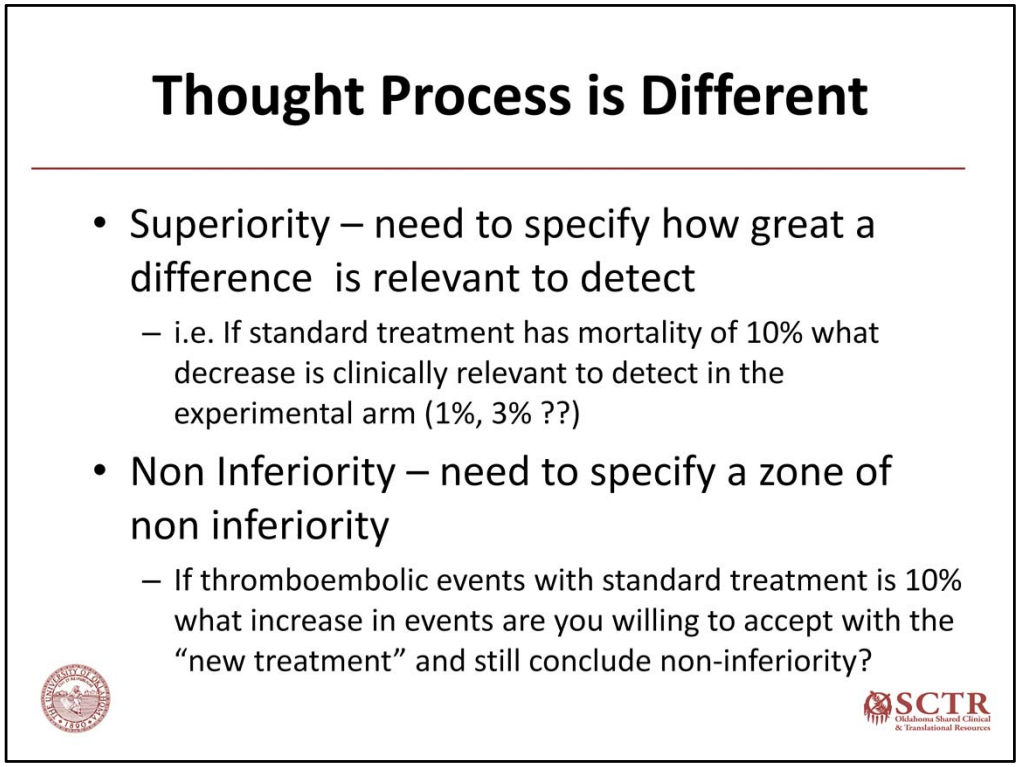

The research hypothesis



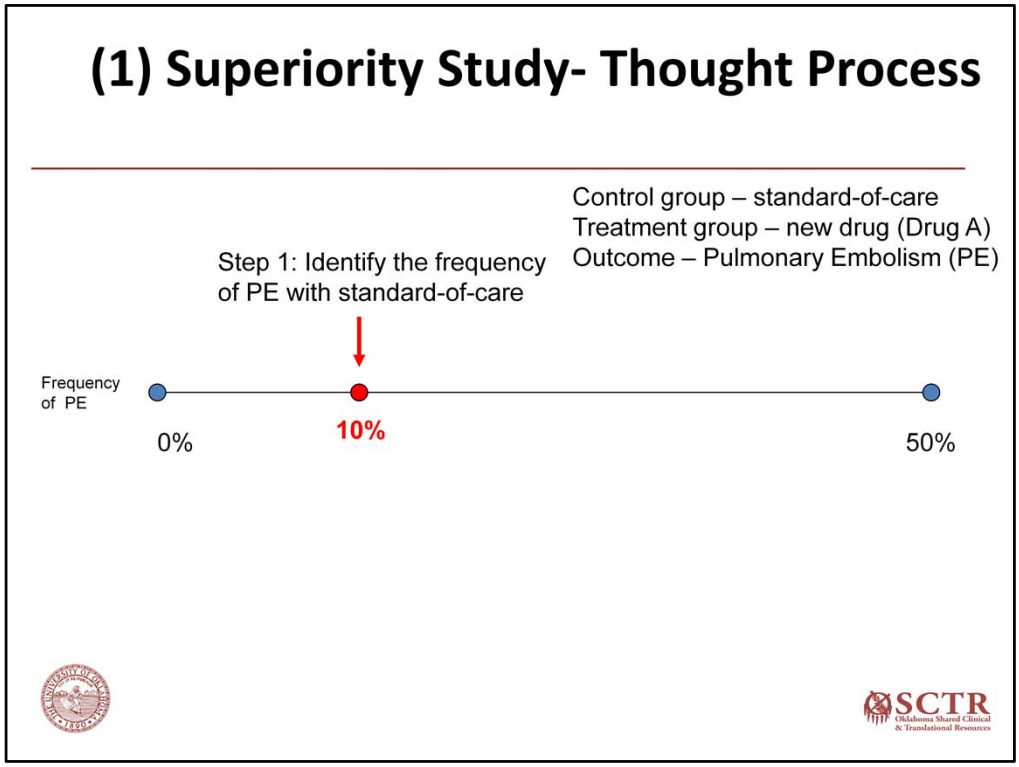

What are the different types of hypotheses? There are three possible types of hypothesis in a clinical trial setting related to human research about treatment or harm. You may conduct a superiority trial where you are trying to determine if one treatment is better than another. You may conduct a noninferiority trial be trying to determine if one treatment is not worse than another treatment. The last type type is an equivalence hypothesis. With this hypothesis you want to determine if one treatment is neither worse nor better than another treatment. The type of hypothesis you choose will impact the interpretation of your result.



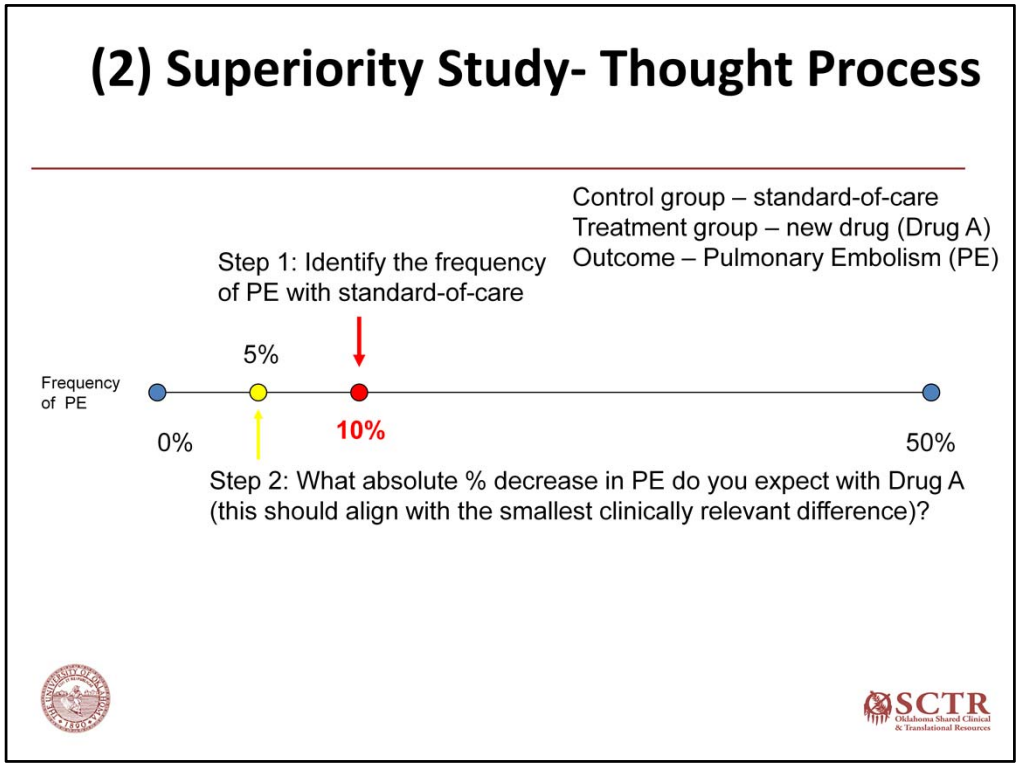

Sometimes the hypothesis or framing of the question may not be so clear. What if we are interested in the storage age of blood and morbidity and mortality. There are several different ways we could frame the question. For example is older blood bad, will it increase harm? Or conversely we could ask is fresh blood better? These are both different ways to state a hypothesis of superiority. We may instead want to know if older blood is non-inferior to fresh blood or conversely we could say fresher blood is not superior to older blood. These are both examples of noninferiority questions. Or we could want to know if the morbidity and mortality outcomes are similar for patients who receive old and fresh blood. This is an example of an equivalence hypothesis.



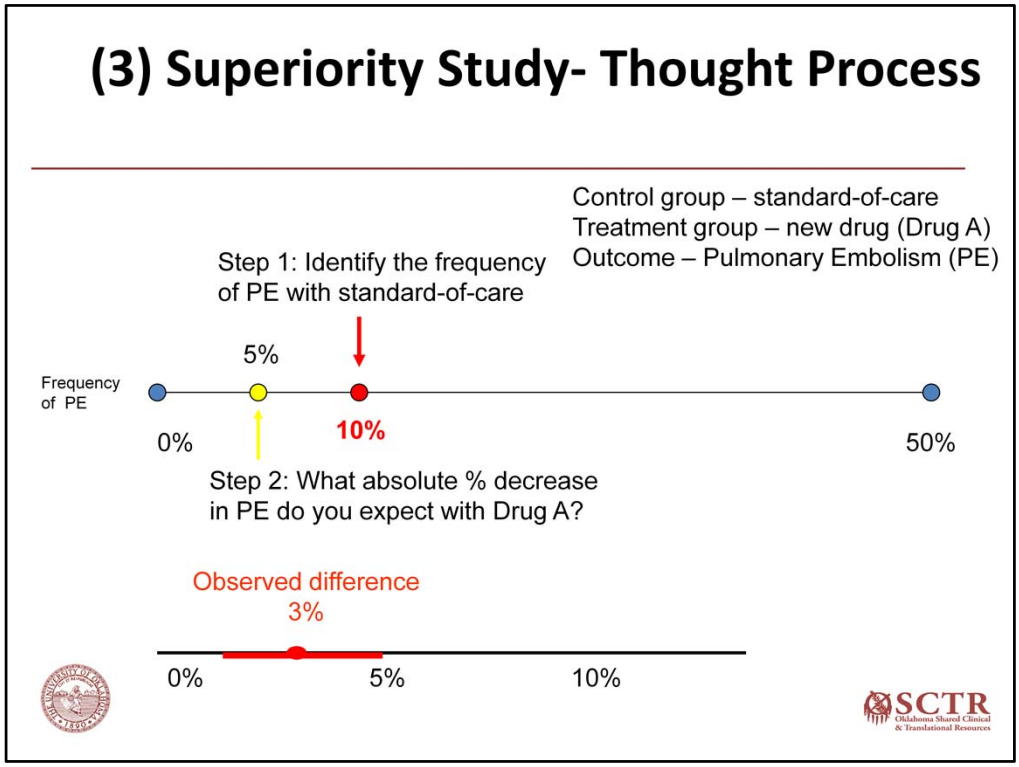

The thought process is difference for these different types of hypotheses. For superiority trial you need to specify how great a difference is relevant to detect. For example if a standard treatment has a mortality of 10%, what decrease is clinically relevant to detect in the experimental arm? 1%, 3%, or 10%? In contrast in a noninferiority trial you need to specify a zone of noninferiority. For example if thromboembolic events with standard treatment occur in 10% of the patients, what increase in events are you willing to accept with the new treatment and still conclude noninferiority? For example if the new treatment is 2% worse or 3% worse would you consider it to be a noninferior treatment?



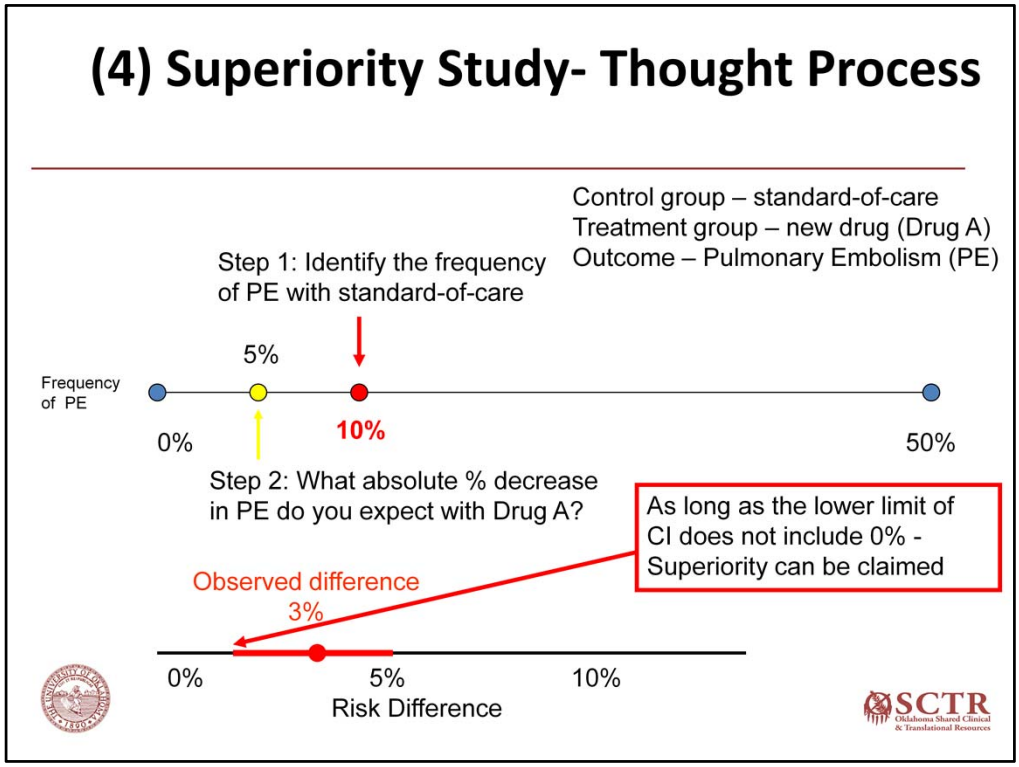

Here is a diagram of the superiority study thought process. Let's say the control group is the standard of care, the treatment group is a new drug , drug A, and the outcome of interest is pulmonary embolism. In step one we will identify the frequency of PE with standard of care. In this example, 10%.



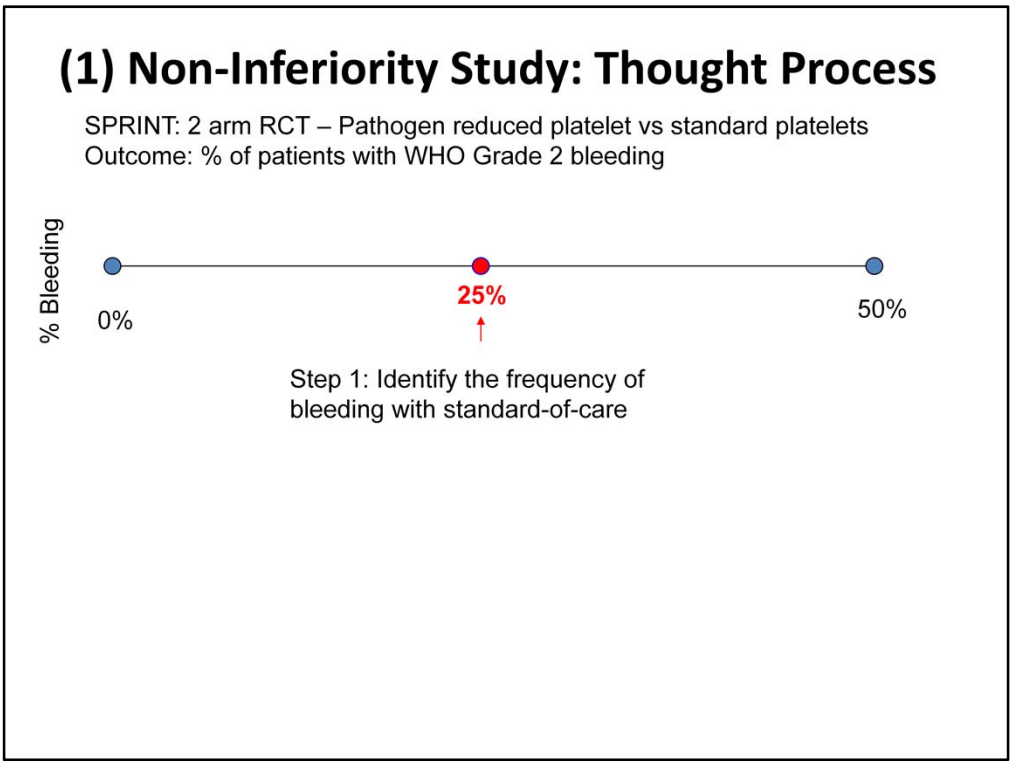

Next, we will identify what absolute percent decrease in pulmonary embolism do you expect with Drug A. Note this should align with smallest clinically relevant difference. When planning a study you want to be able to identify the smallest difference that is deemed clinically relevant. This will be discussed further in other TPIR modules. Here the difference between 10% and 5% is 5%.



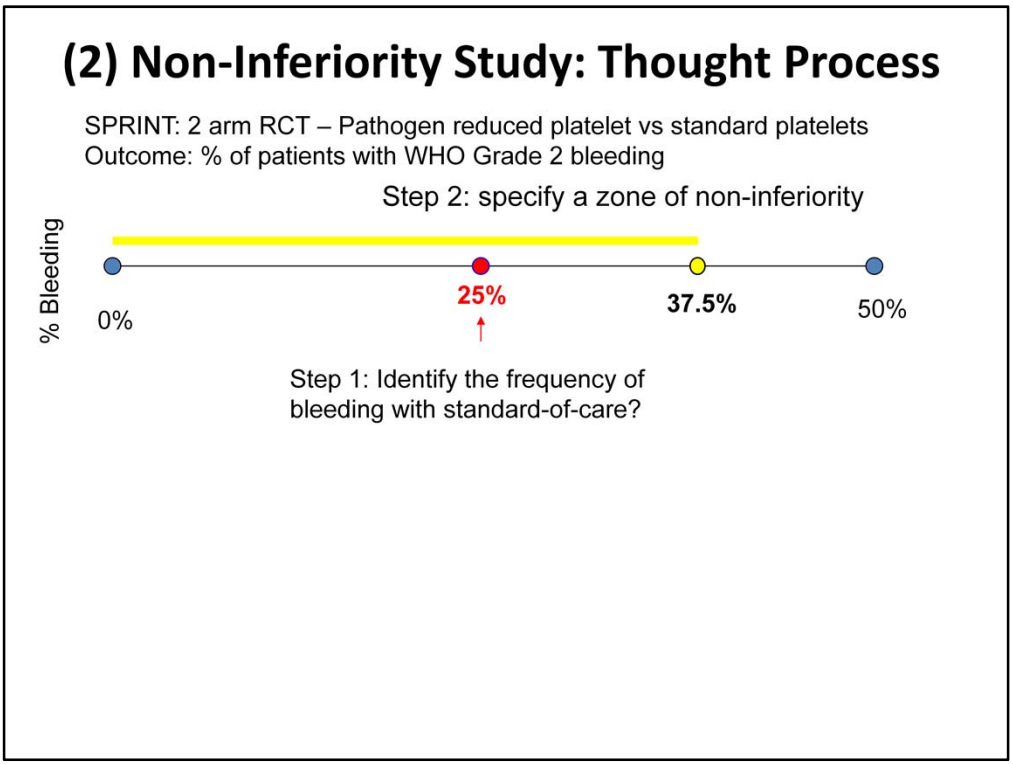

Then we will conduct a clinical trial and calculate the observed difference and the 95% confidence around the observed difference. Here the observed differences was 3% the 95% confidence interval ranged from approximately 2% to 5%.



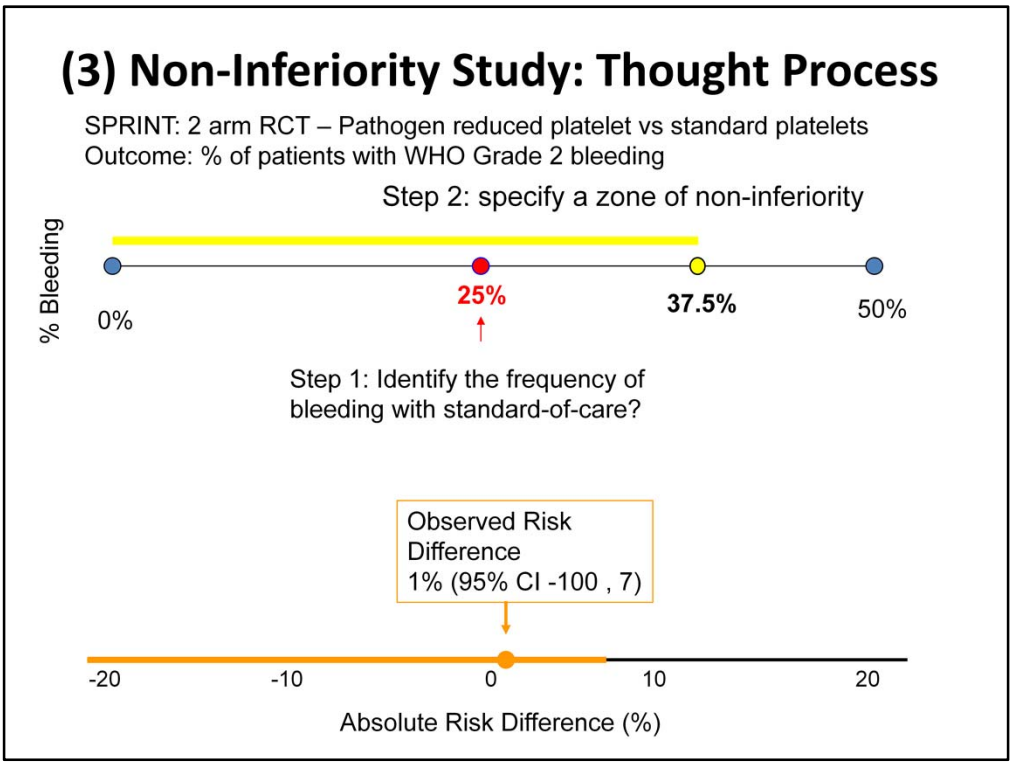

If the percentage who had a pulmonary embolism were the same in the standard of care group and in the intervention group the difference would be zero. So as long as the lower limit the conference of confidence interval does not include zero, superiority can be claimed. So in this example the new drug is superior to the standard of care in terms of percentage of patients experiencing pulmonary embolism.



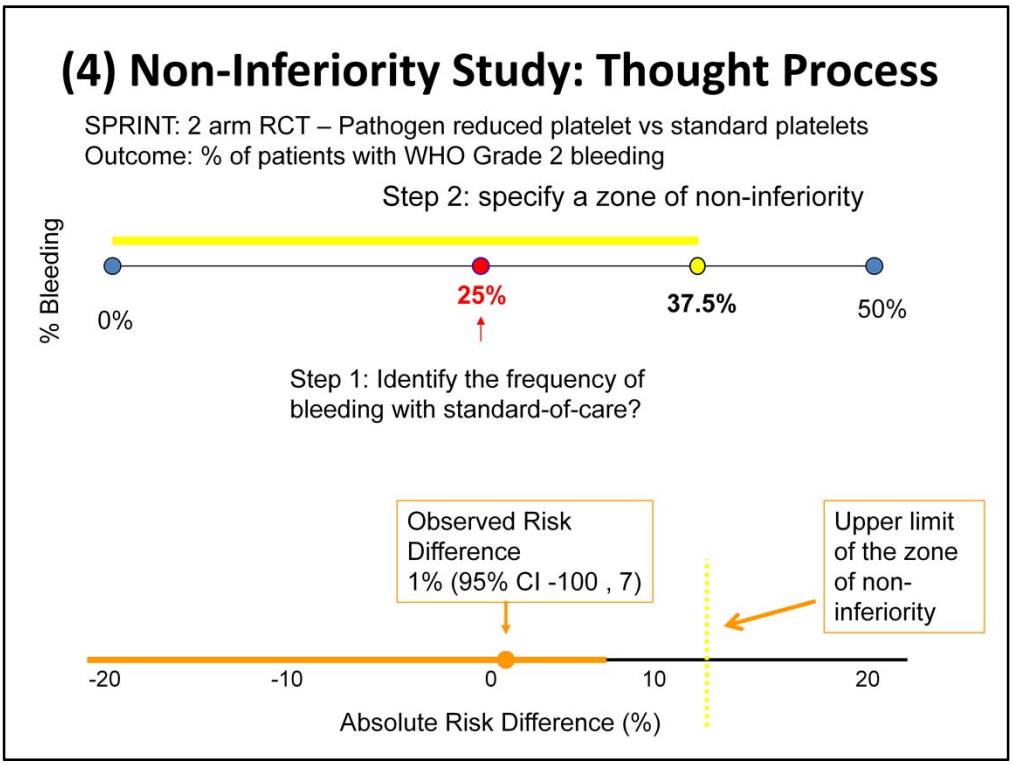

Here's a diagram of the thought process when conducting a noninferiority study. This is an example from the SPRINT trial; it was a randomized controlled trial. The treatment group received pathogen reduced platelets and the control received the standard platelets. The outcome was the percentage of patients who have WHO grade 2 bleeding. The first step is to identify the frequency of bleeding among patients who receive standard platelets, this is the standard care of care group.




Next we need to specify the zone of non-inferiority. This is the largest difference in grade 2 bleeding you could observe and still deem that pathogen reduced platelets are not inferior to standard platelet. Here we are most interested in the right hand side of the zone. We deemed if grade 2 bleeding is 37.5% in the pathogen reduced platelet arm then pathogen reduced platelets are non-inferior to standard platelets. We can then subtract 25% (bleeding in standard care group) from 37.5% (bleeding in treatment group). This is 12.5% so if the percentage who bleed in the treatment group is not more than 12.5% greater than the percentage who bleed in the control group, we will deem the treatment group to be non-inferior to the control group.




The observed risk difference was 1% and the upper limit of the confidence limit was 7%.




To determine if this meets our noninferiority criteria, we need to evaluate if the upper limit exceeds the zone of noninferiority – which in this case is 12.5% - it does not so we can conclude that pathogen reduced platelets are non-inferior to standard platelets in regard to WHO grade 2 bleeding.

# Importance of an *a priori* Hypothesis

- Why is it necessary to consider the hypothesis *a priori*?
  - Affects sample size
  - Analysis based on rejection of null hypothesis
    - Different for each type
  - Impact on interpretation of results

Why is it important to determine a priori what your hypothesis? Isn't it okay just to wait until your research is completed? The type of hypothesis in your study will determine the sample size calculation. Also the null hypothesis varies for the different hypothesis types and analysis of the data is related to the null hypothesis. Your hypothesis will also impact the interpretation of your results. Therefore you need to determine this upfront.

## Sample Size & Hypothesis Type

| Design | Sample Size | |
|---|---|---|
| | Per group | Total |
| Superiority* | 98 | 196 |
| Non-Inferiority** | 268 | 536 |
| Equivalence** | >400 | >800 |

*Designed to detect a 15% difference
**15% difference to define the zone of non-inferiority or zone of equivalence

Here is an example of study size by hypothesis type. Here we are assuming a superiority study to detect a difference of 15% and the zone of non-inferiority or zone of equivalence have also been set at 15%. The sample size per group is smallest for the superiority trial and largest for the equivalence trial the noninferiority trial is in the middle. The important message here is that the sample sizes are all different. If you plan your sample size based on superiority which is the most common and the hypothesis most sample size programs by default calculate, but you analyze your data with a non-inferiority or equivalence hypothesis, you will not have an adequate number of participants and your study will be underpowered. This concludes part III of the research question module.

I would like to acknowledge and thank Professor of Medicine, Nancy Heddle, from McMaster University in Hamilton Canada for sharing her slides with me and allowing me to modify them to fit the needs of this portion of the presentation.
Thanks to:
Nancy Heddle MSc.,FCSMLS(D), Professor
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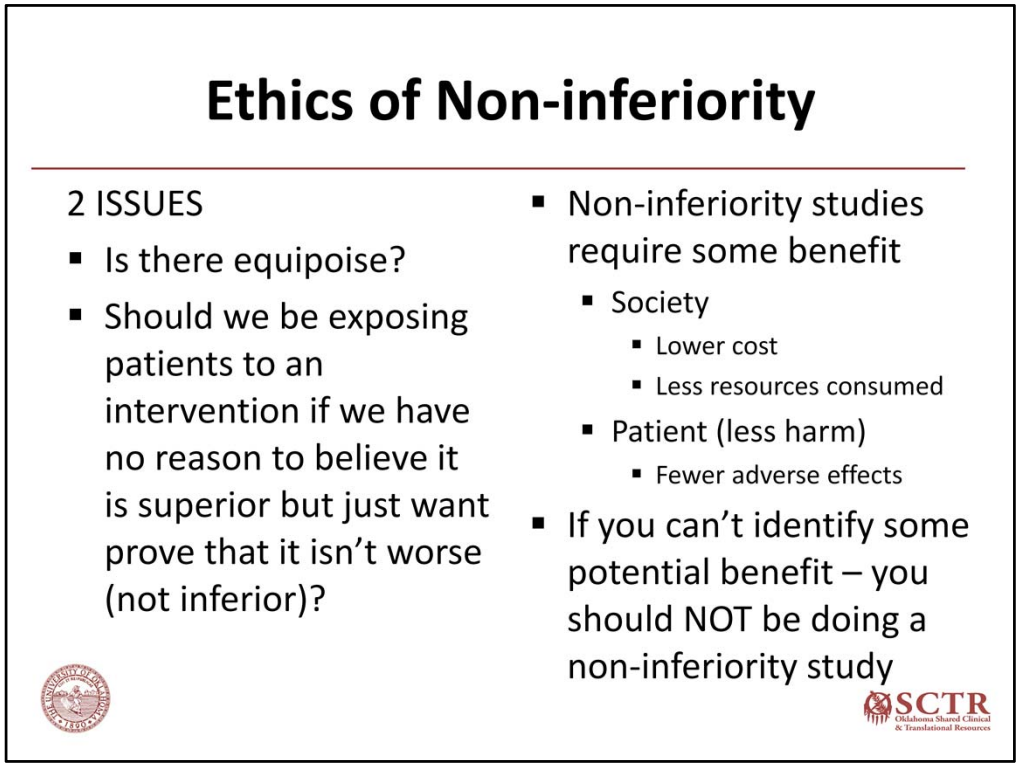


What about the ethics of conducting a noninferiority trial? There are two major issues. One is, is there clinical equipoise? Should we be exposing patients to an intervention if we have no reason to believe it is superior to standard of care but just want to prove that it is not worse or non-inferior. For a noninferiority study to be ethical there needs to be some benefits to the new treatment. This may be a benefit to society such as a lower cost or less resources consumed. Or a benefit directly to the patient such as fewer adverse events, an easier treatment regimen, or better quality of life. If you cannot identify some potential benefit than you should not be conducting a noninferiority study. This concludes part three of the research question module.