Non-Inferiority Design

a randomized control trial should show that a new treatment/experimental therapy (T) is superior to the placebo or no treatment at all

placebo-controlled trials are not appropriate or ethical when effective treatments have already been identified

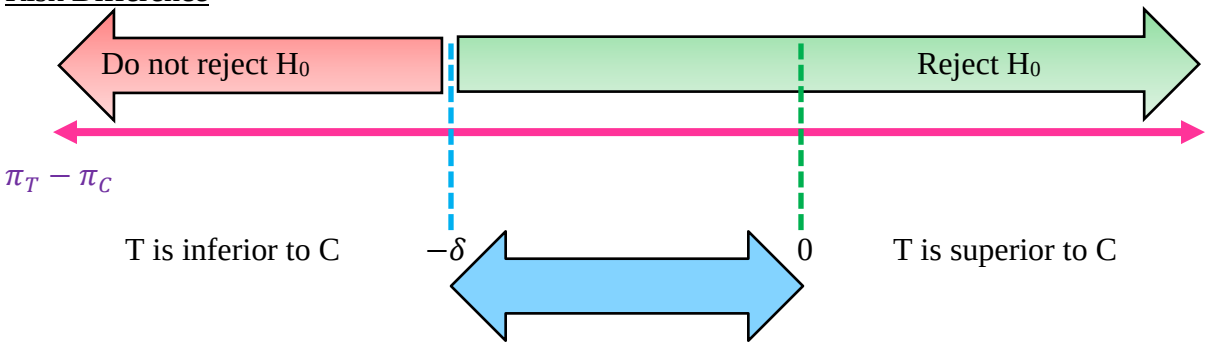
need to demonstrate that T is as good as and not inferior to active control C, the best available treatment, but it's impossible to prove treatment equality

non-inferiority margin (δ) = acceptable threshold that T can be inferior to C and still be considered as clinically important

use one-sided hypothesis test with $\alpha = 0.025$

Non-Inferiority Design for Positive Outcomes

Risk Difference



T is neither superior nor inferior to C
T is within the acceptable margin

H_0: $\pi_T - \pi_C \leq -\delta$	$\pi_T + \delta \leq \pi_C$	T is inferior to C
H_A: $\pi_T - \pi_C > -\delta$	$\pi_T + \delta > \pi_C$	T is not inferior to C

if lower bound is greater than $-\delta$, do not reject H_0 and conclude inferiority

if lower bound is less than $-\delta$, reject H_0 and conclude non-inferiority

Relative Risk/Risk Ratio

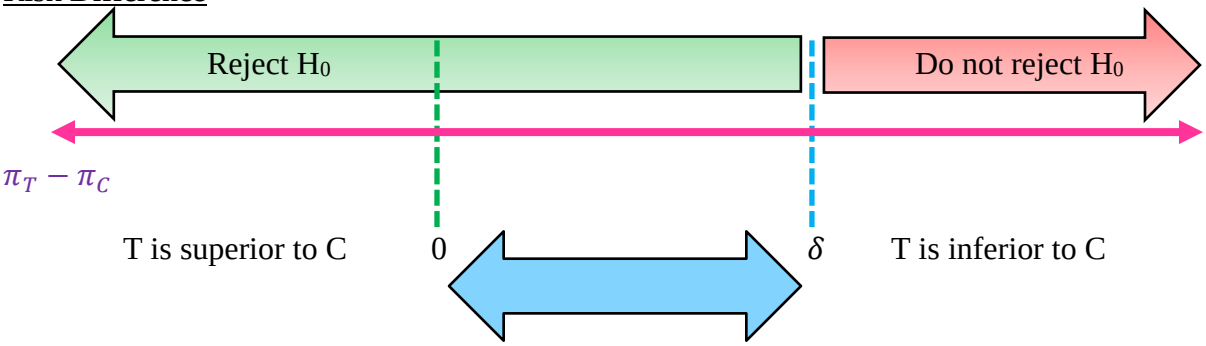
H_0: $\frac{\pi_T}{\pi_C} \leq \frac{\pi_T - \delta}{\pi_C}$	T is inferior to C
H_A: $\frac{\pi_T}{\pi_C} > \frac{\pi_T - \delta}{\pi_C}$	T is not inferior to C

if lower bound is greater than $\frac{\pi_T + \delta}{\pi_C}$, do not reject H_0 and conclude inferiority

if lower bound is less than $\frac{\pi_T + \delta}{\pi_C}$, reject H_0 and conclude non-inferiority

Non-Inferiority Design for Negative Outcomes

Risk Difference



T is neither superior nor inferior to C
T is within the acceptable margin

H0: $\pi_T - \pi_C \geq \delta$	$\pi_C - \pi_T \leq -\delta$	T is inferior to C
HA: $\pi_T - \pi_C < \delta$	$\pi_C - \pi_T > -\delta$	T is not inferior to C

if upper bound is greater than δ, do not reject H0 and conclude inferiority
if upper bound is less than δ, reject H0 and conclude non-inferiority

Relative Risk/Risk Ratio

H0: $\frac{\pi_T}{\pi_C} \geq \frac{\pi_T+\delta}{\pi_C}$ T is inferior to C

HA: $\frac{\pi_T}{\pi_C} < \frac{\pi_T+\delta}{\pi_C}$ T is not inferior to C

if upper bound is greater than $\frac{\pi_T+\delta}{\pi_C}$, do not reject H0 and conclude inferiority

if upper bound is less than $\frac{\pi_T+\delta}{\pi_C}$, reject H0 and conclude non-inferiority

for a negative outcome, it takes a larger sample to prove non-inferiority using RR than RD
for a positive outcome, it takes a larger sample to prove non-inferiority using RD than RR

Choosing Non-Inferiority Margin

Step 1: Define M1

effect of active control relative to placebo

e.g. value of $\pi_P - \pi_C$

the smallest, most conservative estimate of benefit of C against P

$M1 > 0$, otherwise there is no evidence that C is superior to P

Step 2: Define M2

non-inferiority margin $\delta \leq \frac{M1}{2}$

the largest clinically acceptable difference/degree of inferiority of the test treatment compared to the active control