

TRIAL CRABS

Diving into Methodological Waters: Do You Have Methodological Crabs?







CRAB ONE

CONTROL GROUP







CRAB ONE

CONTROL GROUP

BASELINE COMPARISON

By having a group that does not receive the intervention, researchers can assess the true effect of the intervention by comparing outcomes between the two groups







CRAB ONE

CONTROL GROUP

ATTRIBUTION

Without a control group, it would be challenging to attribute observed outcomes solely to the intervention, as other factors could influence the results







CRAB ONE

CONTROL GROUP

NO TREATMENT

Participants in the no-treatment control group do not receive any form of treatment or intervention

PLACEBO

Participants receive a placebo; a substance with no therapeutic effect.

ACTIVE

Participants receive a treatment that is known to have an effect, but it is different from the experimental intervention

WAITLIST

Participants in the waitlist control group do not receive the intervention immediately but are placed on a waiting list to receive it at a later stage







CRAB ONE

CONTROL GROUP

NO TREATMENT CONTROL

Provides a baseline for understanding the natural progression of the condition, helping to attribute observed changes to the intervention







CRAB ONE

CONTROL GROUP

PLACEBO CONTROL

Allows researchers to isolate the specific effects of the active intervention by controlling for the placebo effect

Helps maintain blinding, ensuring that participants and researchers are unaware of who is receiving the active treatment







CRAB ONE

CONTROL GROUP

ACTIVE CONTROL

Allows researchers to assess whether the new intervention is more effective, equally effective, or less effective than the standard treatment

Provides a benchmark against which the experimental treatment can be evaluated







CRAB ONE

CONTROL GROUP

SAMPLE SIZE IMPLICATIONS

The effect size is the magnitude of the difference between the control and experimental groups. The larger the expected effect size, the smaller the required sample size to detect that difference with a given level of confidence









CRAB TWO

RANDOMISATION









CRAB TWO

RANDOMISATION

REDUCE SELECTION BIAS

Every participant has a known probability of receiving either treatment, and the allocation of treatments occurs randomly









CRAB TWO

RANDOMISATION

COMPARABLE GROUPS

The treatment and control groups are likely to be comparable at baseline with respect to both known and unknown variables









CRAB TWO

RANDOMISATION

STATISTICAL ASSUMPTIONS

Many statistical tests and analyses assume that the data is randomly generated









CRAB TWO

RANDOMISATION

ETHICAL CONSIDERATIONS

It ensures fairness and equal opportunities for all participants to receive either the experimental treatment or the standard care or placebo, avoiding any preferential treatment









CRAB TWO

RANDOMISATION

1. RANDOM SEQUENCE GENERATION

Ensures an unpredictable and unbiased assignment of participants to treatment groups

A variety of methods can be used, such as computer-generated random numbers, randomisation tables, or statistical software, to generate a random sequence









CRAB TWO

RANDOMISATION

SIMPLE

The allocation is typically determined by chance through random processes, such as random number generation or a coin toss

BLOCKED

Involves grouping participants into blocks of a fixed size, within each block, randomization is carried out and the blocks are filled one at a time

STRATIFIED

The study population is divided into strata based on specific characteristics, and then randomisation is independently performed within each stratum

STRATIFIED BLOCK

The study population is divided into strata based on specific characteristics, and within each strata randomisation is performed in blocks









CRAB TWO

RANDOMISATION

SIMPLE	BLOCKED	STRATIFIED	STRATIFIED BLOCK
Easy to implement	Balances allocation at specific intervals (block sizes)	Controls confounding	Benefits of both blocked and stratified randomisation
Equal chance of being assigned to any group	N<100, can be useful to ensure a more even distribution characteristics	Minimizes variability within strata	
N>100, balance achieved in baseline characteristics		Examination of Rx effects within specific subgroups	









CRAB TWO

RANDOMISATION

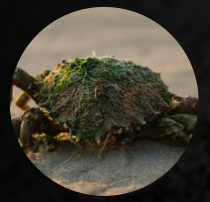
SIMPLE	BLOCKED	STRATIFIED	STRATIFIED BLOCK
Random imbalances	Predictability; if the block size is known, it could be exploited	Complexity	Introduces additional complexity
N<100, potential differences in baseline characteristics	Inflexible	Strict stratification may limit generalizability	May result in less ‘randomness’
		Excessive stratification can lead to overmatching	Potential for Overstratification











CRAB THREE

ALLOCATION

2. ALLOCATION CONCEALMENT

Prevents selection bias by ensuring that neither the investigator nor the participant can anticipate the assigned treatment

A variety of methods can be used, such as such as using sealed envelopes or centralised computer systems









CRAB TWO

RANDOMISATION

3. IMPLEMENTATION

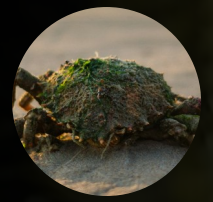
Ensures that the randomisation process is executed accurately and impartially

A variety of methods can be used, such as computer-generated random numbers, randomisation tables, or statistical software, to generate a random sequence









CRAB FOUR

BLINDING

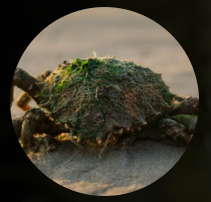
DEFINITION

In the context of a trial refers to the practice of concealing certain information about the treatment assignments from specific individuals involved in the study









CRAB FOUR

BLINDING

PREVENTING PARTICIPANT BIAS

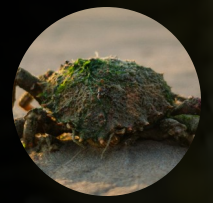
Placebo Effect: Where perceived improvements are not due to the actual treatment but to the psychological belief in its efficacy

Altered Behaviour: Participants might consciously or unconsciously change their behaviour, lifestyle, or adherence to the treatment based on their knowledge of the assigned intervention









CRAB FOUR

BLINDING

PREVENTING PARTICIPANT BIAS

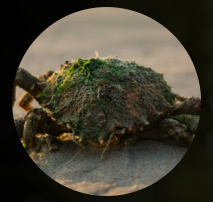
Reporting Bias: Participants who are aware of their treatment status may provide responses that align with their expectations (exaggerating positive outcomes or downplaying negative effects)

Differential Dropout Rates: Participants might be more likely to drop out of the study if they are dissatisfied with their assigned treatment









CRAB FOUR

BLINDING

PREVENTING RESEARCHER BIAS

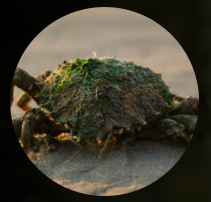
Treatment Administration Bias: researchers might unintentionally administer treatments differently based on their knowledge of the assigned interventions

Outcome Assessment Bias: Researchers may unconsciously interpret or record outcomes in a manner that aligns with their expectations









CRAB FOUR

BLINDING

PREVENTING RESEARCHER BIAS

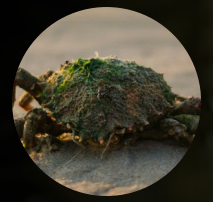
Data Collection Bias: Researchers might inadvertently collect data in a way that aligns with their preconceived notions or biases

Reporting Bias: Researchers may emphasize or downplay certain results based on their knowledge, leading to biased conclusions









CRAB FOUR

BLINDING

PREVENTING STATISTICAN BIAS

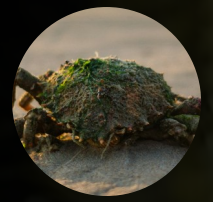
Data Interpretation Bias: Statisticians may interpret the data in a way that aligns with their expectations or assumptions

Analytical Choices Bias: Statisticians might make analytical choices that are influenced by their awareness of treatment groups, that favour certain outcomes









CRAB FOUR

BLINDING

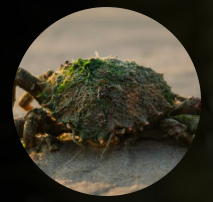
PREVENTING STATISTICAN BIAS

Confirmation Bias: Statisticians might subconsciously seek evidence that confirms their preconceived beliefs about the effectiveness or ineffectiveness of a particular treatment









CRAB FOUR

BLINDING

OPEN-LABEL (NON-BLINDED)

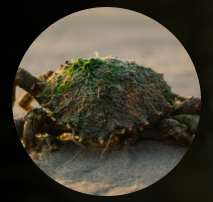
No blinding is implemented

Participants, researchers, and sometimes both are fully aware of the treatment assignments









CRAB FOUR

BLINDING

SINGLE BLIND

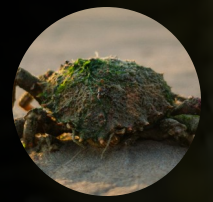
Participants are unaware of their assigned treatment

Researchers and evaluators know the treatment assignments









CRAB FOUR

BLINDING

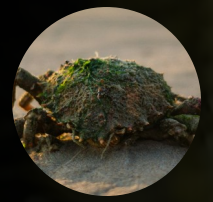
DOUBLE BLIND

Both participants and researchers/evaluators are unaware of treatment assignments









CRAB FOUR

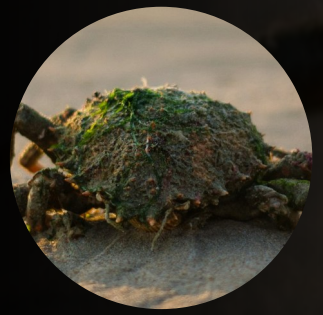
BLINDING

TRIPLE BLIND

In addition to participants and researchers, other parties, such as data analysts or statisticians, may also be blinded







CRAB FIVE

SAMPLE SIZE

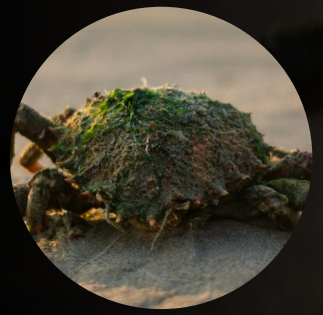
WHY

Researchers often want to demonstrate that two, or more, groups are truly distinct from one another, but will sometimes fail to find significant differences if the sample size is not big enough

If the sample size is already large enough to prove superiority, continuing to randomise to a control group could be viewed as unethical







CRAB FIVE

SAMPLE SIZE

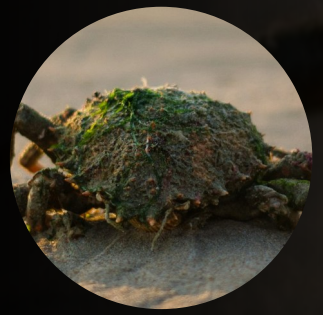
STEP ONE: ESTABLISH THE OBJECTIVE

In terms of hypothesis testing there are four main types of trial type:

- Superiority: show that one treatment is superior to another
- Non-Inferiority: show that a new treatment is not less effective than an established treatment by a predefined margin
- Equivalence: show that a new intervention is statistically equivalent to an existing standard treatment within a predetermined margin







CRAB FIVE

SAMPLE SIZE

STEP ONE: ESTABLISH THE OBJECTIVE

Null Hypothesis

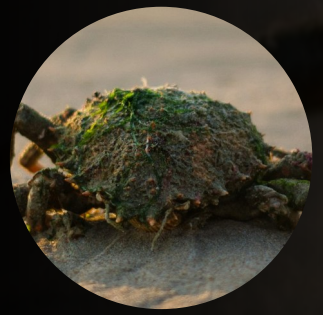
$$H_0: \pi_a = \pi_b$$

Alternate Hypothesis

$$H_1: \pi_a \neq \pi_b$$







CRAB FIVE

SAMPLE SIZE

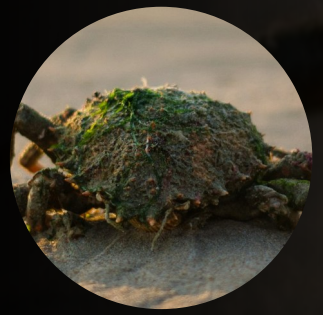
STEP TWO: ESTABLISH THE TRIAL TYPE

There are many trial types, this session will focus on two of the most common ones;

- Parallel: where two groups of treatments, A and B, are given so that one group receives only A, while another group receives only B
- Crossover: each patient receives different treatments, A and B, during the different time periods







CRAB FIVE

SAMPLE SIZE

STEP THREE: DETERMINE THE ALLOCATION RATIO (r)

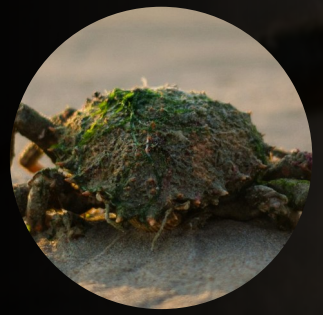
For Parallel trials, the allocation ratio demonstrates whether equal numbers of subjects are allocated to treatment arms

The most efficient allocation ratio is $r = 1$

In certain circumstances it may be desirable to have a larger number of participants receiving a new intervention or control







CRAB FIVE

SAMPLE SIZE

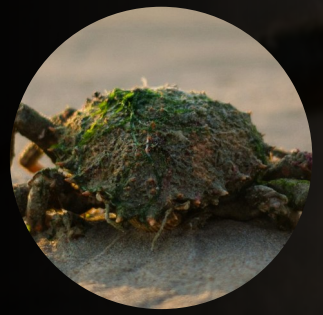
STEP FOUR: IDENTIFY THE ENDPOINT

The sample size should be calculated based on the study primary endpoint. The endpoint can take several forms, including:

- Continuous
- Binary
- Ordinal
- Time to event (survival)







CRAB FIVE

SAMPLE SIZE

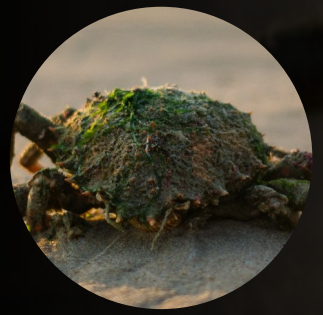
STEP FIVE: ESTABLISH THE DEGREE OF ACCEPTABLE ERROR

When testing a null hypothesis, a degree of error is expected; there are two types of error which can occur

1. Type I Error: (α) Rejecting the H_o when it is actually true
   - Conventionally set at 5% ($p<0.05$)
2. Type II Error: (β) Failing to reject H_o when it is actually false
   - Conventionally set at 20% or β = 80% (power)







CRAB FIVE

SAMPLE SIZE

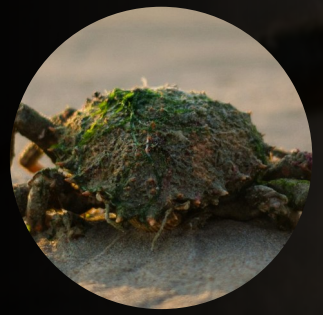
STEP SIX: SPECIFY A CLINICALLY IMPORTANT DIFFERENCE (Δ)

Determined by:

- Previous findings in the literature (ideally, Meta-Analysis)
- Clinical importance, intuition and practice (Policy)
- Early phase or pilot/feasibility studies
- Cohens effect sizes (small, moderate and large)







CRAB FIVE

SAMPLE SIZE

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