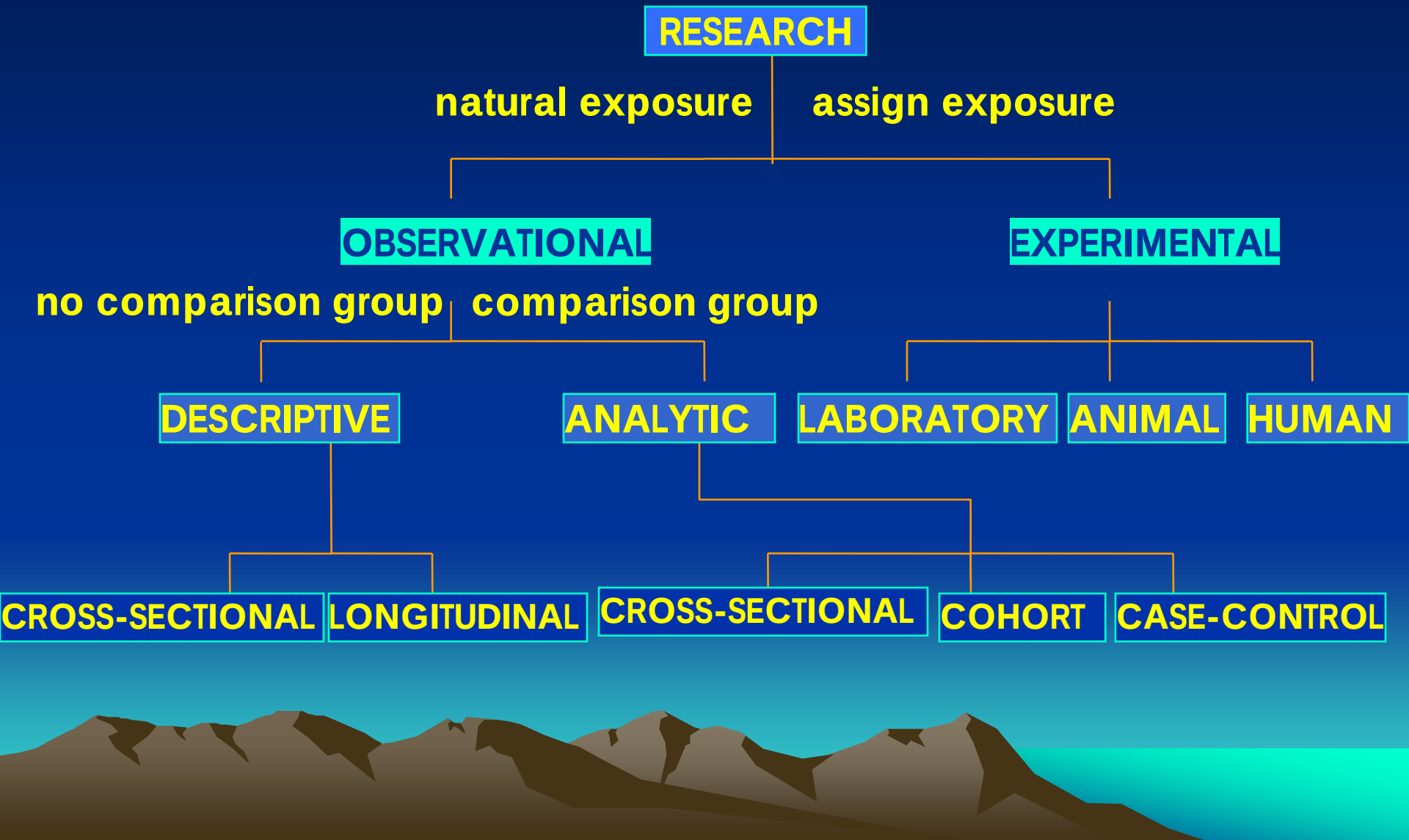
RANDOMIZED CONTROLLED TRIAL
RCT

Apichart Ploysangwal
Department of Surgery
Bhumibol Adulyadej Hospital

STUDY DESIGN



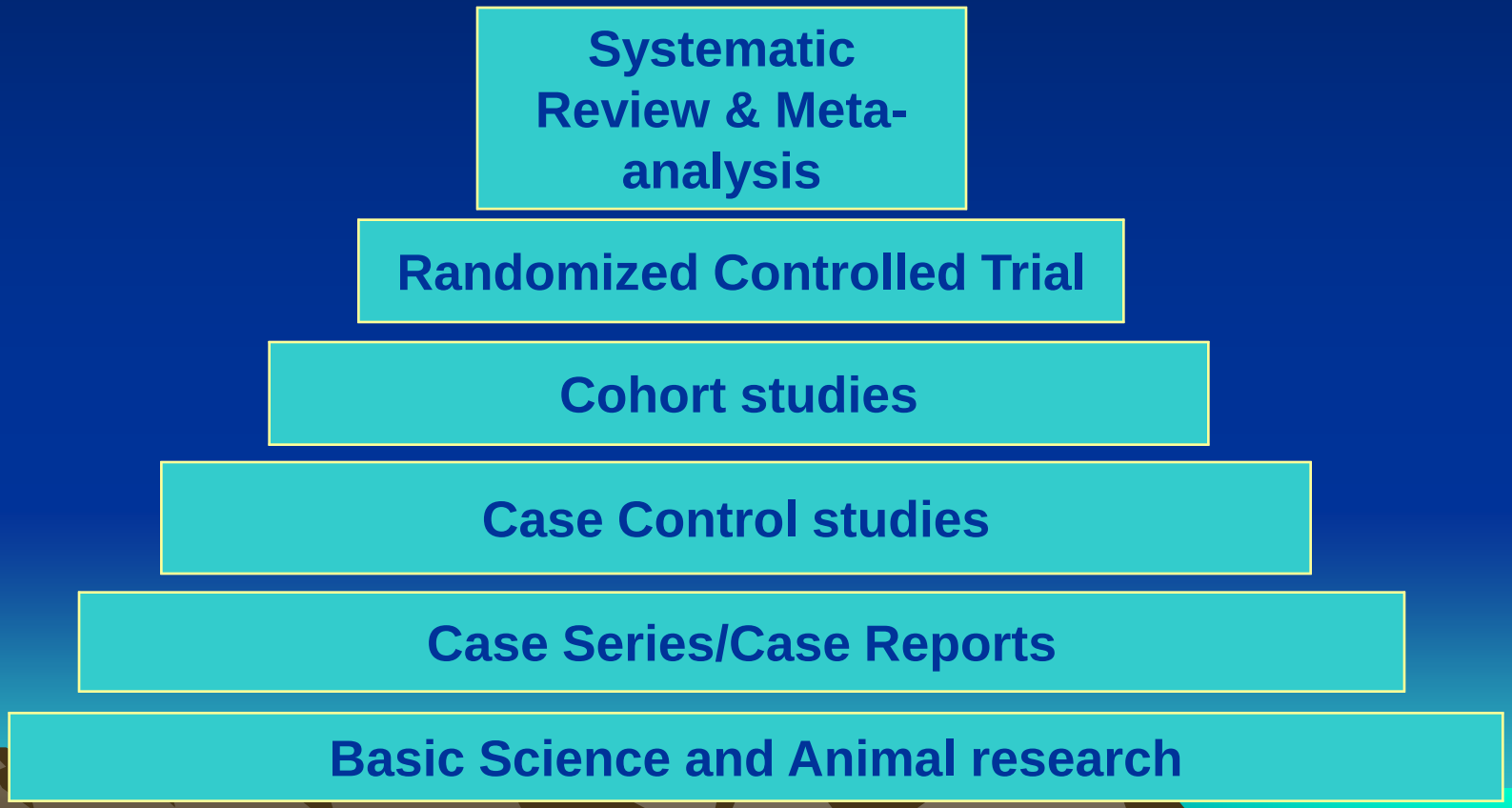
Definition of RCT

- An experiment in which investigators *randomly allocate* eligible people into intervention groups to receive or not to receive one or more interventions that are being compared.
- The results are assessed by comparing *outcomes* in the treatment and control groups.

RCT vs. Cohort study

- Prospective
- Comparison group
- Intervention
  - Assign exposure = RCT
  - Natural exposure = Cohort study

Evidence Pyramid



Justification for Randomized Controlled Trials

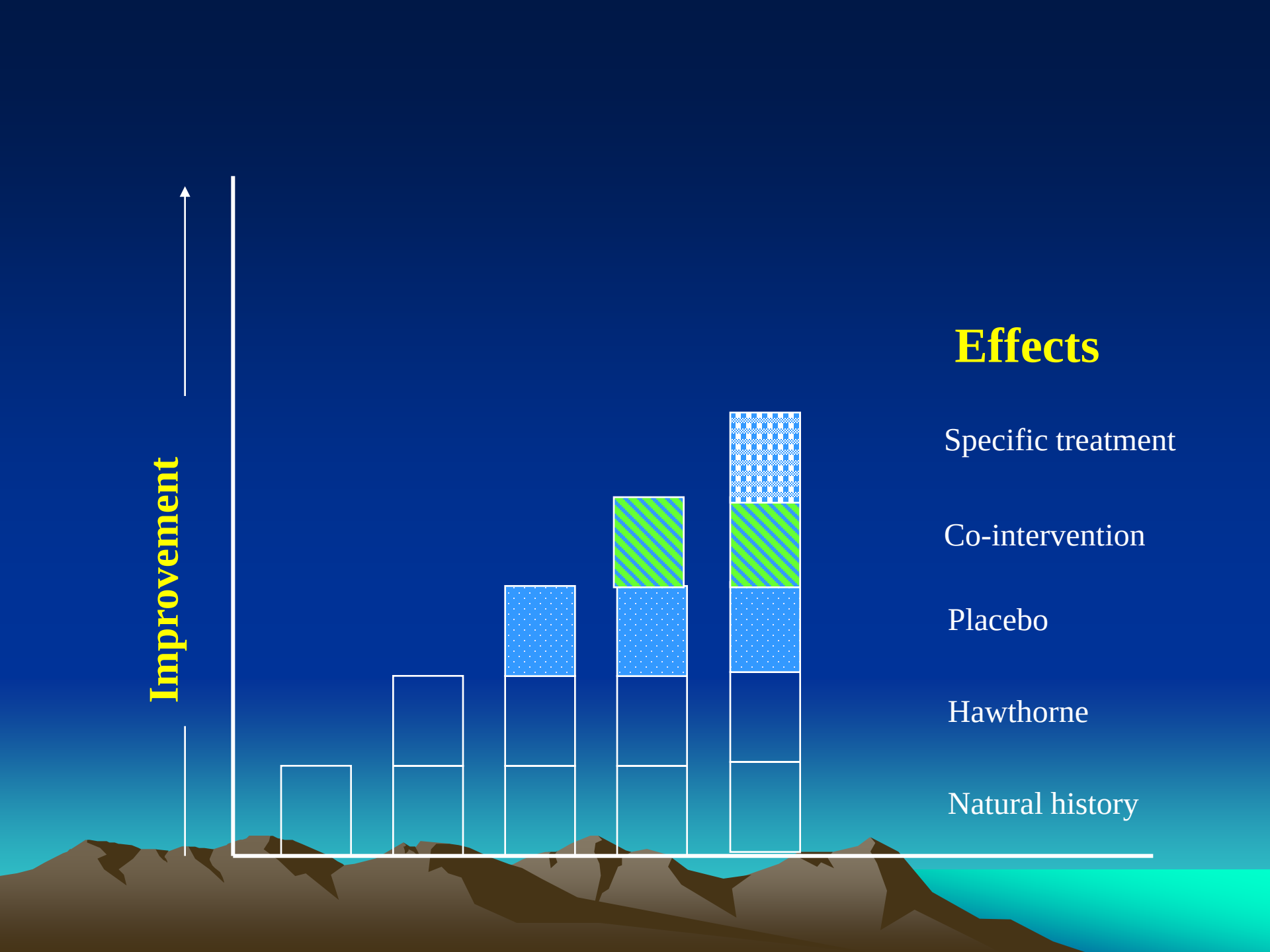
- Problems with uncontrolled trials (experiment, 1 group)
- Problems with historical controls
- Problems with concurrent non-randomized controls

Problems with Uncontrolled Trials

- **Predictable improvement – recover without treatment**
- **Fluctuating disease severity – exacerbation and remission**
- **Volunteer – anxious to please the investigator "Hawthorne effect"**

Problems with Uncontrolled Trials

- Might select less seriously ill patients
- Tend to place greater emphasis on successes
- Might fail to report some failures

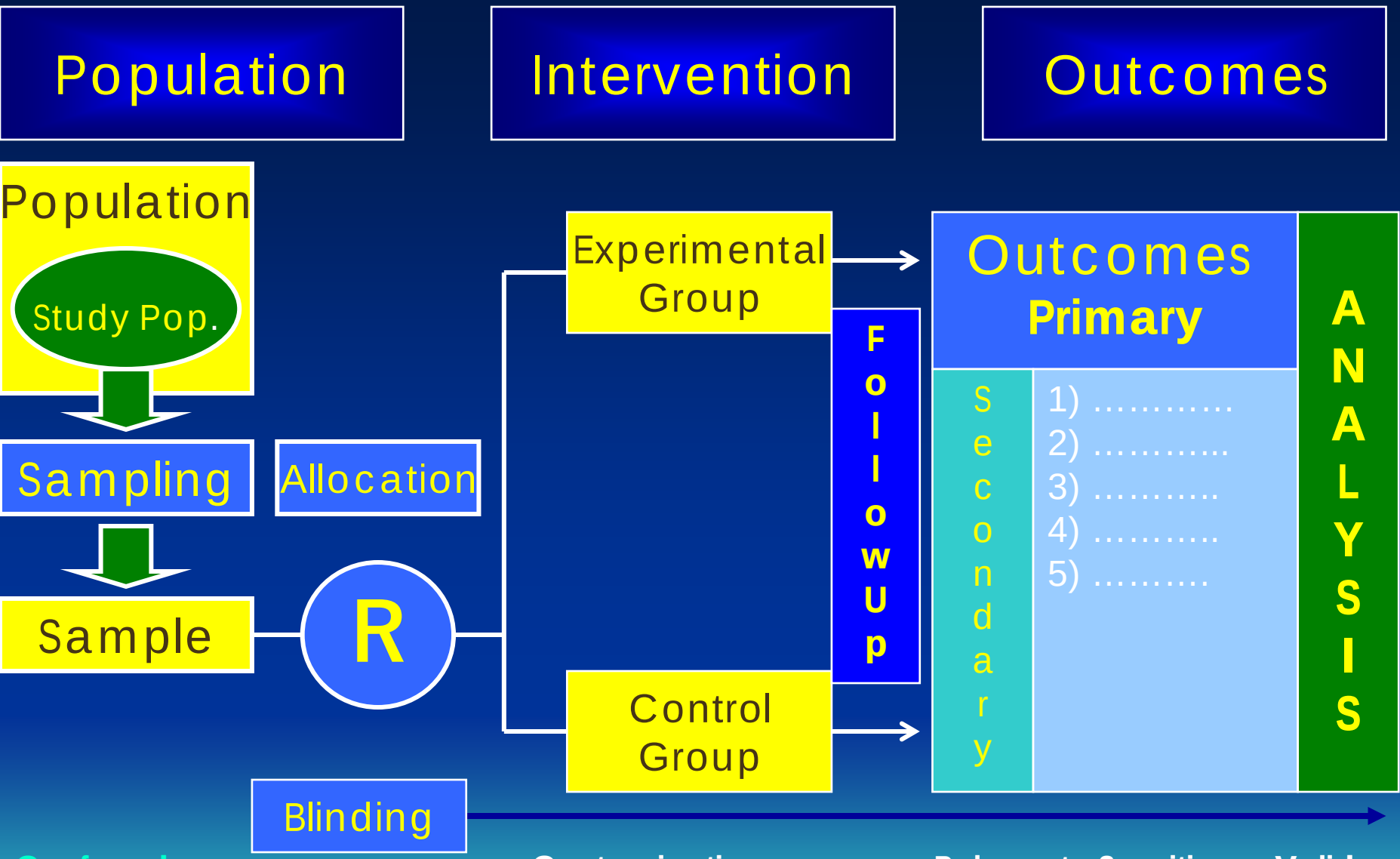

Improvement
Effects
Specific treatment
Co-intervention
Placebo
Hawthorne
Natural history

Uncontrolled Clinical Trial is Useful for:

- **Almost always fatal condition and there is no current effective intervention**
- **Very rare/uncommon conditions**
- **The study response is dramatic without any explainable biases**

Problems with Historical Controls: bias due to

- Improvements in overall patient care
- Improvements in diagnostic procedures
- Altered virulence of the disease
- Psychological effect such as Hawthorne effect
- Unconscious supportive therapy provided to the experimental group
- Differences in confounding variables, such as age, sex or race


Population
Intervention
Outcomes
Population
Study Pop.
Sampling
Allocation
Sample
R
Experimental Group
Control Group
Follow Up
Outcomes
Primary
Secondary
1) .....
2) .....
3) .....
4) .....
5) .....
ANALYSIS
Blinding
Confounder
Comorbidity
Age, Sex,
Strata
Balance
Contamination
Cointervention
Compliance
Dropout
Duration
Relevant
Credible
Accurate
Sensitive
Construct
Cost
Valid
Benefit
Applicable

Research Question in RCT

- Primary research question – most important – sample size calculation
- Secondary research questions
- PICO - Population
  - Intervention
  - Comparison, clinical significant
  - Outcome :- efficacy, effectiveness

Efficacy versus Effectiveness

- **Efficacy = Does it work in *ideal* condition?**
- **Effectiveness = Does it work in *real life* or practice?**
- **Efficiency = *Economic consideration***

In post menopausal patients with early breast cancer, can AI reduce the recurrent rate at least 10 % compared with Tamoxifen?

- **P = post menopausal patients with early breast cancer**
- **I = AI (Aromatase inhibitor)**
- **C = Tamoxifen**
  = 10%reduction
- **O = recurrent rate**

Population

- Target population
- Population to be sampled
- Sample
- Diagnostic criteria - Generalizability
  - Inclusion criteria
  - Exclusion criteria

Sampling techniques

- Nonprobability sampling
- Probability sampling

Nonprobability sampling

- Accidental sampling
- Quota sampling
- Purposive sampling
- Convenient sampling

Probability sampling

- Simple random sampling
- Systematic random sampling
- Stratified sampling
- Cluster sampling

Sample size calculation

- Primary outcome
- Event in control group
- Clinical significant
- Type I error
- Type II error
- Varience

α and β error

		THE TRUTH	
		Treatment Benefit	No Benefit
Result	Treatment Benefit	Correct	Type I (α) Error
	No Benefit	Type II (β) Error	Correct

Allocation

- Simple randomization
- Block randomization
- Stratified randomization

Table of random digits

89	11	77	99	94
35	83	73	68	20
84	85	95	45	52
56	80	93	52	82
97	62	98	71	39
79	36	13	72	99
34	96	98	54	89
69	56	88	97	43
09	17	78	78	02
83	17	39	84	16
24	23	36	44	14
39	87	30	20	41
75	18	53	77	83
33	93	39	24	81
22	52	01	86	71

Block randomization

- Block of 4 in 2 groups in the study
  1. AABB 2. ABAB 3. ABBA
  4. BBAA 5. BABA 6. BAAB
- Generate random sequence of numbers 1 to 6, say 6,5,2,1,3,4 and substitute from above to give allocation sequence of
  "BAAB BABA ABAB AABB
  ABBA BBAA"

Blinding

- *Single blind*: only study subjects are blinded
- *Double blind*: both subjects and researchers are blinded
- *Triple blind*: subjects, researchers and evaluator are blinded

Characteristics of Intervention

- Precision :- procedure, formula, dose
- Sensibility:- scientific proof
- Availability:- for the others
- Acceptability
- Bias control
  - Contamination
  - Co-intervention
  - Compliance

Outcome measurement

- **Characteristics of outcome**
  - **Relevant to research question - Hernia**
  - **Capable of operational definition**
  - **Acceptable**
  - **Accuracy:- random & systematic error**
- **Outcome measurement**
  - **Subjective measurement**
  - **Objective measurement**

Scales of measurement

- Qualitative scales
  - Nominal scales
  - Ordinal scales
- Quantitative scales
  - Interval scales
  - Ratio scales

Data analysis

- Descriptive statistics
- Statistics for the outcomes:- recurrent rate, mortality rate, complication rate, success rate
- Statistics for hypothesis testing:- unpaired t-test, Chi-square test
- Time for analysis:- interim analysis, final analysis

Problems in data analysis

- Missing data
- Lost to follow up
- Non complier
- Contamination
- Co-intervention
- Death from other causes

The difference between “Intention to treat analysis” and “Per-protocol analysis”

Interpretation of analysis

- Statistical significance
- Clinical significance
- No statistical significance ≠ the same result

Guide for RCT evaluation

1. **Are the results of the study valid?**

- **Primary guides:**

- Was the assignment of patients to treatments ramdomized?

- Were all patients who entered the trial properly accounted for and attributed at its conclusion?

 # Was follow-up complete?

 # Were patients analyzed in the groups to which they were randomized?

Guide for RCT evaluation

- **Secondary guides**

  - Were patients, health workers, and study personnel "blind" to treatment?

  - Were the groups similar at the start of the trial?

  - Aside from the experimental intervention, were the groups treated equally?

Guide for RCT evaluation

2. What were the results?

- **How large was the treatment effect?**
- **How precise was the estimate of the treatment effect?**

3. Will the results help me in caring for my patients?

- **Can the results be applied to my patient care?**
- **Were all clinically important outcomes considered?**
- **Are the likely treatments benefits worth the potential harms and costs?**

Estimating the size of the treatment effect

	outcome	outcome	
	+	-	Risk of outcome
Treatment(Y)	a(20)	b(80)	Y = a/(a+b)
Control(X)	c(40)	d(60)	X = c/(c+d)

Estimating the size of the treatment effect

- The absolute risk reduction is the difference in risk between the control group(X) and the treated group(Y):

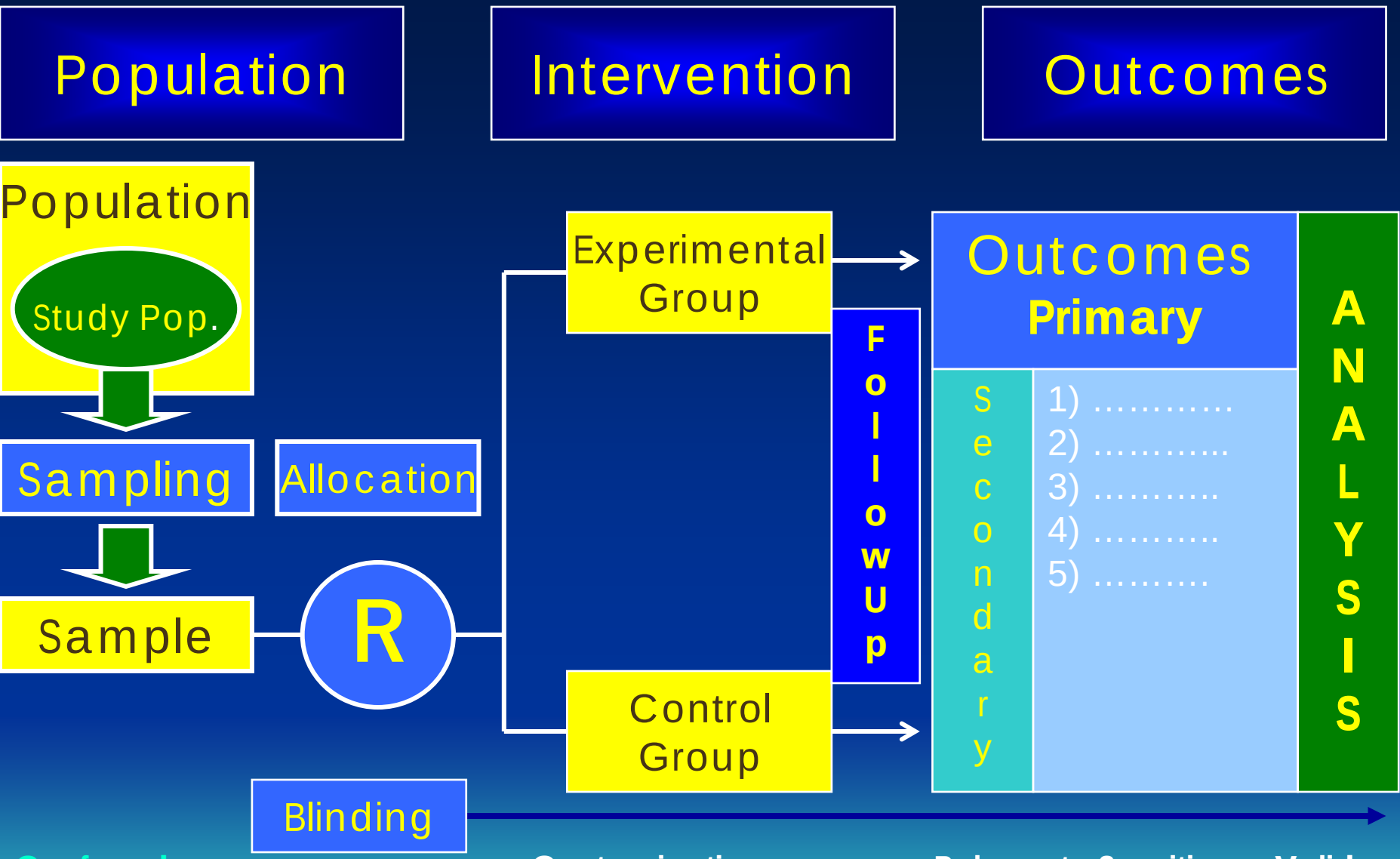
  ARR = X- Y (0.4-0.2 = 0.2)
- The relative risk, or risk ratio, is the ratio of the risk in the treated group(Y) to the risk in the control group(X):

  RR = Y/X (0.2/0.4 = 0.5)
- The relative risk reduction expresses the percent reduction in events in treated(Y) compared to control(X):

  RRR = (1- Y/X)* 100% (1-0.5)*100 = 50%

  RRR = [(X-Y)/X]* 100% [(0.4-0.2)/0.4]*100 = 50%
- The number needed to treat is the inverse of the absolute risk reduction:

  NNT = 1/ARR (1/0.2 = 5)


Population
Intervention
Outcomes
Population
Study Pop.
Sampling
Allocation
Sample
R
Experimental Group
Control Group
Follow Up
Outcomes
Primary
Secondary
1) .....
2) .....
3) .....
4) .....
5) .....
ANALYSIS
Blinding
Confounder
Comorbidity
Age, Sex,
Strata
Balance
Contamination
Cointervention
Compliance
Dropout
Duration
Relevant
Credible
Accurate
Sensitive
Construct
Cost
Valid
Benefit
Applicable