Therapy

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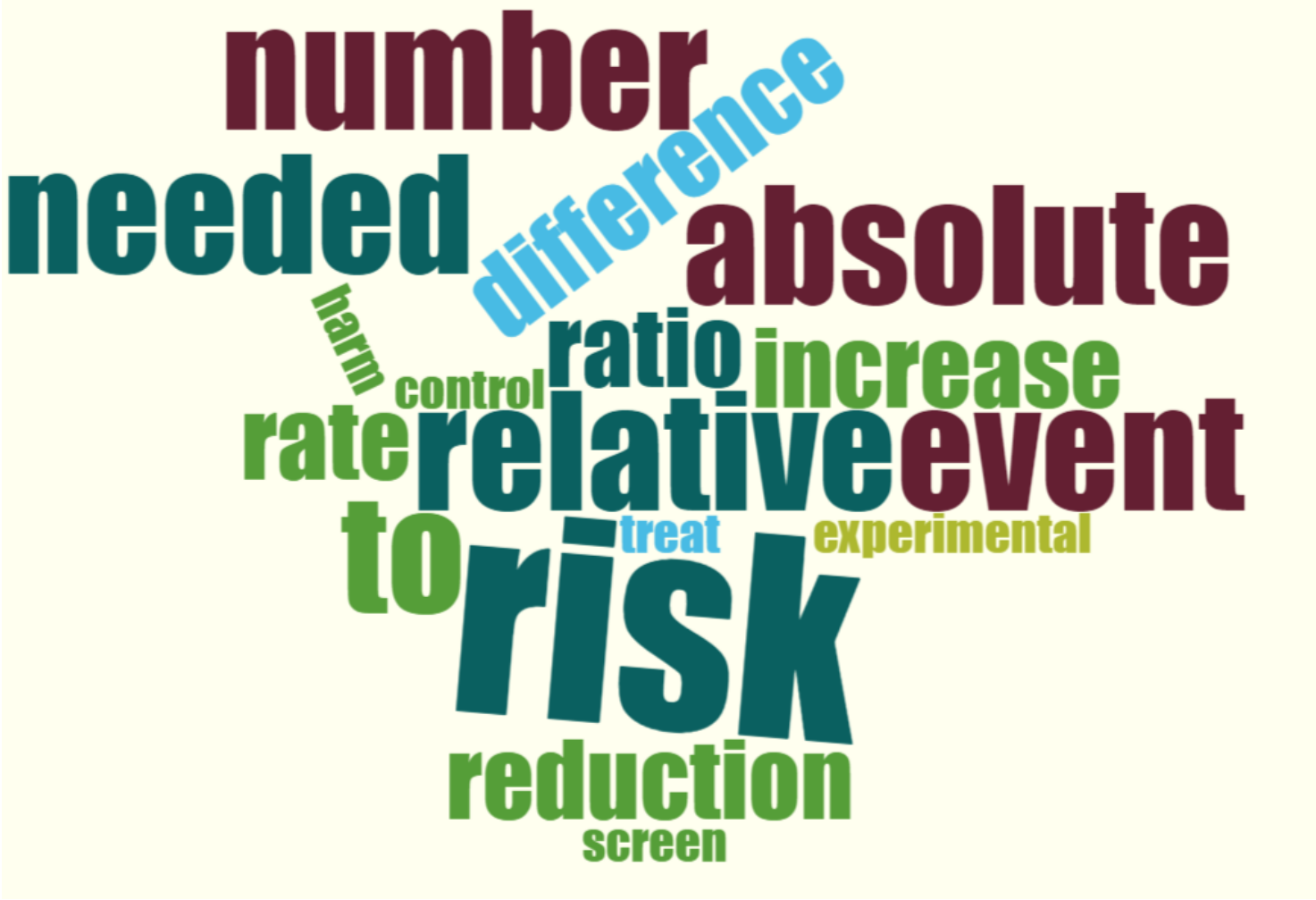
Miami

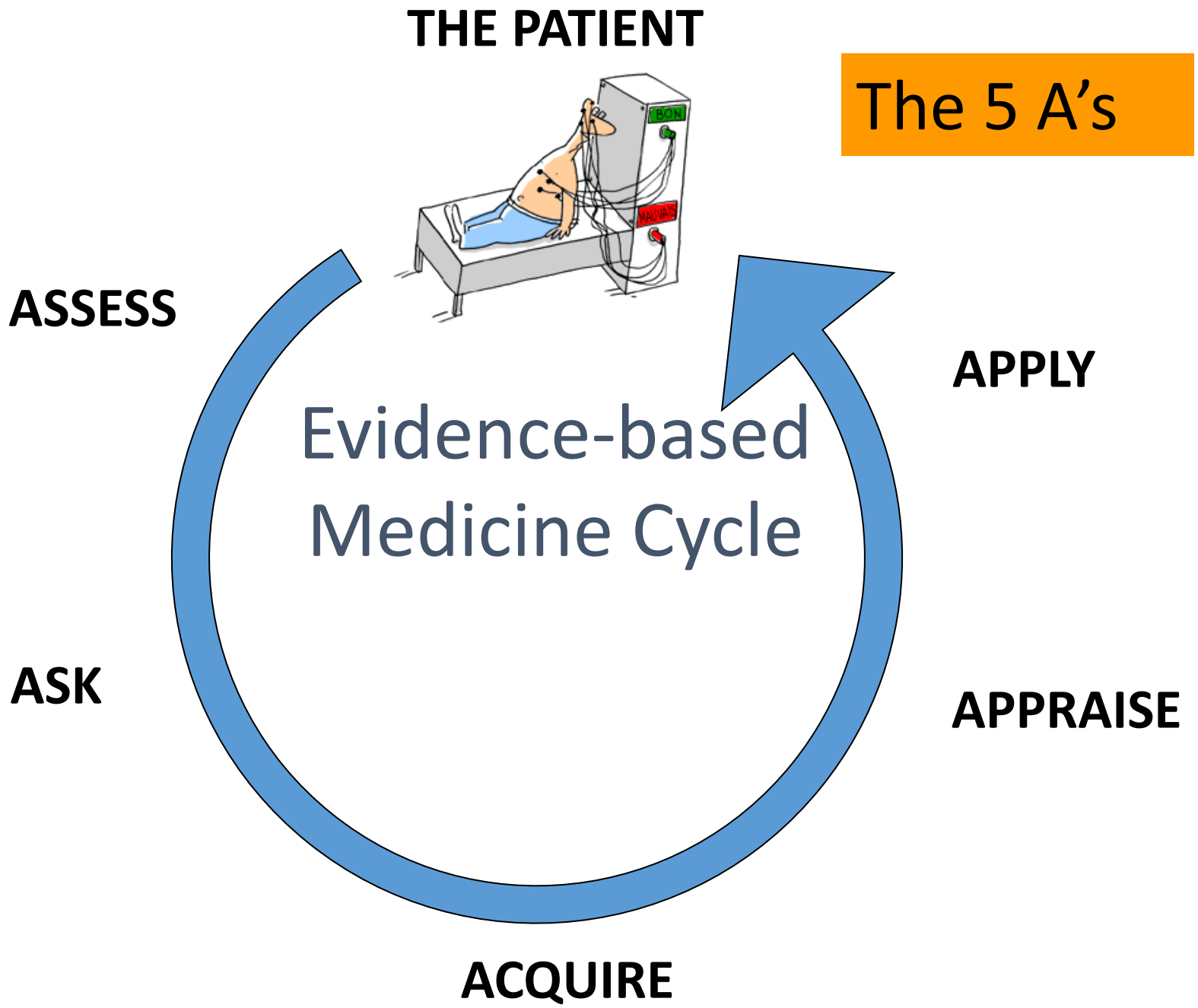
Outline

- The Evidence Cycle
- Case Scenario
- RCT appraisal
  - Did the groups start with a similar prognosis?
  - Did we maintain the similarities?
  - What are the outcomes?
- MATH!
- Closing the Case
- Take Home Points

Therapy first impressions:



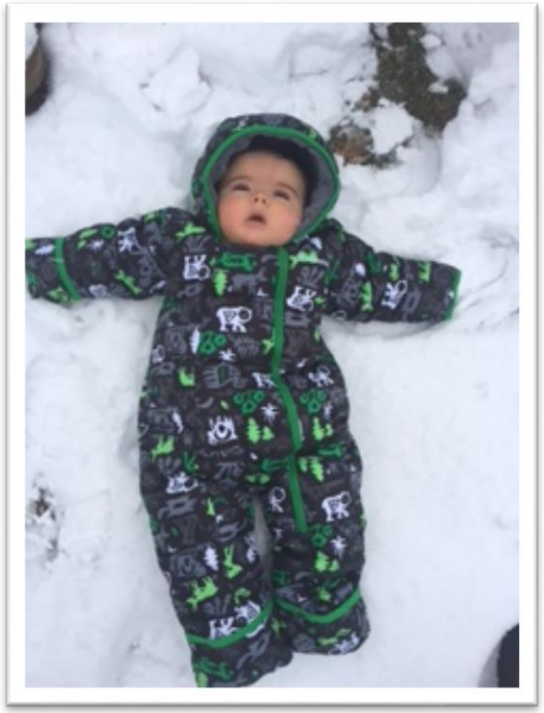
The 5 A's


THE PATIENT
BON
MAUVAIS
ASSESS
APPLY
Evidence-based
Medicine Cycle
ASK
APPRAISE
ACQUIRE

ASSESS

Case scenario

- Martin lived in Iowa for 3 $\frac{1}{2}$ years
- Lots of good things happened in Iowa



Iowa is beautiful

But Iowa can be cold

Hawaii is beautiful… and warm

Recruiters convince him to come for a visit.

The visit is a success…

He’s about to sign a new contract

But then there’s this:

Man Of War jellyfish

(You don’t see this in Iowa)

Case scenario

- Martin is stung by a jellyfish
- Brought to lifeguard station
- Pain over his right leg
- No nausea

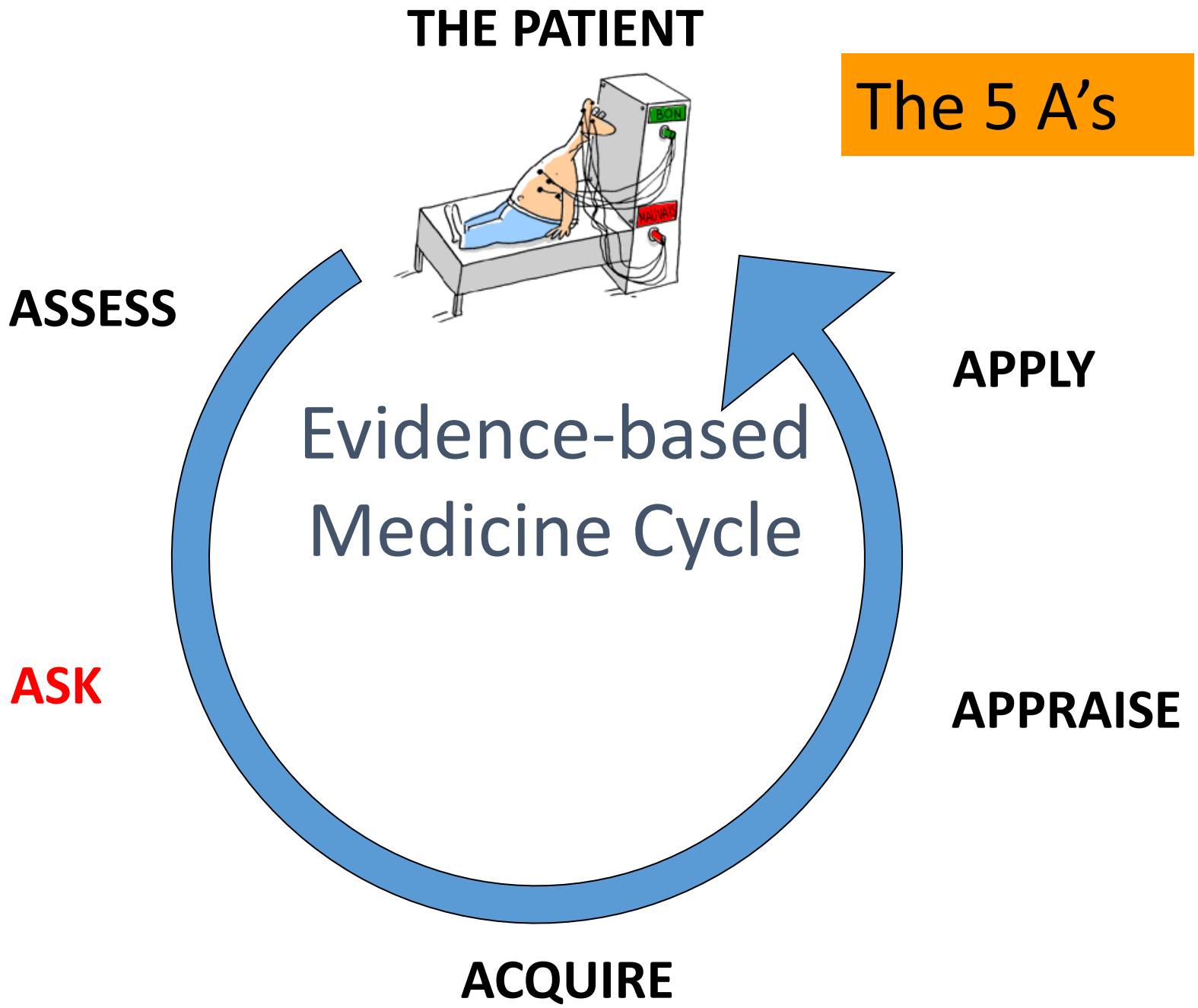
Case Scenario

- An expert at evidence based medicine who has come to the Duke workshop many times,
- Martin wonders

What is the best treatment for my jellyfish sting?

He thinks there might have been an episode of Friends that addressed this…

The 5 A's


THE PATIENT
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Evidence-based Medicine Cycle
ASK
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ACQUIRE

ASK: PICOTT

P opulation

I ntervention

C omparison

O utcome

T ype of question

T ype of ideal study

Libraries | University of Miar Cnidarian Venoms - Me

ncbi.nlm.nih.gov/mesh/?term=jellyfish+venom

ACQUIRE

NCBI Resources How To Sign in to NCBI

MeSH MeSH jellyfish venom Search

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Full Send to:

Cnidarian Venoms

Venoms from jellyfish; CORALS; SEA ANEMONES; etc. They contain hemo-, cardio-, dermo- , and neuro-toxic substances and probably ENZYMES. They include palytoxin, sarcophine, and anthopleurine.

Year introduced: 1995

PubMed search builder options

Subheadings:

- administration and dosage
- adverse effects
- analysis
- antagonists and inhibitors
- biosynthesis
- blood
- chemical synthesis
- chemistry
- classification
- economics
- enzymology
- etiology
- genetics
- history
- immunology
- isolation and purification
- metabolism
- organization and administration
- pharmacokinetics
- pharmacology
- physiology
- poisoning
- secretion
- standards
- therapeutic use
- toxicity

Restrict to MeSH Major Topic.

Do not include MeSH terms found below this term in the MeSH hierarchy.

Tree Number(s): D20.888.230, D23.946.580.230, D23.946.833.230

MeSH Unique ID: D003064

Entry Terms:

- Venoms, Cnidarian
- Cnidarian Venom
- Venom, Cnidarian
- Sea Anemone Venom
- Venom, Sea Anemone
- Sea Anemone Venoms
- Venoms, Sea Anemone
- Nematocyst Venoms
- Venoms, Nematocyst
- Portuguese Man-of-War Venom
- Portuguese Man of War Venom
- Venom, Portuguese Man-of-War
- Chironex Venoms
- Venoms, Chironex
- Chironex Venom
- Venom, Chironex
- Jellyfish Venoms
- Venoms, Jellyfish

PubMed Search Builder

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Related information

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Recent Activity

Turn Off Clear

Cnidarian Venoms MeSH

jellyfish venom (1) MeSH

A randomised controlled trial of hot water (45 degrees C) immersion versus ice p... PubMed

"Cnidarian Venoms"[Mesh] AND (Clinical Trial[ptyp]) (6) PubMed

jellyfish stings (0) MeSH

See more...

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"cnidarian venoms"[MeSH
Terms] OR jellyfish venom
[Text Word]
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9:26 AM

Libraries | University of Miar "Cnidarian Venoms"[Me

ncbi.nlm.nih.gov/pubmed?term=%22Cnidarian+Venoms%22%5BMesh%5D

NCBI Resources How To Sign in to NCBI

PubMed.gov US National Library of Medicine National Institutes of Health

PubMed "Cnidarian Venoms"[Mesh] Search

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Publication dates
- 5 years
- 10 years
- Custom range...

Species
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- Other Animals

Clear all

Show additional filters

Format: Summary Sort by: Most Recent Per page: 20 Send to

Filters: Manage Filters

Search results

Items: 6

Filters activated: Clinical Trial. Clear all to show 1348 items.

1. Randomised trial of magnesium in the treatment of Irukandji syndrome.
McCullagh N, Pereira P, Cullen P, Mulcahy R, Bonin R, Little M, Gray S, Seymour J.
Emerg Med Australas. 2012 Oct;24(5):560-5. doi: 10.1111/j.1742-6723.2012.01602.x.
PMID: 23039299
Similar articles

2. Sea-anemone toxin ATX-II elicits A-fiber-dependent pain and enhances resurgent and persistent sodium currents in large sensory neurons.
Klinger AB, Eberhardt M, Link AS, Namer B, Kutsche LK, Schuy ET, Sittl R, Hoffmann T, Alzheimer C, Huth T, Carr RW, Lampert A.
Mol Pain. 2012 Sep 15;8:69. doi: 10.1186/1744-8069-8-69.
PMID: 22978421 Free PMC Article
Similar articles

3. Prophylactic treatment of jellyfish stings--a randomised trial.
Tønseth KA, Andersen TS, Pripp AH, Karlsen HE.
Tidsskr Nor Laegeforen. 2012 Jun 26;132(12-13):1446-9. doi: 10.4045/tidsskr.11.0652. English, Norwegian. Erratum in: Tidsskr Nor Laegeforen. 2012 Aug 7;132(14):1587. Andresen, Torgrim Salvesen [corrected to Andersen, Torgrim Salvesen].
PMID: 22766815 Free Article
Similar articles

4. A randomized, controlled field trial for the prevention of jellyfish stings with a topical sting inhibitor.
Boulware DR.
J Travel Med. 2006 May-Jun;13(3):166-71.
PMID: 16706948 Free PMC Article
Similar articles

5. A randomised controlled trial of hot water (45 degrees C) immersion versus ice packs for pain relief in bluebottle stings.
Loten C, Stokes B, Worsley D, Seymour JE, Jiang S, Isbister GK.
Med J Aust. 2006 Apr 3;184(7):329-33.
PMID: 16584366
Similar articles

Efficacy of a jellyfish sting inhibitor in preventing jellyfish stings in normal volunteers.

Titles with your search terms

Hemolytic venoms from marine cnidarian jellyfish - an overview. [J Venom Res. 2014]

Cytotoxic and cytolytic cnidarian venoms. A review on health implicatio [Toxins (Basel). 2013]

Cnidarian toxins and venoms. Preface. [Toxicon. 2009]

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Database: Select

Find items

Search details

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"Cnidarian Venoms"[Mesh] AND
Clinical Trial[ptyp]
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Search

See more...

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- A randomised controlled trial of hot water (45 degrees C) immersion versus ice p... PubMed
- "Cnidarian Venoms"[Mesh] AND (Clinical Trial[ptyp]) (6) PubMed
- jellyfish venom (1) MeSH
- Cnidarian Venoms MeSH
- jellyfish stings (0) MeSH

9:25 AM

A randomised controlled trial of hot water (45° C) immersion versus ice packs for pain relief in bluebottle stings

Conrad Loten, Barrie Stokes, David Worsley, Jamie E Seymour, Simon Jiang and Geoffrey K Isbister

ABSTRACT

Objective: To investigate the effectiveness of hot water immersion for the treatment of *Physalia* sp. (bluebottle or Portuguese Man-of-War) stings.

Design: Open-label, randomised comparison trial. Primary analysis was by intention to treat, with secondary analysis of nematocyst-confirmed stings. One halfway interim analysis was planned.

Setting: Surf lifesaving first aid facilities at two beaches in eastern Australia from 30 December 2003 to 5 March 2005.

Participants: 96 subjects presenting after swimming in the ocean for treatment of an apparent sting by a bluebottle.

Interventions: Hot water immersion (45° C) of the affected part versus ice pack application.

Main outcome measures: The primary outcome was a clinically important reduction in pain as measured by the visual analogue scale (VAS). Secondary outcomes were the development of regional or radiating pain, frequency of systemic symptoms, and proportion with pruritus or rash on follow-up.

Results: 49 patients received hot water immersion and 47 received ice packs. The two groups had similar baseline features, except patients treated with hot water had more severe initial pain (VAS [mean ± SD]: 54 ± 22 mm versus 42 ± 22 mm). After 10 minutes, 53% of the hot water group reported less pain versus 32% treated with ice (21%; 95% CI, 1%–39%; $P = 0.039$). After 20 minutes, 87% of the hot water group reported less pain versus 33% treated with ice (54%; 95% CI, 35%–69%; $P = 0.002$). The trial was stopped after the halfway interim analysis because hot water immersion was shown to be effective ($P = 0.002$). Hot water was more effective at 20 minutes in nematocyst-confirmed stings (95% versus 29%; $P = 0.002$). Radiating pain occurred less with hot water (10% versus 30%; $P = 0.039$). Systemic effects were uncommon in both groups.

Conclusions: Immersion in water at 45° C for 20 minutes is an effective and practical treatment for pain from bluebottle stings.

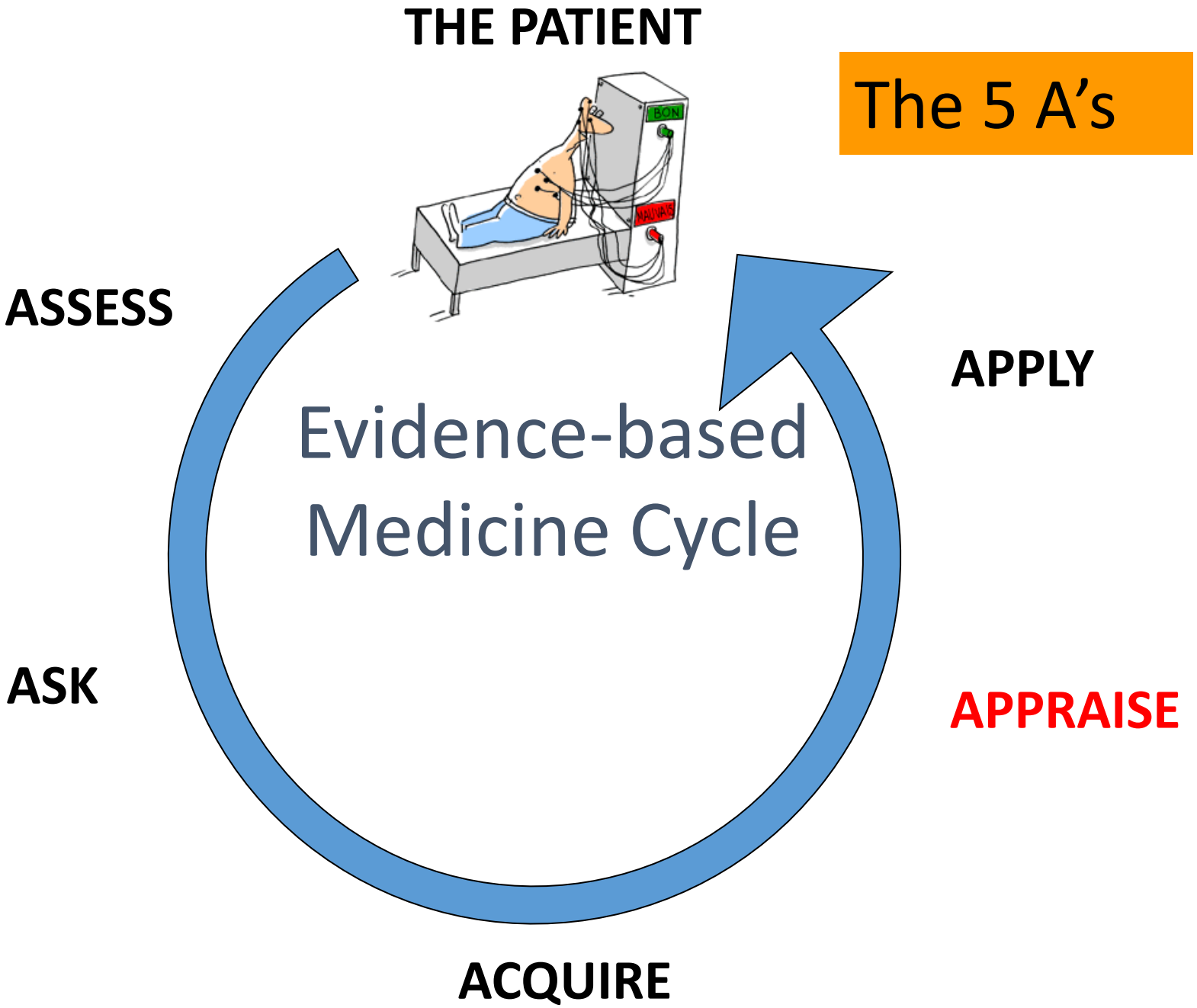
MJA 2006; 184: 329–333

Thousands of bluebottle (*Physalia* sp.) stings occur each year in Australia.[1] Stings cause immediate, intense pain that usually resolves within an hour and is associated with a characteristic linear erythematous eruption (Box 1).[2] The first aid management of bluebottle stings is a daily problem for surf lifesavers. Currently, most first aid bodies, including the International Life Saving Federation,[3] recommend treatment by topical application of ice packs. There is little scientific evidence to support this,[2] and the only study to investigate ice packs was observational with no objective measure of pain, or control or comparator treatment.[4]

Many marine venoms are heat-labile in vitro.[5-8] It is feasible that heat penetrates the human dermis to the estimated depth that nematocysts inject toxins (100–1000 μm),[1] and recent clinical research suggests heat may be effective for treating jellyfish stings.[9,10] However, previous studies of heat therapy were small[10,11] or not randomised,[11,12] and only one was published in full.[12] A randomised controlled trial showed that, compared with ice packs, hot showers significantly reduced pain and treatment duration for bluebottle stings.[10]

If heat is to be used, it needs to be applied

The 5 A's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Outline

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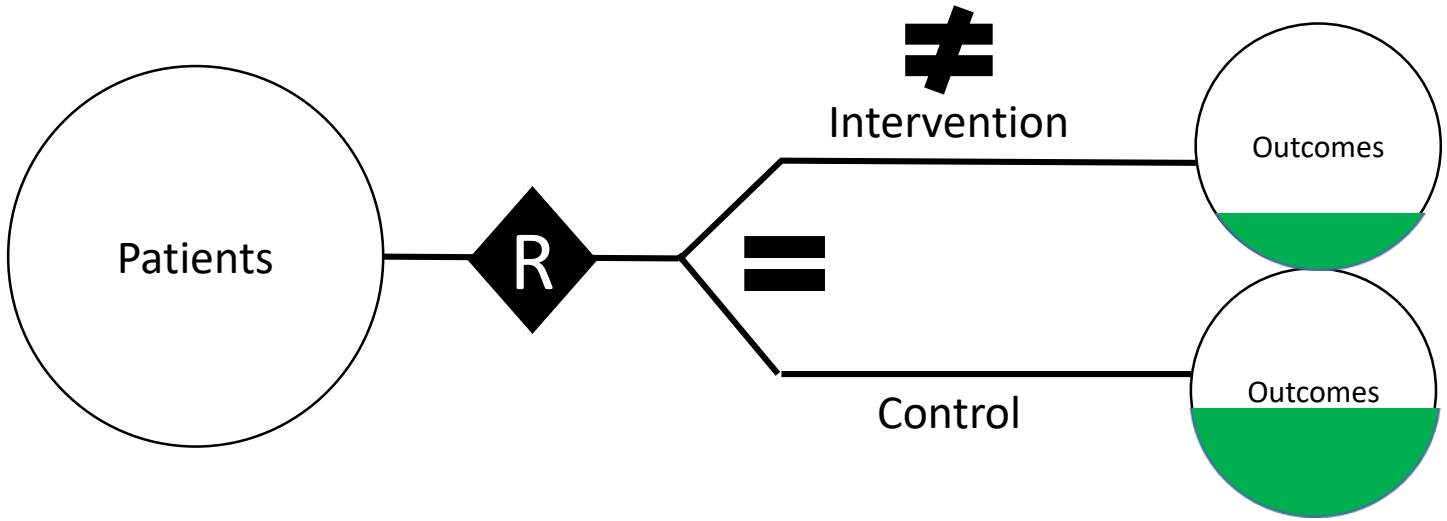
- Case Scenario
- RCT appraisal
  - Did the groups start with a similar prognosis?
  - Did we maintain the similarities?
  - What are the outcomes?
- MATH!
- Closing the case
- Take Home Points

Article Marked In Advance

Therapy
Citation:

How serious is the risk of bias?	
Did intervention and control groups start with the same prognosis?	
Were patients randomized?	1
Was randomization concealed?	2
Were patients in the study groups similar at baseline with respect to prognostic factors?	3
Was prognostic balance maintained as the study progressed?	
To what extent was the study blinded?	4
Were groups prognostically balanced at the study's conclusion?	
Was follow-up complete?	5
Were patients analyzed in the groups to which they were randomized?	6
Was the trial stopped early?	7

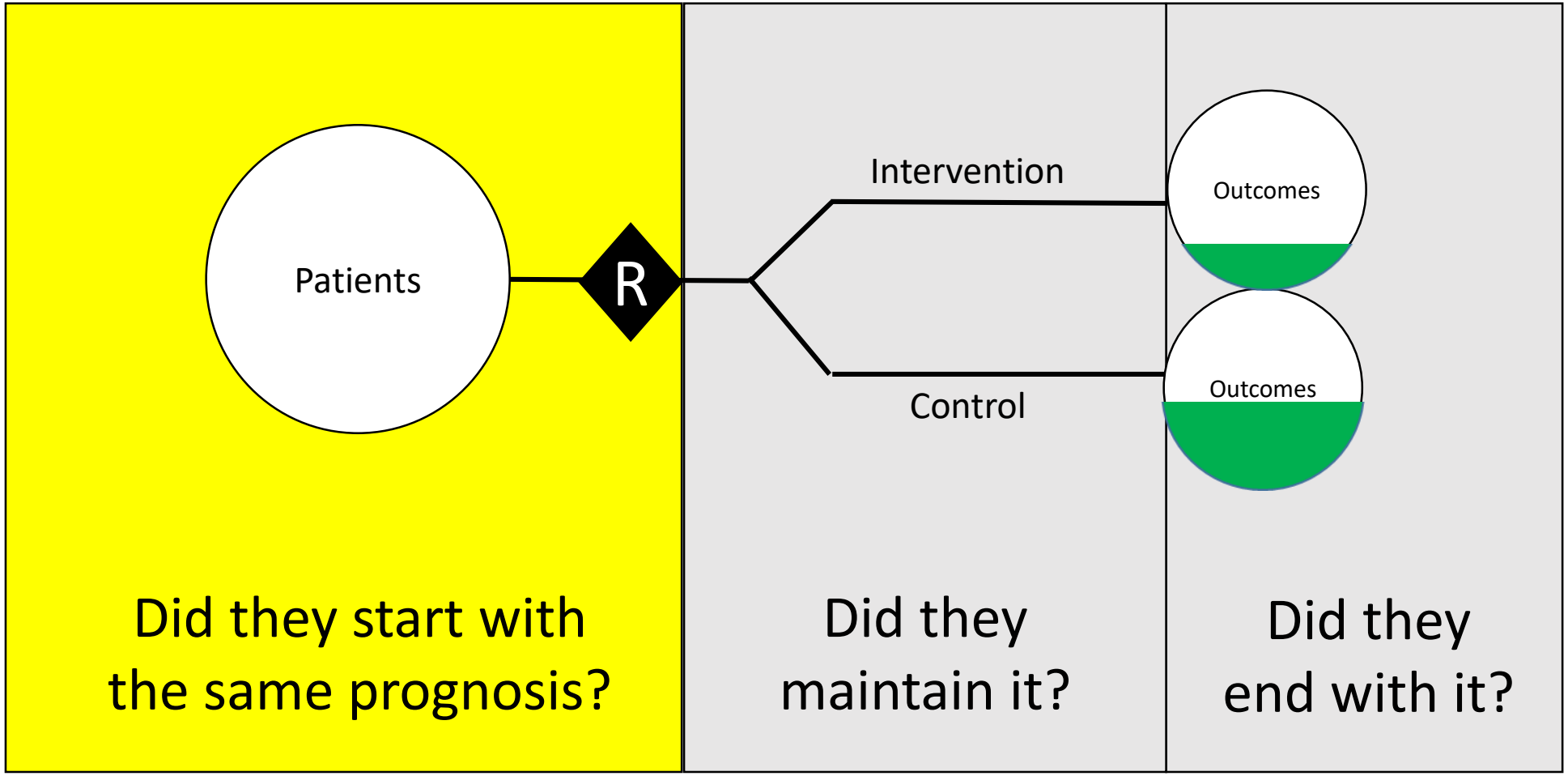
Ideal RCT



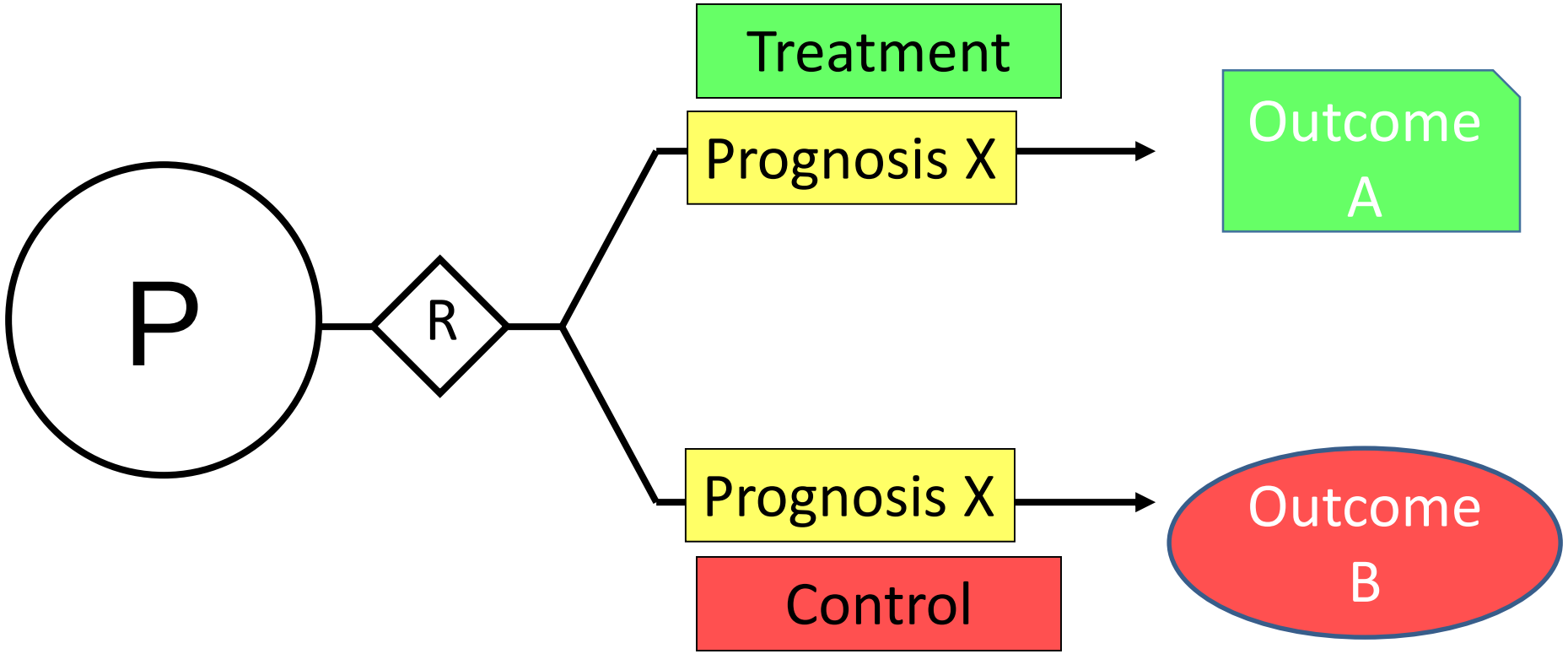
Perfect *is the enemy of* ***good***

-Voltaire

RCT validity:



Goals of randomization

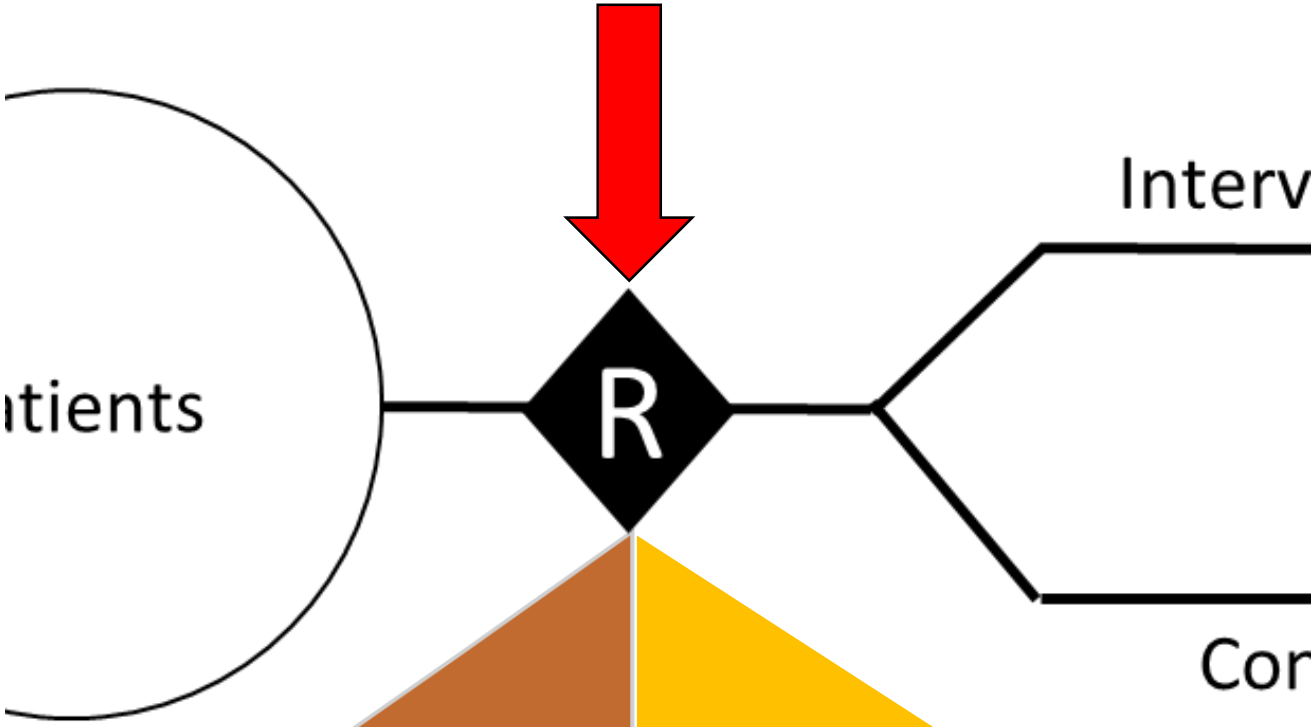


✓ To keep all **known and unknown** prognostic variables evenly distributed between the groups

Were patients randomized in the paper?

1 RANDOMIZATION

Did they start with the same prognosis?



✓ To keep all known and unknown prognostic variables evenly distributed between the groups

List generation

Allocation concealment

LET’S DO OUR OWN STUDY:

When we were preparing for this talk we were nervous about people asking difficult questions.

To make it fair, we are are going to randomly determine which people in the audience we will take questions from.

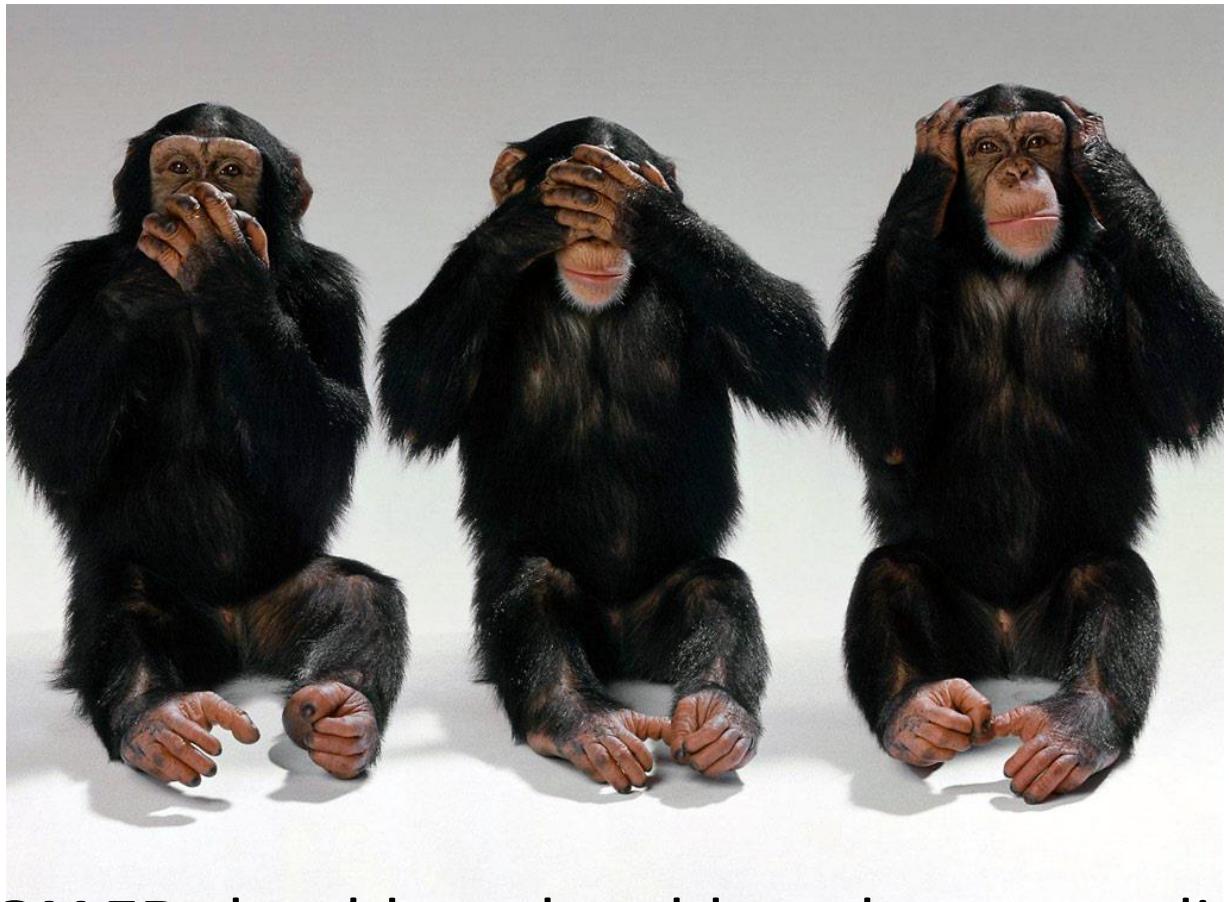
CAN I HAVE A VOLUNTEER?

List generation

Head: allowed to ask questions

Tail: no questions permitted

Allocation concealment:



ENROLLER should not be able to know, predict or manipulate which group each subject is allocated to.

List generation

Head: Hot water treatment

Tail: Ice treatment

Was randomization (allocation) concealed in the paper?

2 ALLOCATION CONCEALMENT

Were patients in the study groups similar at baseline with respect to prognostic factors?

If not similar:

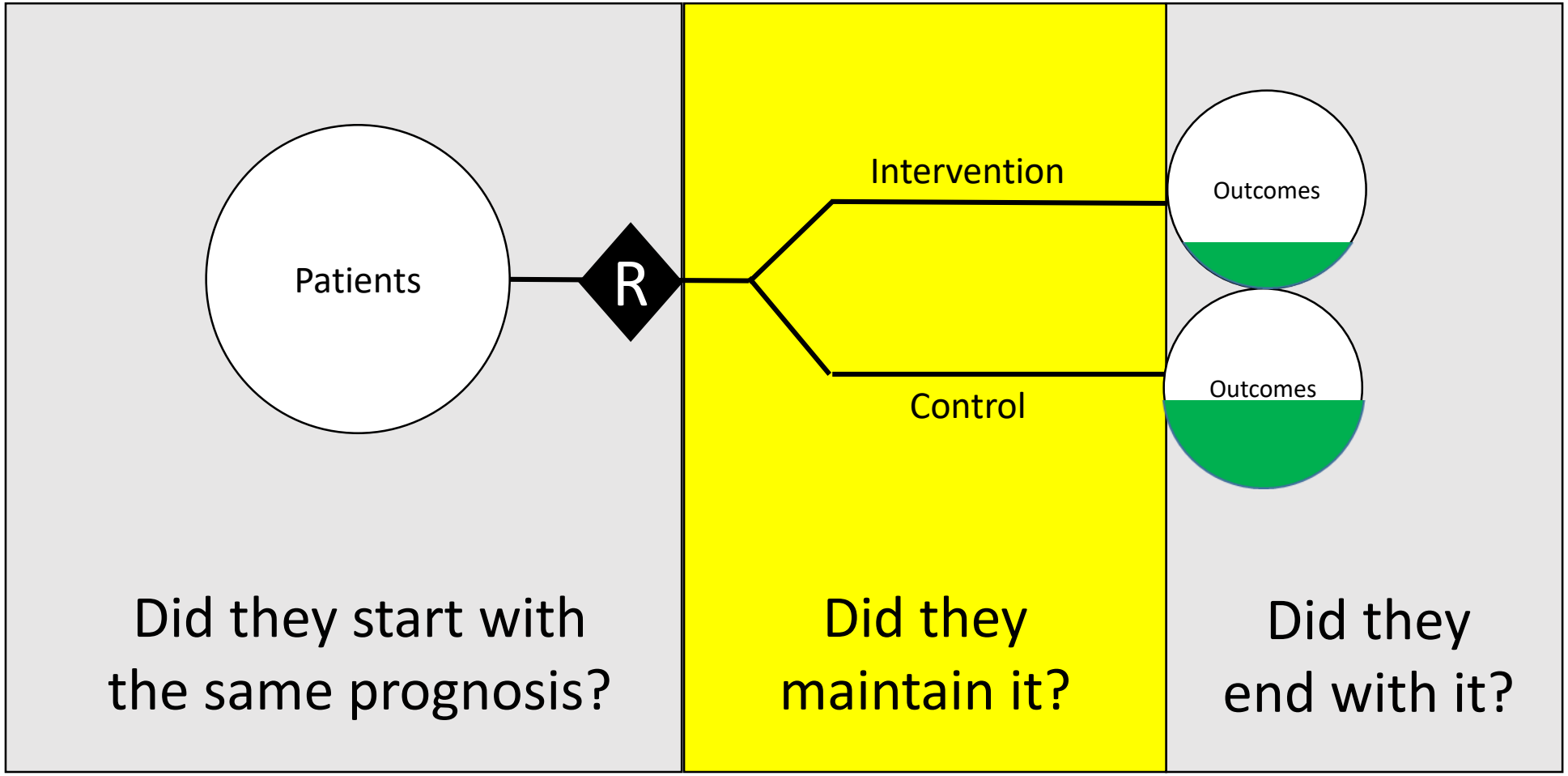
- Is the difference clinically meaningful?
- If it is clinically meaningful, what is the direction of the bias?
- Which is the sicker group?

4 Baseline characteristics of the two treatment groups

3	Hot water immersion ($n = 49$)	Ice packs ($n = 47$)
Mean (SD) age* (years)	19 (10)	18 (10)
Sex (male)	55%	57%
Location of sting		
Proximal limb	47%	47%
Distal limb	16%	17%
Trunk	12%	9%
Head and neck	6%	9%
Multiple sites	14%	17%
Unknown	4%	2%
Mean (SD) initial VAS (mm)	54 (22)	42 (22)

* Age was not known for two patients receiving hot water and one receiving ice packs.

RCT validity:



To what extent was the study blinded?

BLINDING

Blinding

Single Blinded

Double Blinded

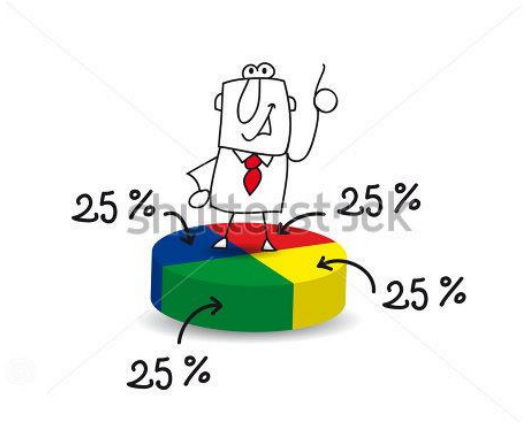
Triple Blinded

Blinding

Patient

Data collector

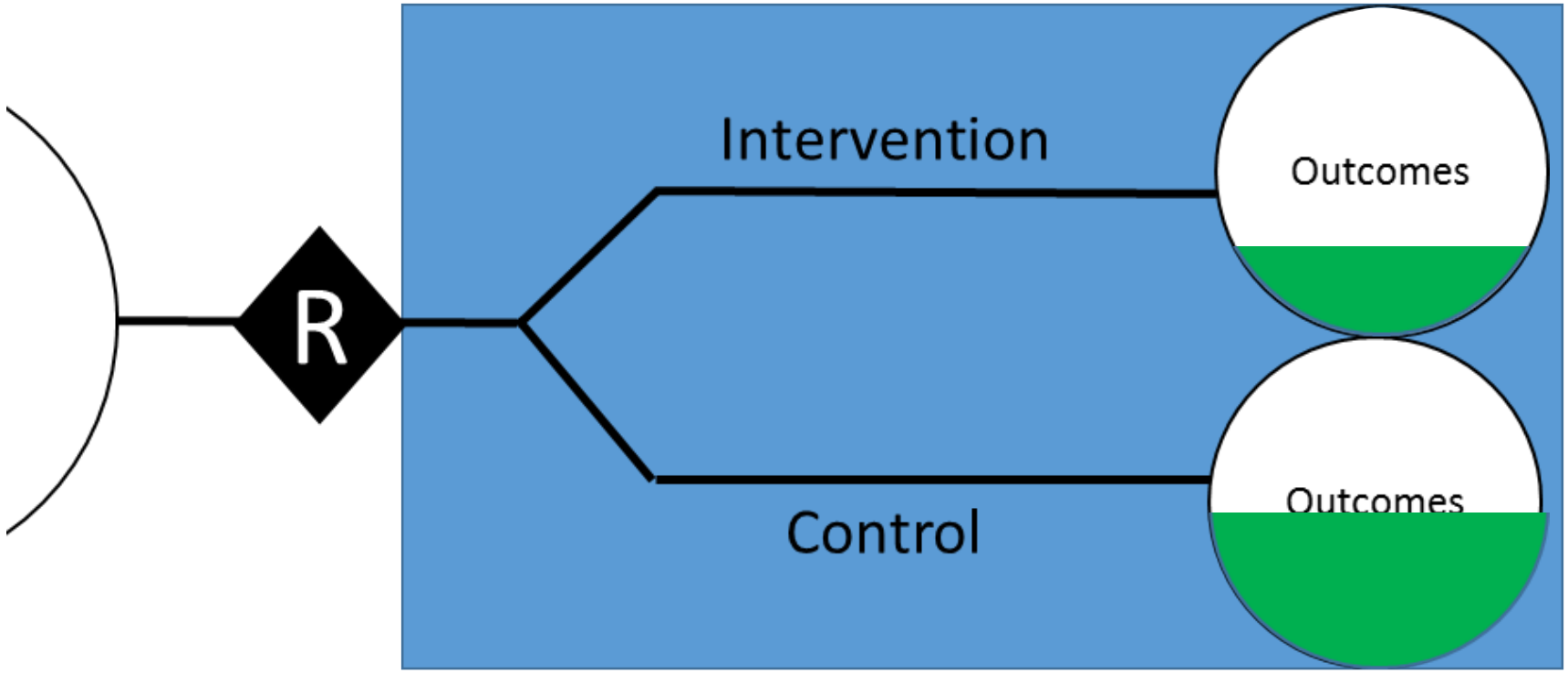
Data Analyst



Provider

Outcome adjudicator

Did they maintain the prognosis?



Blinding

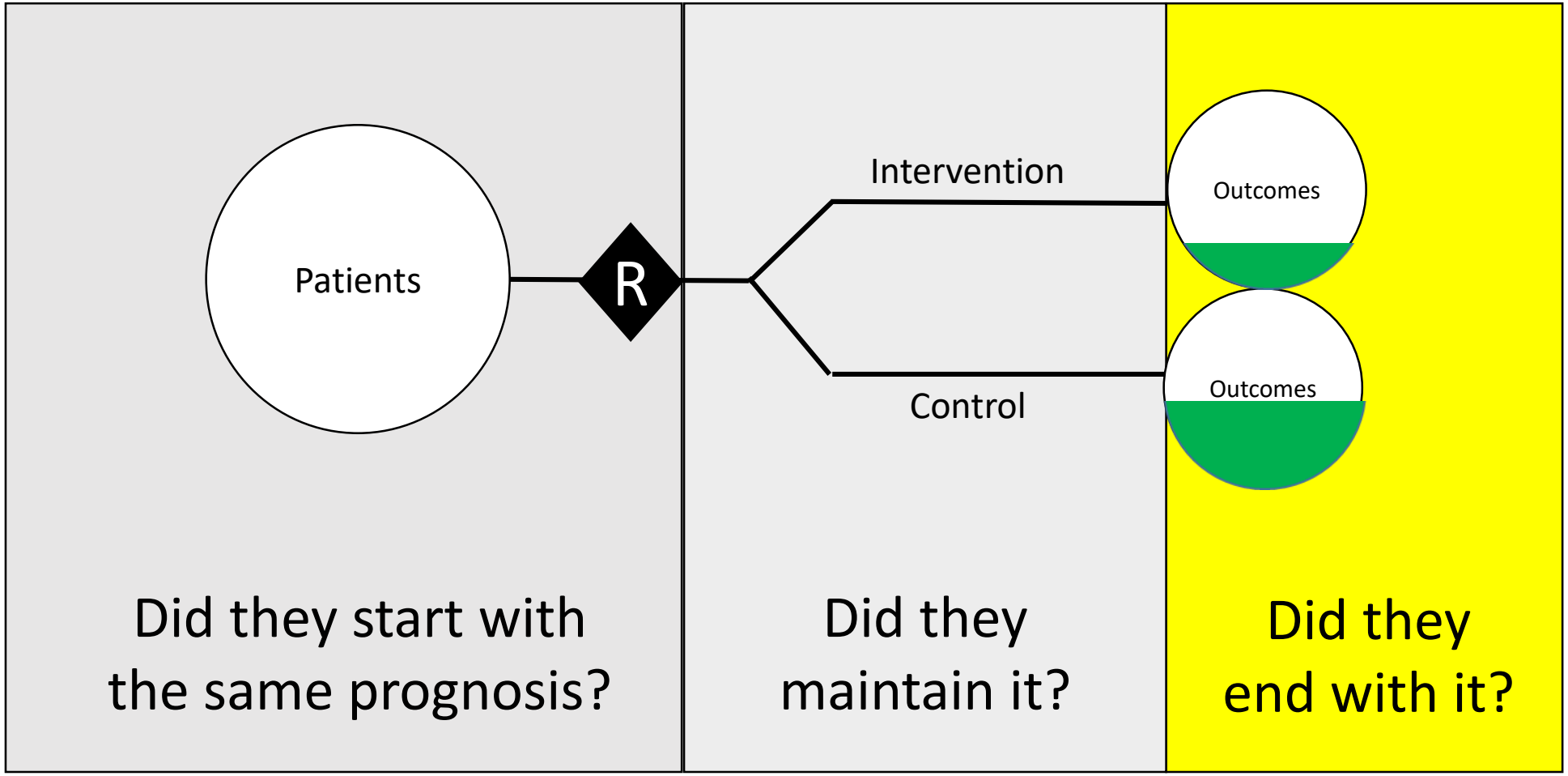
To what extent was the study blinded in the paper?

4 BLINDING

Allocation Concealment vs Blinding

	Allocation Concealment	Blinding
Who?	Enroller	Patients, caregivers, data collectors, adjudicators, analysts
What?	The list	Group assignments
When?	Part of randomization	After randomization

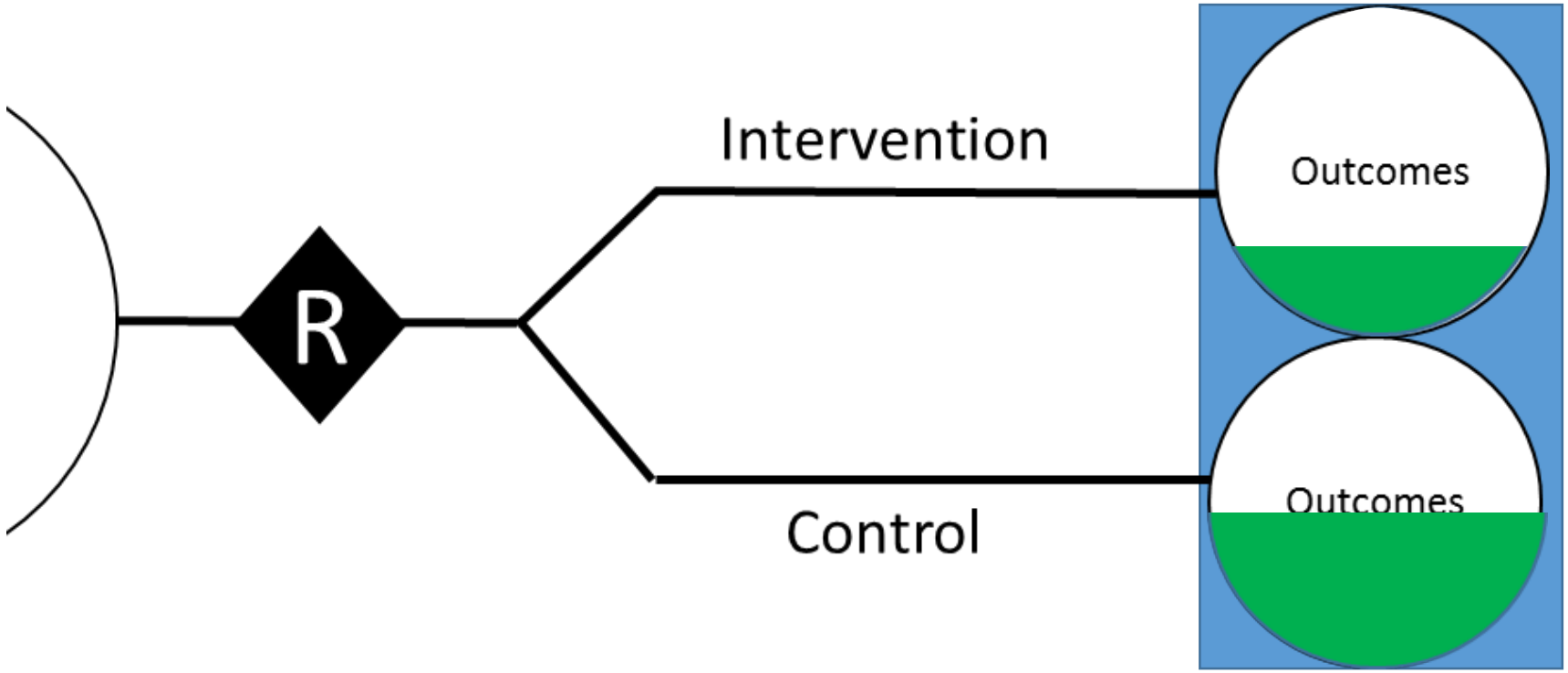
RCT validity:



Was follow up complete?

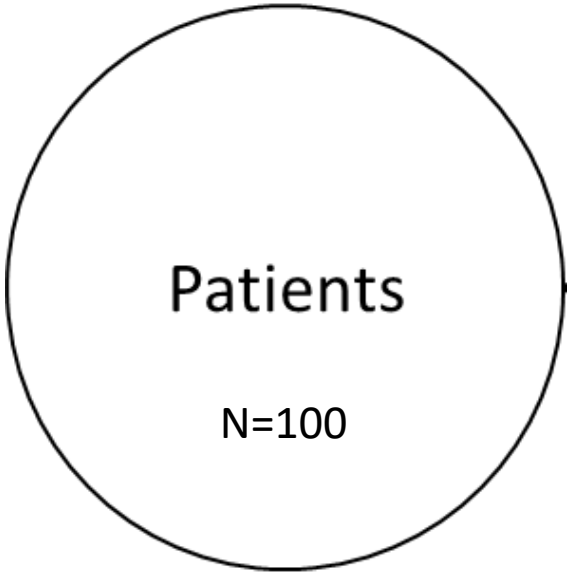
LOSS TO FOLLOW UP

Did they end with the same prognosis?

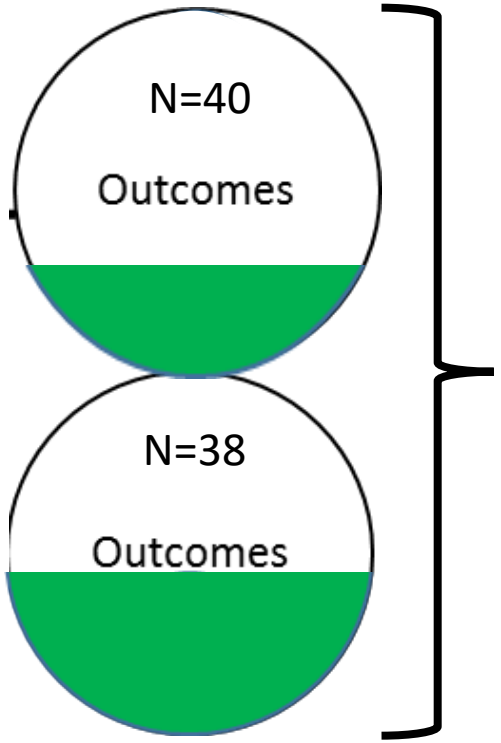


Loss to follow up

Loss to follow up



At the start



At the end

Where would the missing patients be?

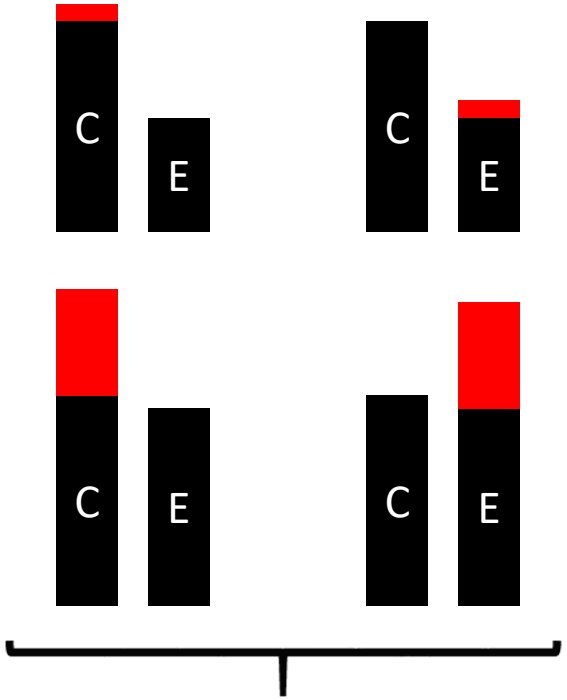
N = 22

Loss to follow up

- We assume they maintained the proportions.
- We carry the last observation forward

If mortality difference is 10% of the patients?
How does a loss of follow up of 1% affect the study?

If mortality difference is 1%?
How does a loss of follow up of 10% affect the study?



Sensitivity analysis:

Loss to follow up

- Patients who are lost often have different prognoses from those who are retained

- Strategies to deal with lost to follow up: last observation carried forward, worst-case scenario, other statistical modeling

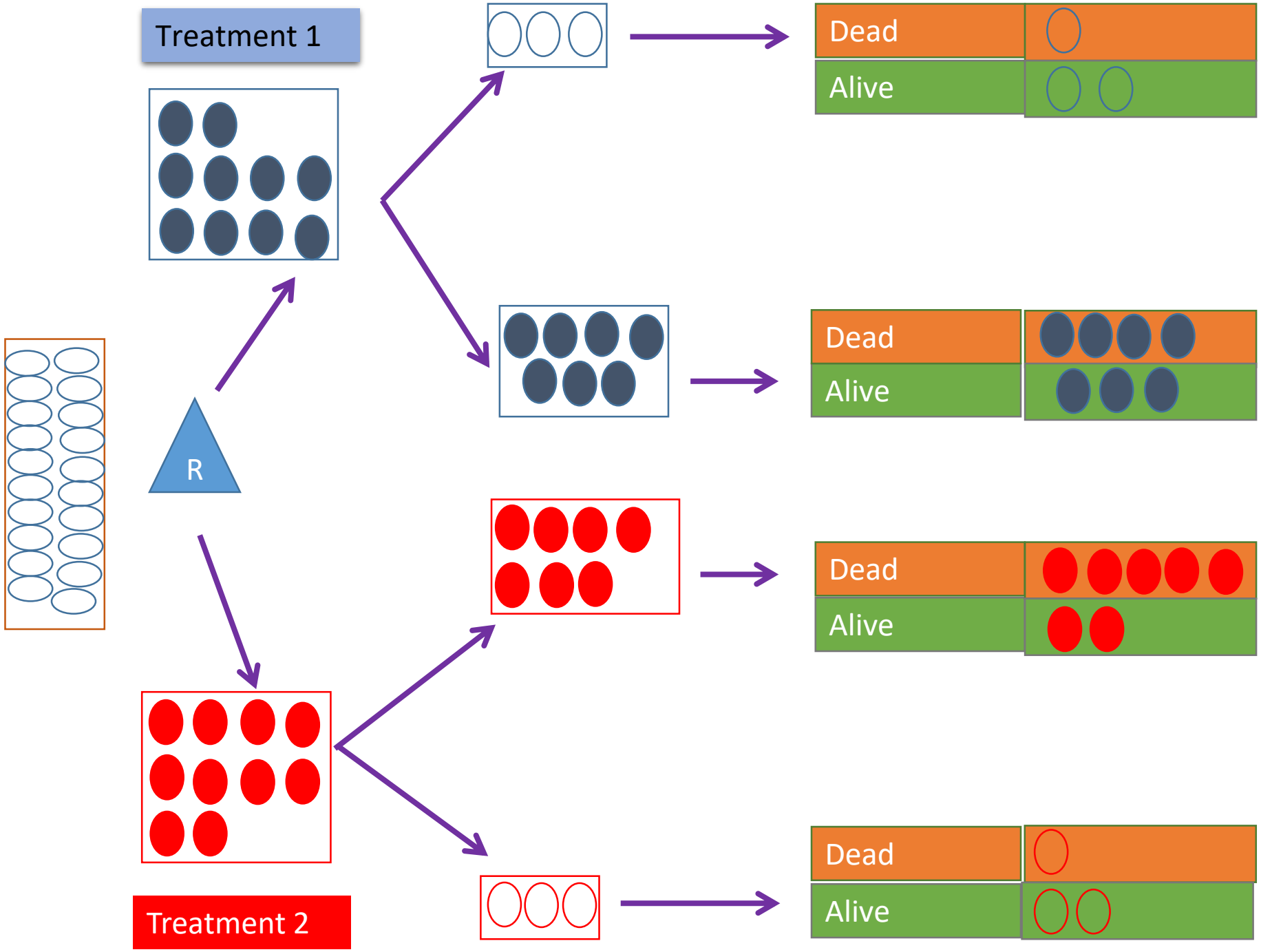
- The best solution is to assure a good follow up

Was follow up complete in the paper?

5 LOSS TO FOLLOW UP

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

INTENTION TO TREAT


Treatment 1
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Treatment 2
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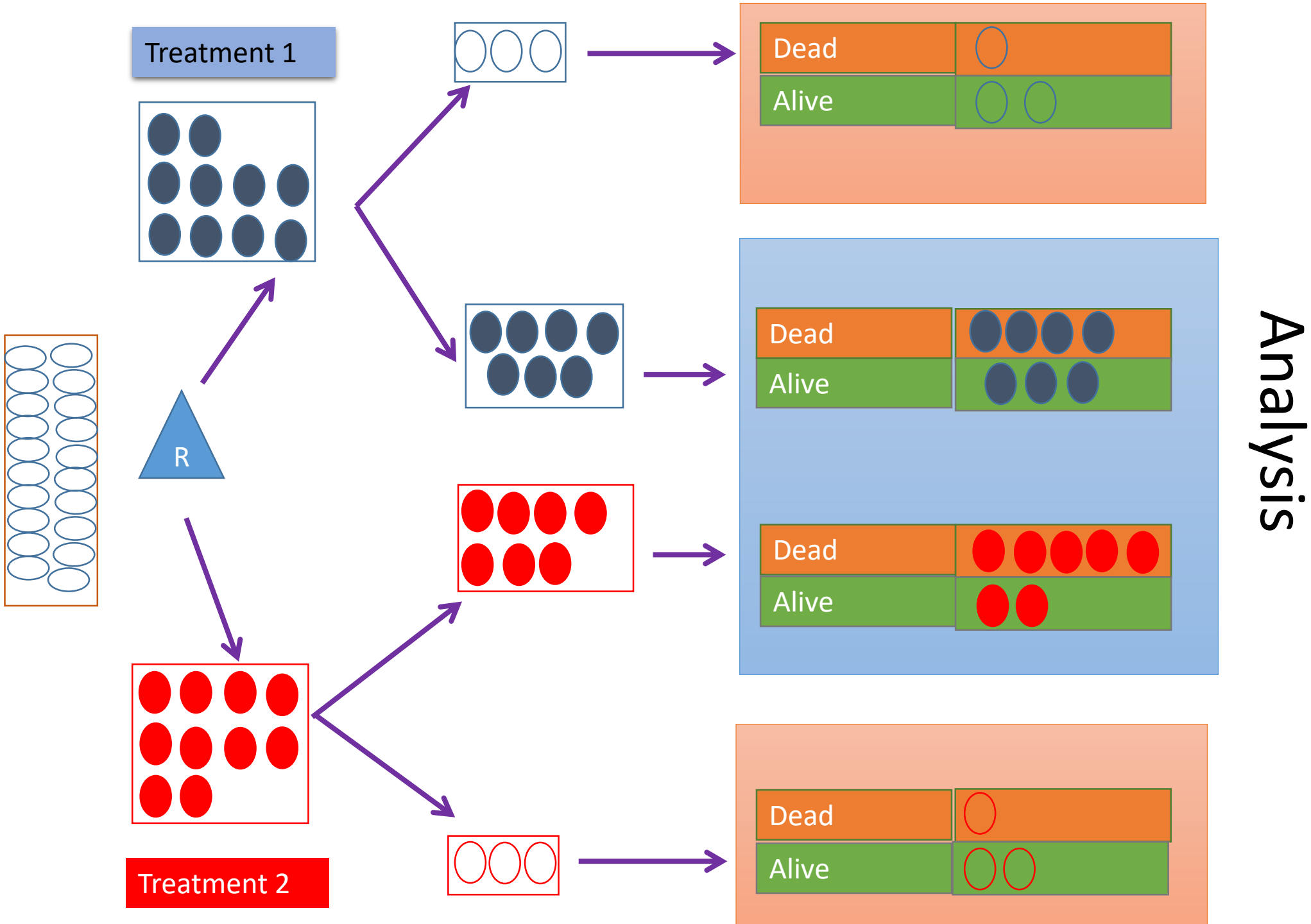
Alive
Dead
Alive
Dead
Alive
Dead
Alive


Treatment 1
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Treatment 2
Dead
Alive
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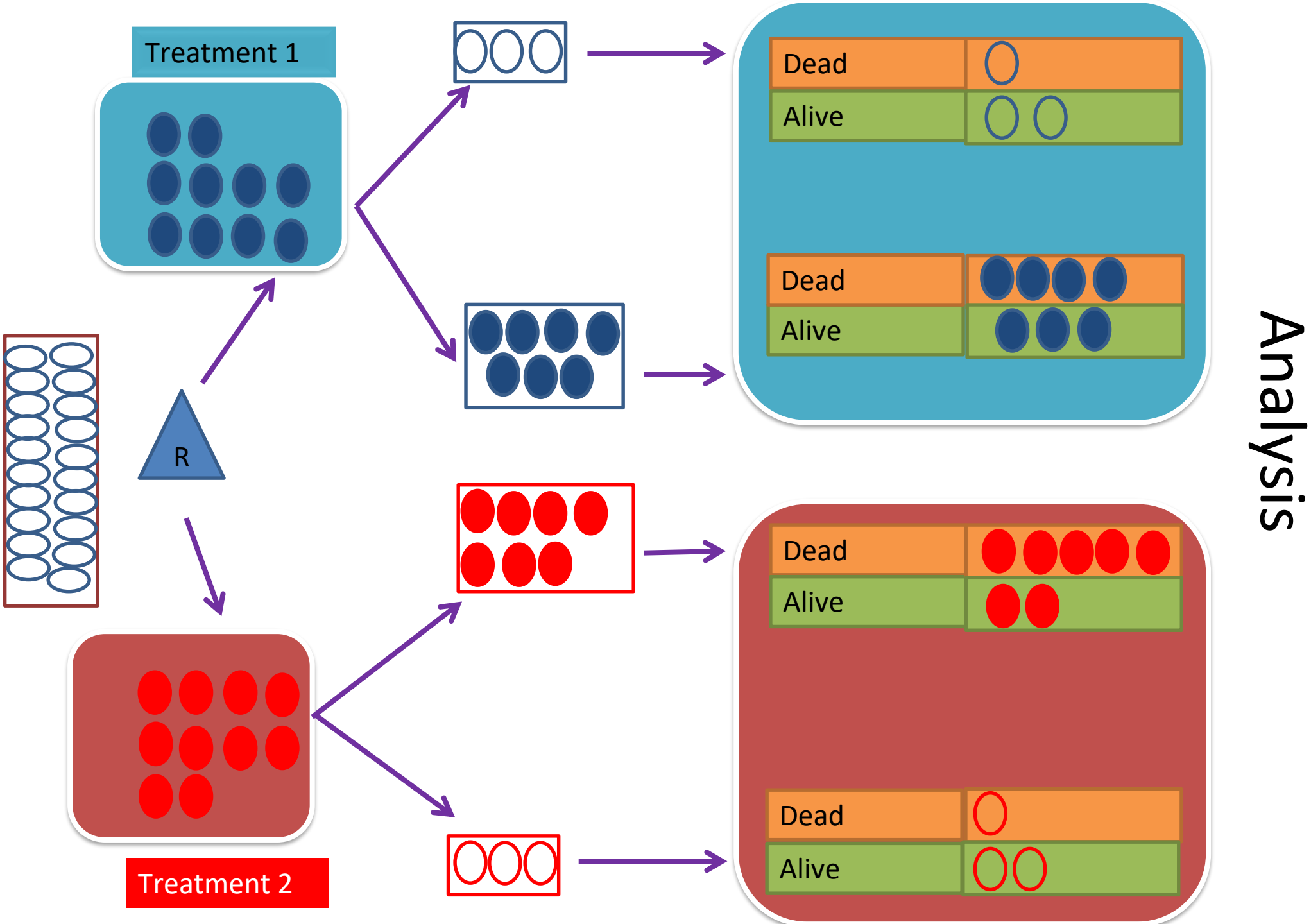
Alive
Dead
Alive
Analysis


Treatment 1
R
Treatment 2
Dead
Alive
Dead
Alive
Dead
Alive
Dead
Alive
Analysis

Intention-to-treat… Why??

- Preserves balance between the groups.
- Reflects real life.
- Provides a more conservative estimate of effect.

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

6 INTENTION TO TREAT

FIVE MINUTE STRETCH BREAK

Outline

- The Evidence Cycle
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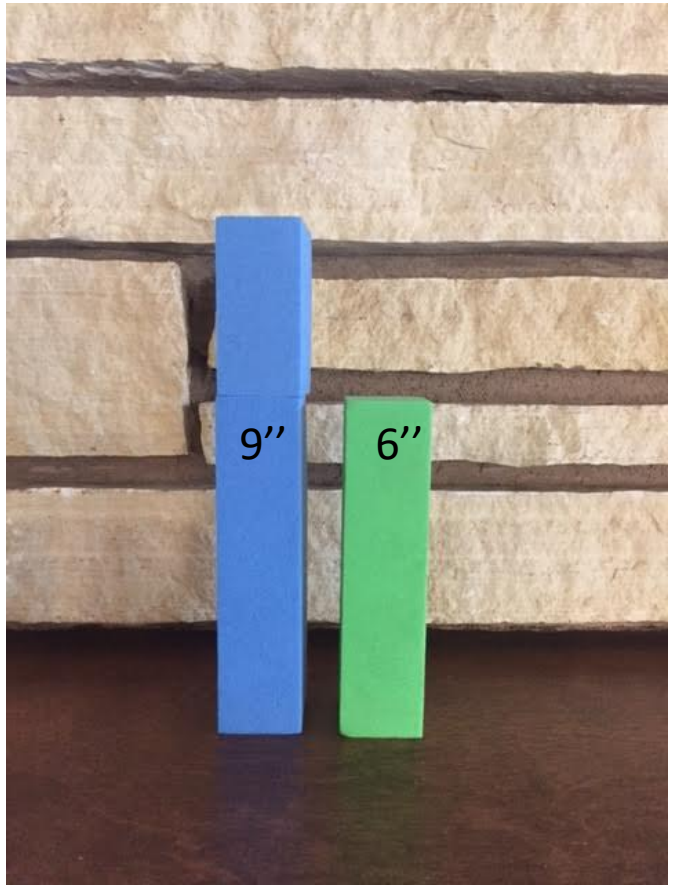
- MATH!
- Closing the case
- Take Home Points

Math!

Math!

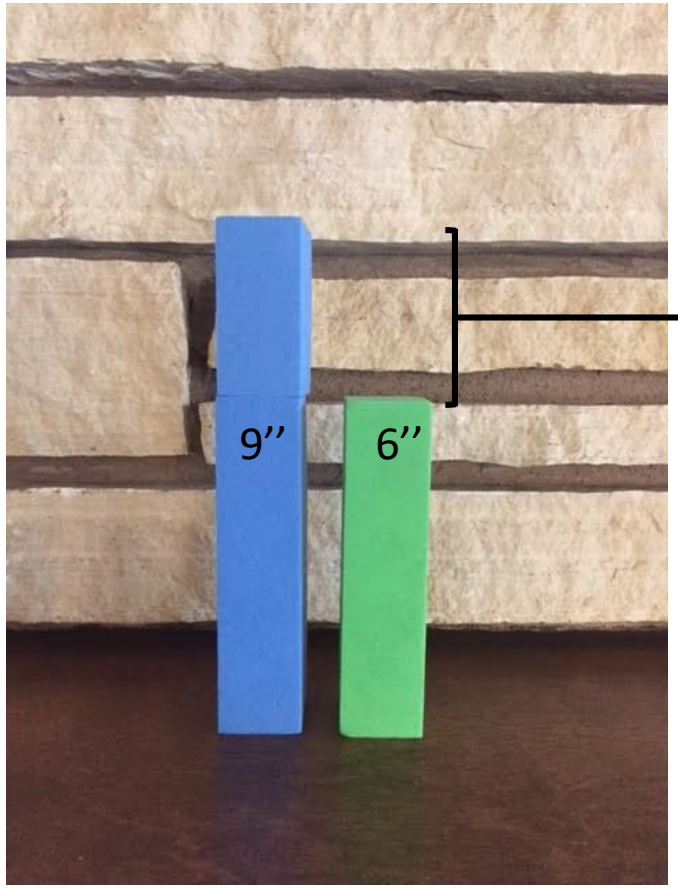


How can we compare the height?

+ ×

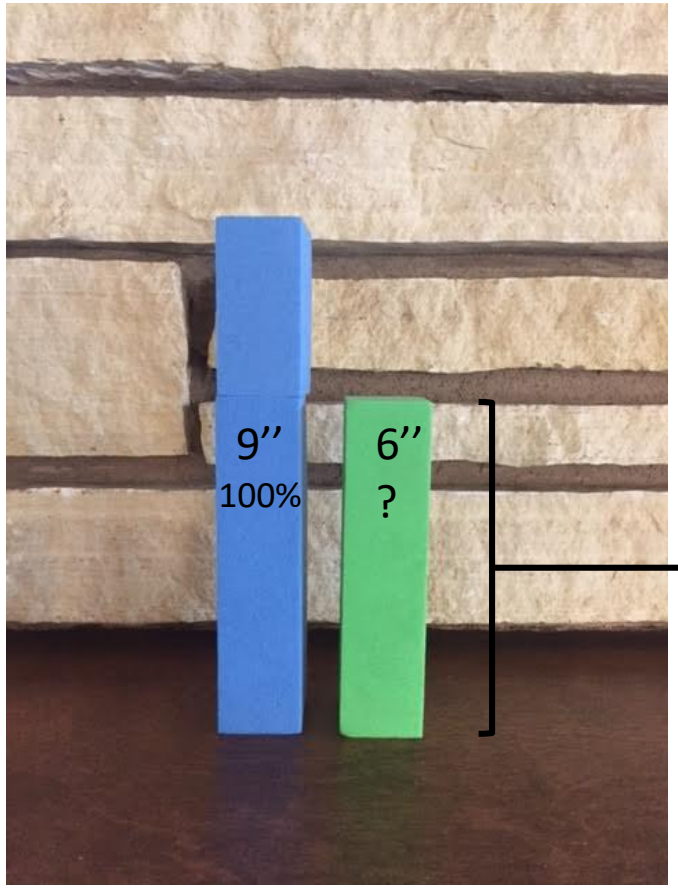
− ÷

Math!



Height Difference (subtraction) = 9’’ – 6’’ = 3’’

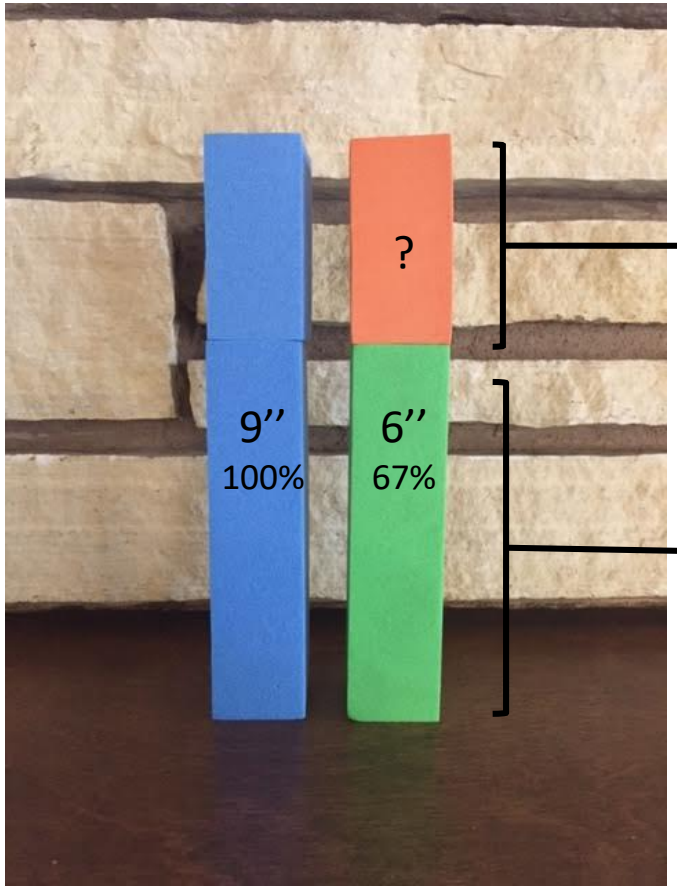
Math!



Relative height (ratio) = 6” : 9” = 0.667

66.7%

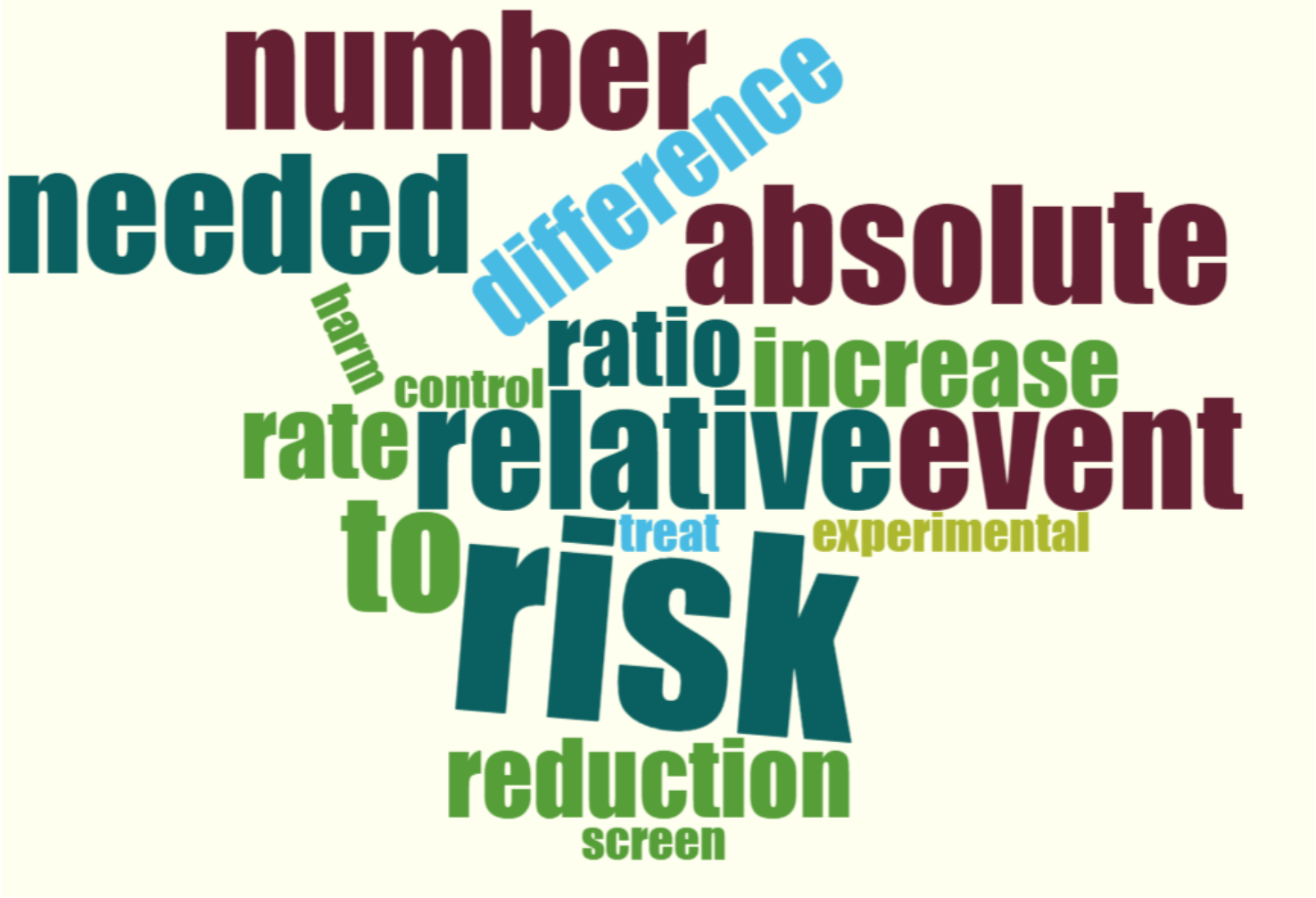
Math!



Risk
Relative ~~height~~ difference = 100% – RR = 33%
(ratio and subtraction!) 1 – 0.67 = 0.33

Risk
Relative ~~height~~ (ratio) = 6" : 9" = 0.667
66.7%

Math Summary



Math Summary

Results	Alternative name	Operation
Risk Difference		
Risk Ratio		
Relative Risk Difference		

Back to our paper

A randomised controlled trial of hot water (45° C) immersion versus ice packs for pain relief in bluebottle stings

Conrad Loten, Barrie Stokes, David Worsley, Jamie E Seymour, Simon Jiang and Geoffrey K Isbister

Thousands of bluebottle (*Physalia* sp.) stings occur each year in Australia.[1] Stings cause immediate, intense pain that usually resolves within an hour and is associated with a characteristic linear erythematous eruption (Box 1).[2] The first aid management of bluebottle stings is a daily problem for surf lifesavers. Currently, most first aid bodies, including the International Life Saving Federation,[3] recommend treatment by topical application of ice packs. There is little scientific evidence to support this,[2] and the only study to investigate ice packs was observational with no objective measure of pain, or control or comparator treatment.[4]

Many marine venoms are heat-labile in vitro.[5-8] It is feasible that heat penetrates the human dermis to the estimated depth that nematocysts inject toxins (100–1000 μm),[1] and recent clinical research suggests heat may be effective for treating jellyfish stings.[9,10] However, previous studies of heat therapy were small[10,11] or not randomised,[11,12] and only one was published in full.[12] A randomised controlled trial showed that, compared with ice packs, hot showers significantly reduced pain and treatment duration for bluebottle stings.[10]

If heat is to be used, it needs to be applied

ABSTRACT

Objective: To investigate the effectiveness of hot water immersion for the treatment of *Physalia* sp. (bluebottle or Portuguese Man-of-War) stings.

Design: Open-label, randomised comparison trial. Primary analysis was by intention to treat, with secondary analysis of nematocyst-confirmed stings. One halfway interim analysis was planned.

Setting: Surf lifesaving first aid facilities at two beaches in eastern Australia from 30 December 2003 to 5 March 2005.

Participants: 96 subjects presenting after swimming in the ocean for treatment of an apparent sting by a bluebottle.

Interventions: Hot water immersion (45° C) of the affected part versus ice pack application.

Main outcome measures: The primary outcome was a clinically important reduction in pain as measured by the visual analogue scale (VAS). Secondary outcomes were the development of regional or radiating pain, frequency of systemic symptoms, and proportion with pruritus or rash on follow-up.

Results: 49 patients received hot water immersion and 47 received ice packs. The two groups had similar baseline features, except patients treated with hot water had more severe initial pain (VAS [mean ± SD]: 54 ± 22 mm versus 42 ± 22 mm). After 10 minutes, 53% of the hot water group reported less pain versus 32% treated with ice (21%; 95% CI, 1%–39%; $P = 0.039$). After 20 minutes, 87% of the hot water group reported less pain versus 33% treated with ice (54%; 95% CI, 35%–69%; $P = 0.002$). The trial was stopped after the halfway interim analysis because hot water immersion was shown to be effective ($P = 0.002$). Hot water was more effective at 20 minutes in nematocyst-confirmed stings (95% versus 29%; $P = 0.002$). Radiating pain occurred less with hot water (10% versus 30%; $P = 0.039$). Systemic effects were uncommon in both groups.

Conclusions: Immersion in water at 45° C for 20 minutes is an effective and practical treatment for pain from bluebottle stings.

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Executive Teaching Decision

- Because of something we learned last year…
- Let’s look at one of the secondary outcomes instead of the primary outcome.
- Box 7 on page 332.

Results: Radiating Pain

7 Secondary outcomes at initial treatment and at 24-hour follow-up

	Hot water immersion		Ice packs	
	n/N	% (95% CI)	*n/N*	% (95% CI)
Clinical effects				
Pain radiating	5/49	10% (4%–22%)	14/47	30% (17%–45%)
Generalised pain	1/49	2% (0–11%)	3/47	6% (1%–18%)
Nausea/vomiting	2/49	4% (1%–14%)	5/47	11% (4%–23%)
Crossed over to other treatment*	5/45	11% (4%–24%)	11/43	26% (14%–41%)
Follow-up				
Itchiness (24 hours or later)	18/42	43% (28%–59%)	17/41	41% (26%–58%)
Red mark or minor rash	18/42	43% (28%–59%)	17/41	41% (26%–58%)
Raised and red/wheal reaction	8/42	19% (10%–33%)	11/41	27% (14%–43%)
Bullous reaction	1/42	3% (0–13%)	1/41	2% (0–13%)

* Four patients in each group did not remain for 20 minutes (after which crossover was offered). Thirteen patients could not be contacted for follow-up.

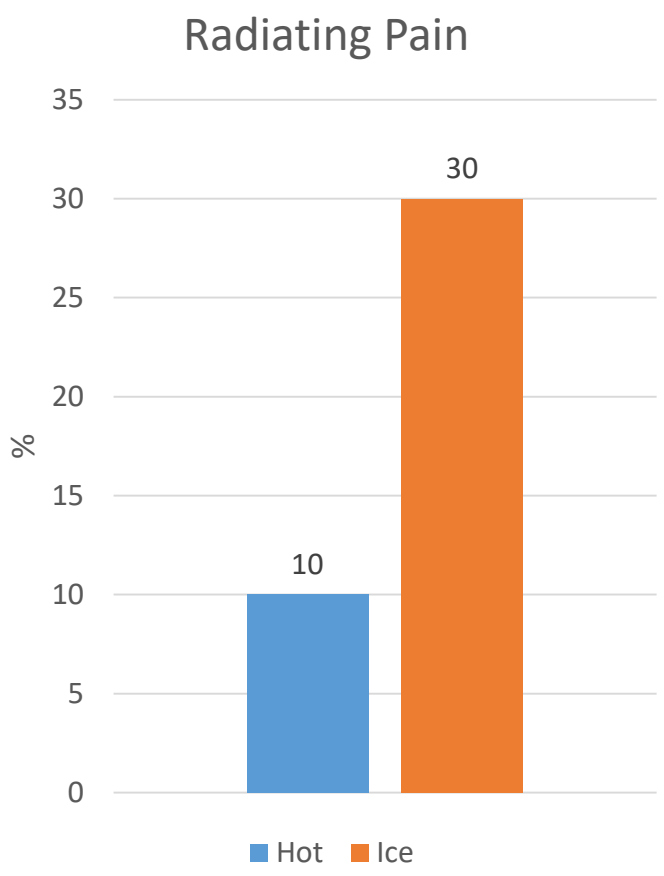
Radiating Pain

	Yes	No	Risk (%)
Hot water			
Ice packs			

Radiating Pain

	Yes	No	Risk
Hot water	5	44	5/49 ~ 10%
Ice packs	14	33	14/47 ~ 30%

Math!



Radiating Pain:

Absolute Risk Difference:

$Risk_{con} – Risk_{exp}$

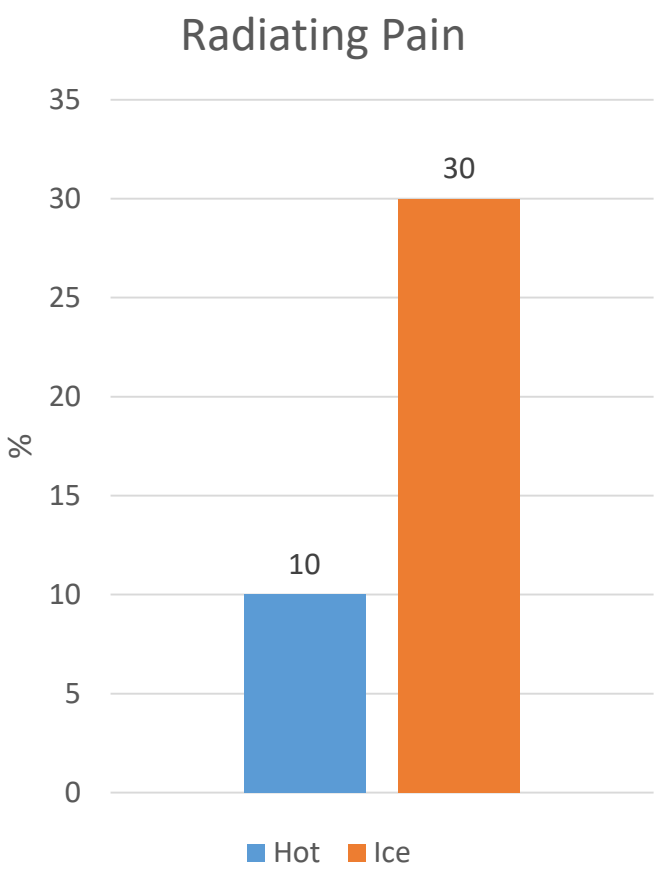
Relative Risk:

$Risk_{exp} : Risk_{con}$

Relative Risk Reduction:

1 – RR =

Math!

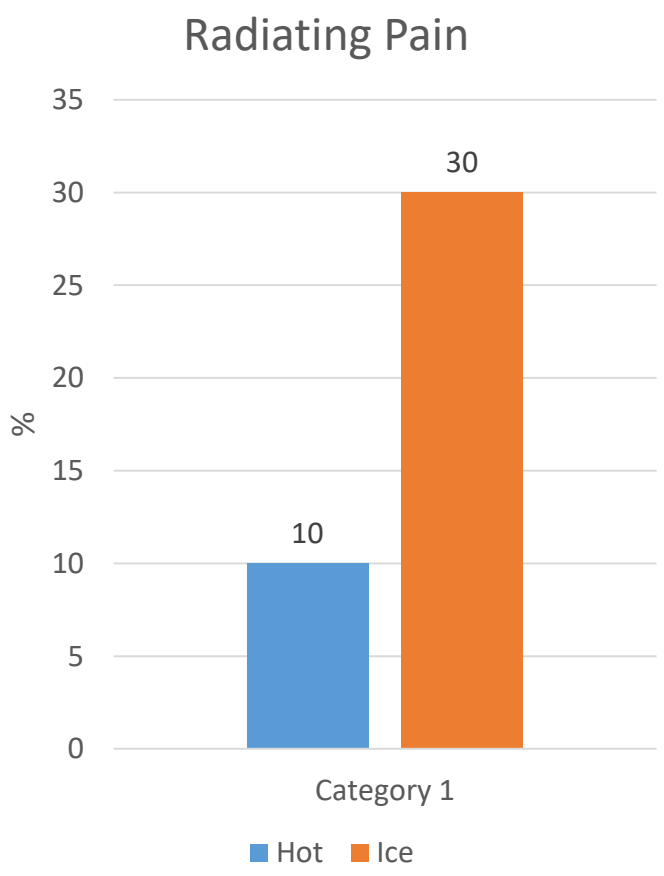


Number needed to treat

How many patients do I need to treat to obtain / prevent one extra outcome *in the study period*.

Number needed to treat = 100% / Risk difference (%)

Math!



Radiating Pain:

Absolute Risk Difference: 30% - 10% = 20%

Relative Risk: 10% : 30% = 0.33

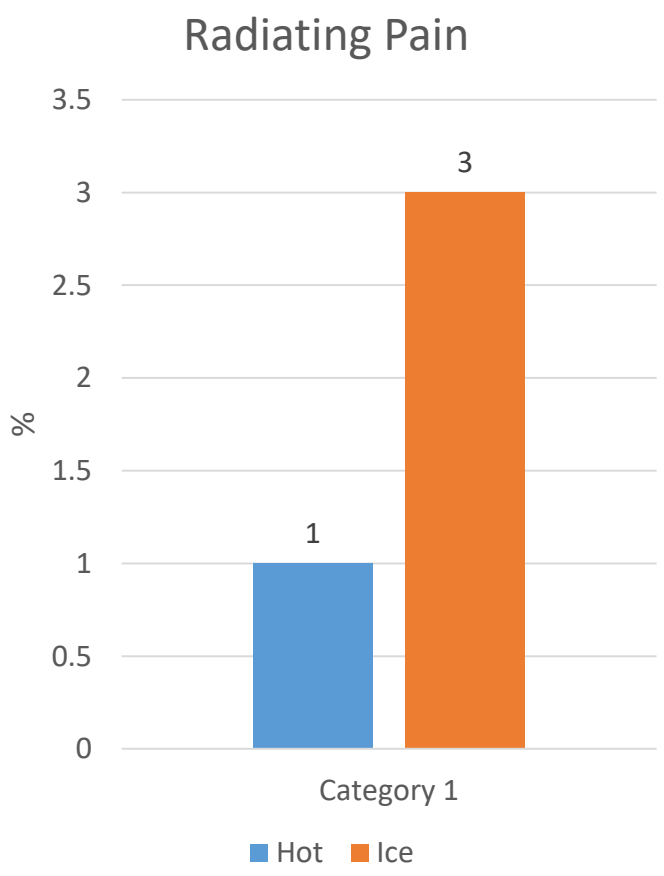
Relative Risk Difference: 1 – 0.33 = 0.67

Number needed to treat = 100% / Risk difference

Number needed to treat = 100% / 20% = 5

Usual stumbling block: absolute differences are usually smaller than relative differences

What if?



Risk Difference: 3% - 1% = 2%

Relative Risk: 1% : 3% = 0.33

Relative Risk Difference: 1 – 0.33 = 0.67

Number needed to treat = 100 / Risk difference

Number needed to treat = 100 %/ 2% = 50

Done with the math

Outline

- The Evidence Cycle
- Case Scenario
- RCT appraisal
  - Did the groups start with a similar prognosis?
  - Did we maintain the similarities?
  - What are the outcomes?
- MATH!
- Closing the case
- Take Home Points

Case Resolution

- Pain was significantly better with hot water
- Martin decided never to go back to Hawaii
- He moved with his family to Orlando instead

Take-home points

- EBM should be focused on our clinical questions about patients or populations
- Failure to do **allocation concealment** can overestimate the effect size and can be a major source of bias
- For “regular” therapy papers, ITT is preferred to per-protocol analysis
- Don’t be blinded by blinding!
- Make the math simple! Remember to subtract and divide!

Teaching Take-home Points

What strategies did we use to teach these concepts?

Teaching Take-home Points

- Real clinical case – make it applicable!
- Clinical question relevant to different specialties, and even non-medical learners
- Group activities
- Pre-mark article – saves time; reduces stress
- Imperfect articles (you *can* teach with them)
- Interactivity
- Different teaching strategies (visual learners, math lovers)
- Simplicity: one step at a time, with “no man left behind”
- Triage: you can’t do it all

Questions?