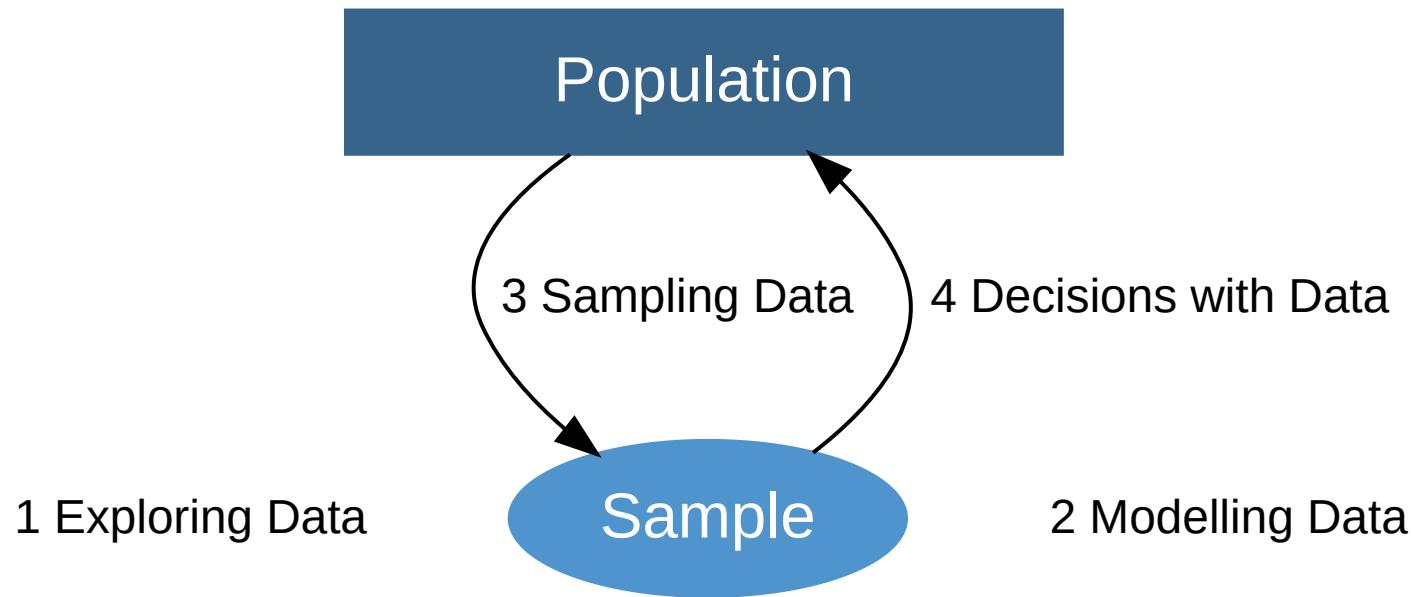


Controlled Experiments

Exploring Data | Design of Experiments

Unit Overview





Module1 Exploring Data

Design of Experiments

Where did the data come from & can we make reliable conclusions?

Data & Graphical Summaries

What type of data do we have & how can we visualise it?

Numerical Summaries

What are the main features of the data?



Controlled Experiments

Data Story | Does an anti-acne drug cause depression?

Domain Knowledge

Types of Evidence

Design of the Study

The Method of Comparison

Three Potential Confounders

RCT Trial for Roaccutane

Summary

Data Story

Does an anti-acne drug cause depression?

“Should I take Roaccutane?”

This question was posted on an online medical forum.

 24 Users in this discussion +30 following

[Follow this discussion](#) 


Rafapk4
48 points

I want to take roaccutane but
im afraid of it's side effects or
of acne coming back
afterwards! Help

Posted 3 years ago

Hello, im new in this page and im doing this from my phone but im really desperate and i need help. I am 15 years old and i want to take roaccutane. My mom tells me she doesnt want me to take it because she's afraid of the side effects but i am desperate for a solution. I do not have sever acne but im right there in the path to it. I have a lot of whitespots and everyweek two to five new HUGE pimples appear in my face and most of my face is red. I have tried everything and have wasted thousands of dollars in treatments, natural or not. I have even tried minocycline but it did not work on me! Im currently going to 10th grade and i have had acne since 7th grade!! My acne is starting to spread to my back and my chest and you can see some of it going for my arms too. I am bullied at school because of my acne and I have days I dont even want to go to school but I have never suffered of depression or anything like it. I am the only one in my grade to have acne along with another girl so i want the quickest solution out there but Roaccutane seems very risky but I feel it has more pros than cons. Girls think that my acne is disgusting and that really kills my morale and I am even ashamed of being close to people or taking selfies. When i look myself in the mirror I hate my face so much!!! Should I take roaccutane?? I really want to but im looking for others opinions please help me!

 Report this  2

Prevalance of acne for Australian teenagers

2.3.2.1 Prevalence Estimates in Adolescents

For instance, to consider first, the Kilkenny study [1998] of adolescents, the prevalence of students with cysts to age 18 approached 2.5%¹. In Australian youths surveyed at schools in Victoria, the prevalence rates for all acne forms were about 27.7% (10 to 12 year olds) to 93.3% in 16 to 18 year olds [Kilkenny et al., 1998] (Table 2). The prevalence of moderate to severe acne was 24% in males and 11% in females.

Table 2 Prevalence of Different Components of Acne by Age in Australian School Children*

Age Groups	N	Papules/Pustules % (95% CI)	Cysts or Nodules % (95% CI)	Acne Scars % (95% CI)
10-12 years	636	19.9 (13.6-26.2)	0.17 (0-1.0)	1.2 (0.4-2.1)
13-15 years	539	64.7 (58.3-71.0)	1.60 (0.6-4.0)	11.6 (7.5-15.7)
16-18 years	266	80.7 (74.6-86.9)	2.56 (1.8-5.3)	26.1 (19.1-33.1)

*Adapted (corrected decimal point) from Kilkenny et al., 1998.

News articles about Roaccutane

We might google for more information on side effects.

BBC NEWS

Watch One-Minute World News

News services Your news when you want it

Last Updated: Tuesday, 19 September 2006, 09:14 GMT 10:14 UK

E-mail this to a friend | Printable version

Acne drug 'linked to depression'

A popular treatment for severe acne has been found to produce depressive behaviour in mice.

University of Bath scientists tested Roaccutane after claims it has caused depression and suicide in patients since its introduction in 1982.

Their work, published in the journal *Neuropsychopharmacology*, is the first to back up these reports with firm scientific evidence.

The drug's maker, Roche, does include a warning about depression in packets.

The drug is highly effective acne treatment

SEE ALSO

- Acne drug 'should be banned' 17 May 02 | Health
- Acne 09 Mar 06 | Medical notes

RELATED INTERNET LINKS

- University of Bath
- Neuropsychopharmacology
- Roche UK

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TOP HEALTH STORIES

- Stem cell method put to the test
- Hospitals 'eyeing private market'
- Low vitamin D 'Parkinson's link'

| News feeds



BEAUTY

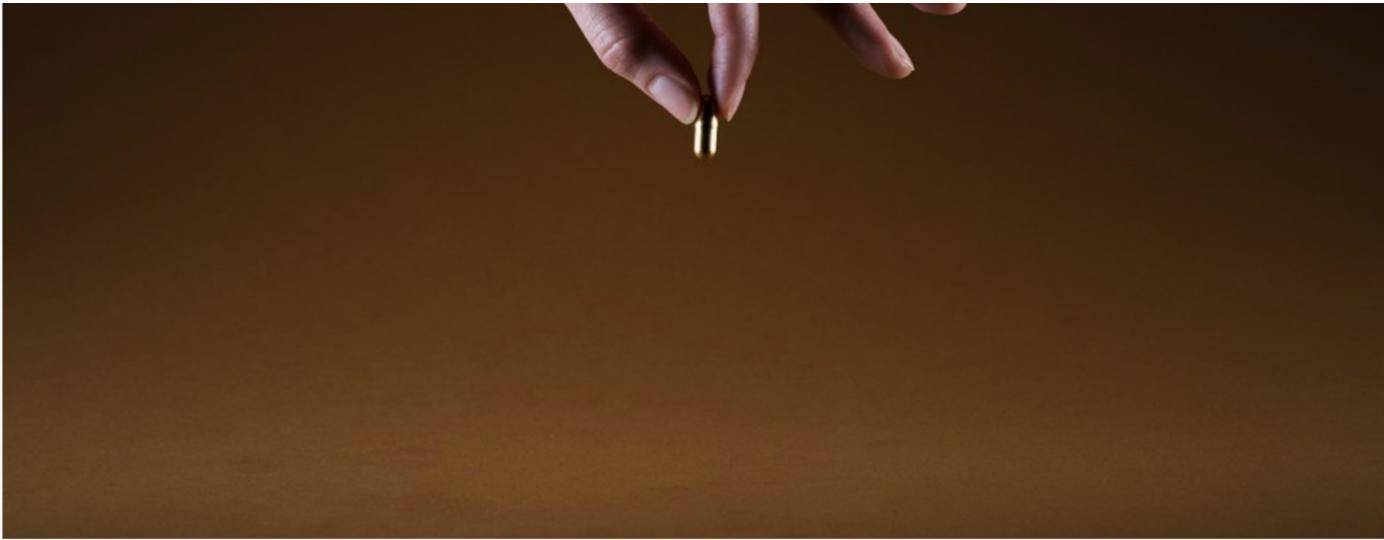
"MIRACLE" PILL THOUSANDS OF WOMEN ARE PRESCRIBED FOR ACNE IS HAVING DEVASTATING EFFECTS ON THEIR SEX LIVES...

"My sex life ground to a halt - it took years for it to stop being painful".

By: Polly Dunbar November 2, 2015 4:08pm



 Cosmopolitan



Katie Martin / Emily Jan / The Atlantic

The Scorched-Earth Acne Solution

Isotretinoin, better known as Accutane, is the acne drug of last resort. It let me shed my skin—literally—for the price of some gnarly side effects.

EMILY GOLDBERG | FEB 13, 2017 | HEALTH

 The Atlantic

ACNE DRUG DEATH Family claim son killed himself after controversial acne drug Roaccutane 'changed his personality'

Heartbroken parents of 21-year-old said he became 'irrational' and 'lethargic' after taking drug linked to 20 suicides in just two years

By Tom Gillespie

2nd May 2017, 8:46 am | Updated: 2nd May 2017, 10:10 am



1 COMMENTS

THE devastated family of a young man who was found dead have claimed his "personality changed" when he started taking a controversial acne drug.

Robert and Becky Reeves have said their tragic son Luke, 21, became "irrational" after he took Roaccutane – a drug previously linked to 20 suicides in just two years.

MOST POPULAR



LIVE BLOG

ROYAL MEETING Prince Philip to stand down from Royal duties LIVE – latest news and updates



The Sun



Statistical Thinking

- If you had very bad acne, would you take Roaccutane?
- Would the articles affect your decision?

Domain knowledge

What do we know about Roaccutane?

-  **Domain knowledge** is background context information that helps you to understand the data.
- Data Scientists need an interest and curiosity in whatever area is being investigated, and good collaboration skills.
- Sometimes a data scientist ends up specialising in one field, and so becomes a domain expert.

Questions on Roaccutane might include:

- What is Roaccutane prescribed for and how does it chemically work?
- What are known side affects?
- What other drugs are prescribed for acne?

Domain knowledge on Roaccutane



From the BBC article, Roaccutane:

- belongs to a group of medicines called **retinoids** (vitamin A-related compounds) known to affect development of the nervous system;
- is usually only prescribed to teenagers with particularly severe cystic acne;
- is highly effective and has been used by approximately 13 million patients worldwide;
- has been involved in 1,588 reports of suspected adverse events, including 25 people who died from suicide.



Statistical Thinking

What questions do you still have about the drug?

- Do teenagers with severe acne suffer depression, or vice versa (psychosocial effects)?
- What were the 1,588 “reports” of “adverse events”?
- How does this rate of 25/13 million suicides compare to the rate of [2.4 per 100,000](#) for youth aged 5-17 in Australia in 2017?
- Why does Roche have a warning about depression on their Roaccutane packet?

Types of Evidence

Evidence about Roaccutane

- Each piece of evidence needs to be weighed up separately.
 - A personal testimony or observation can only suggest a more generalised finding.
 - The source(s) behind a media article are often poorly cited.
- In a reputable research journal, every stage of the statistical study (design, data collection, statistical methods, conclusion) should be documented and checked in the review process.
- Increasingly, journals are requiring **reproducible research**, which requires “data sets and software to be made available for verifying published findings and conducting alternative analyses”.

Design of the Study

Sources behind the BBC article

Press Release - 18 September 2006

Researchers establish scientific link between acne treatment and depression

A drug commonly used to treat severe acne can lead to depressive behaviour in mice, according to research published in the journal *Neuropsychopharmacology*.

Since the drug's introduction in the early 1980s there have been controversial reports of depression and suicidal behaviour that may have occurred in some people taking Roaccutane (Accutane in the US).

This has led to the drug's manufacturers, Roche, including a warning in the product information that taking the medication may cause depression, psychosis and suicidal behaviour.

However, the chemical mechanism by which this might happen has never been established.

In new independent research, scientists at the universities of Bath and Texas at Austin gave Roaccutane to mice over a period of six weeks, and then monitored the rodents' behaviour.

 Press Release  Research Paper

What do we know about the trial?



The Scientists at the University of Bath

- gave Roaccutane to young adult mice for a 6-week period and tested their response to stress in a range of laboratory assessments;
- found that mice on Roaccutane were less mobile, and interpreted this as a sign of depression.



Statistical Thinking

What questions do you have about the trial?

- Why did the University of Bath scientists test the drug on young adult mice?
- Is immobility to stress a measure of depression in mice?
- How big was the difference in mobility that they observed?
- If Roaccutane causes depression in mice, does that imply that it causes depression in people?

The method of comparison

Controlled experiment

- We want to study whether Roaccutane (“treatment”) causes depression/suicide (“response”).
- However, depression/suicide may be due to other health factors (variables).
- Hence, we conduct 2 parallel experiments which only differ in whether the treatment is administrated or not.
- This is called a **controlled experiment** - ie we **control** the effects of the other variables on the treatment.

■ The **Treatment Group** is given the new drug.

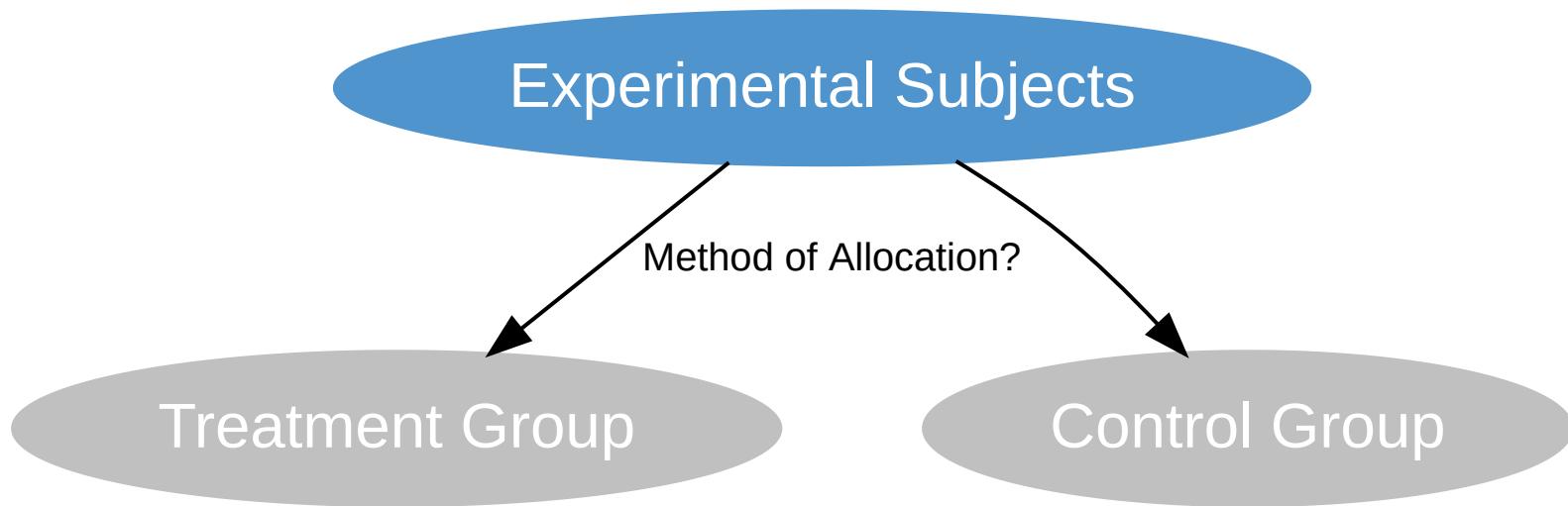
■ The **Control Group** is not given the new drug.

2 types of control

- There are 2 types of control, depending on the time of administering the control.
- **Contemporaneous** control groups are preferred to **Historical** control Groups.

- The **Contemporaneous control groups** occur at the same time as the treatment groups.
- **Historical control groups** occur earlier than treatment groups.

How to we allocate subjects into the 2 groups?



3 potential confounders

Confounding & Bias

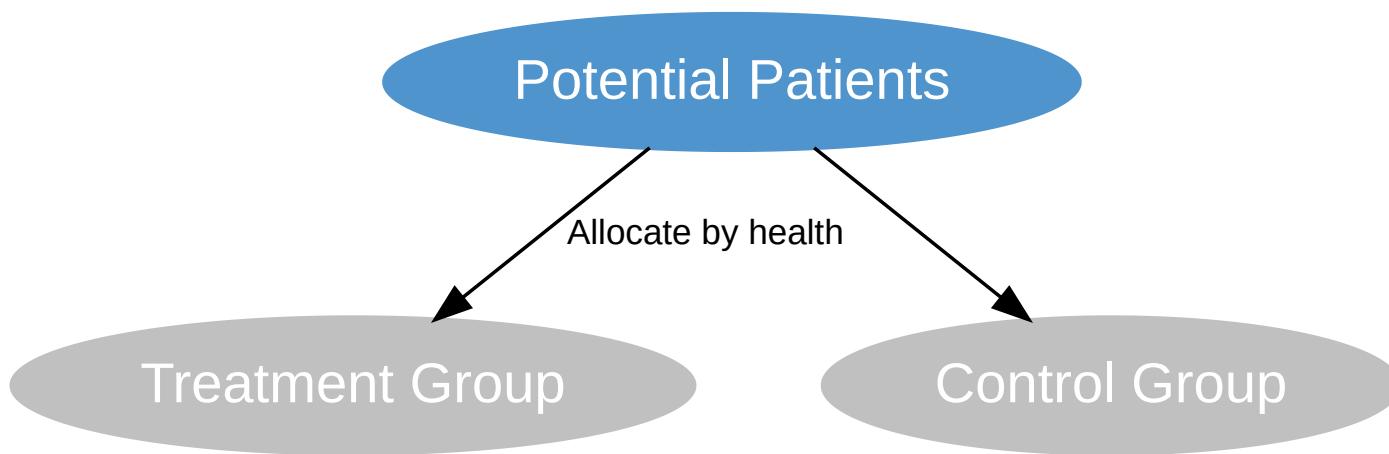
 **Confounding** is when the effect of 1 variable something mixes up with another variable, and hence causes confusion in interpretation.

Confounding can be caused by many type of bias, including selection, observer and consent.

 **Bias** is something which effects the ability of the data to accurately measure the treatment effect.

Problem1: Selection Bias

- If the Treatment Group is not comparable to the Control Group, then the differences between the 2 groups can **confound** the effect of the treatment.



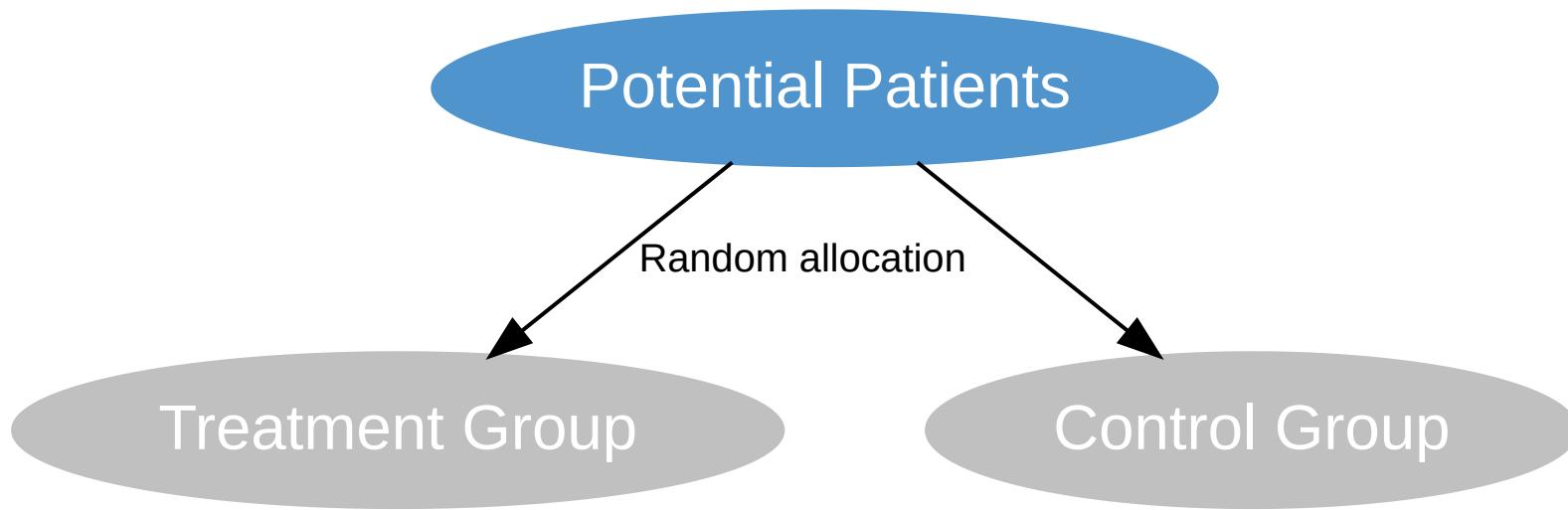
Example of selection bias

The portacaval shunt (1966)

- A portacaval shunt redirects the flow of blood in cases of cirrhosis of the liver. The operation is long and dangerous, but a [study in 1966](#) seemed to imply that it was worth the risk, given the increased life expectancy of patients, compared to those who didn't have the operation.
- However, the design of experiment was biased toward the operation, as healthier patients tended to have the surgery. Hence the increase in life expectancy may be due to healthier patients.
- In controlled experiments, if the assignment of subjects is based on an investigator's judgment, it is a non-randomised controlled experiment.

 [Recent Paper](#)

Solution1: Randomised Controlled Trial (RCT)

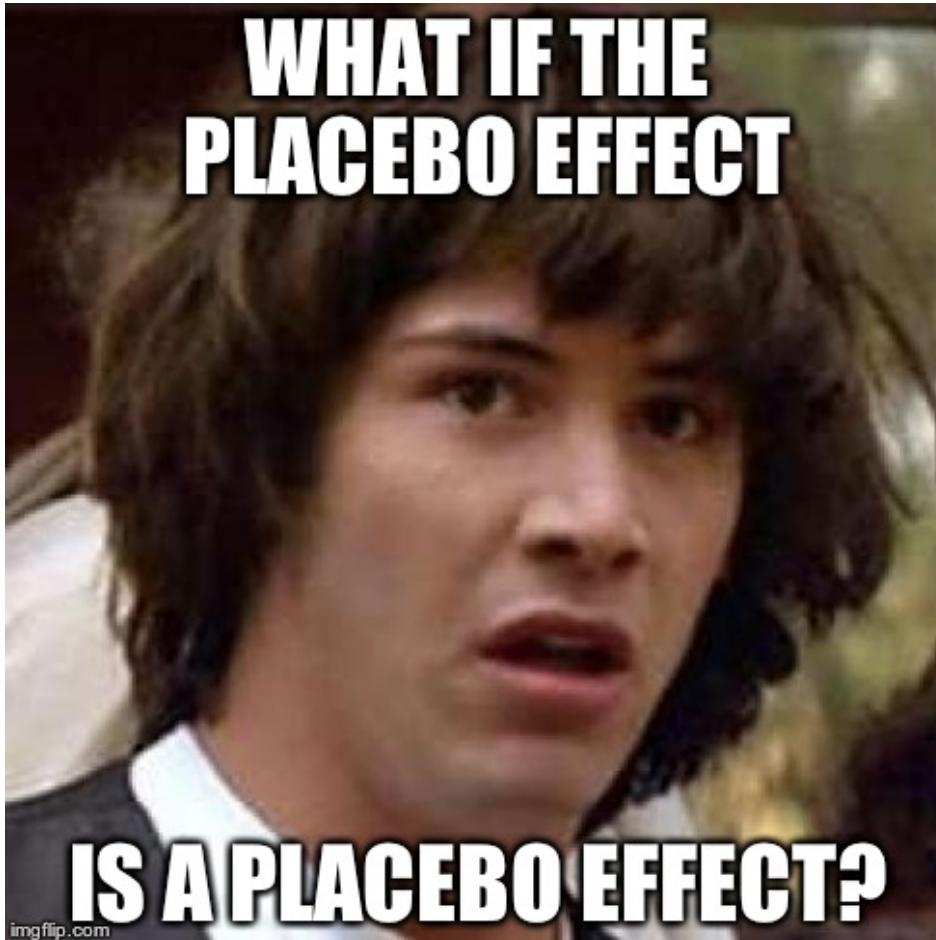


Problem2: Observer bias

- If the subjects or investigators are aware of the identity of the 2 groups, we can get **bias** in either the responses or evaluations, as they may deliberately or subconsciously report more or less favourable results.
- In fact, the subject may even respond to the idea of the treatment - this is called the **placebo effect**.

❑ The **placebo** is a pretend treatment. It is designed to be neutral and indistinguishable from the treatment.

❑ The **placebo effect** is an effect which occurs from the subject thinking they have had the treatment.



imgflip.com

Solution2: Randomised Controlled Double-Blind Trial

- We need to conduct a Randomised Controlled **Double-Blind** Trial where both the subjects (“single blind”) and investigators (“double blind”) are not aware of the identity of the 2 groups.
- In addition, the placebo should be designed to resemble the treatment as closely as possible.
- This allows the control of the patient’s expectations (ie their response) and the investigator’s observations (evaluation of response).

To do so we usually:

- Have a 3rd party administrator of the treatment and placebo.
- Design the placebo to mimic the treatment as much as possible.

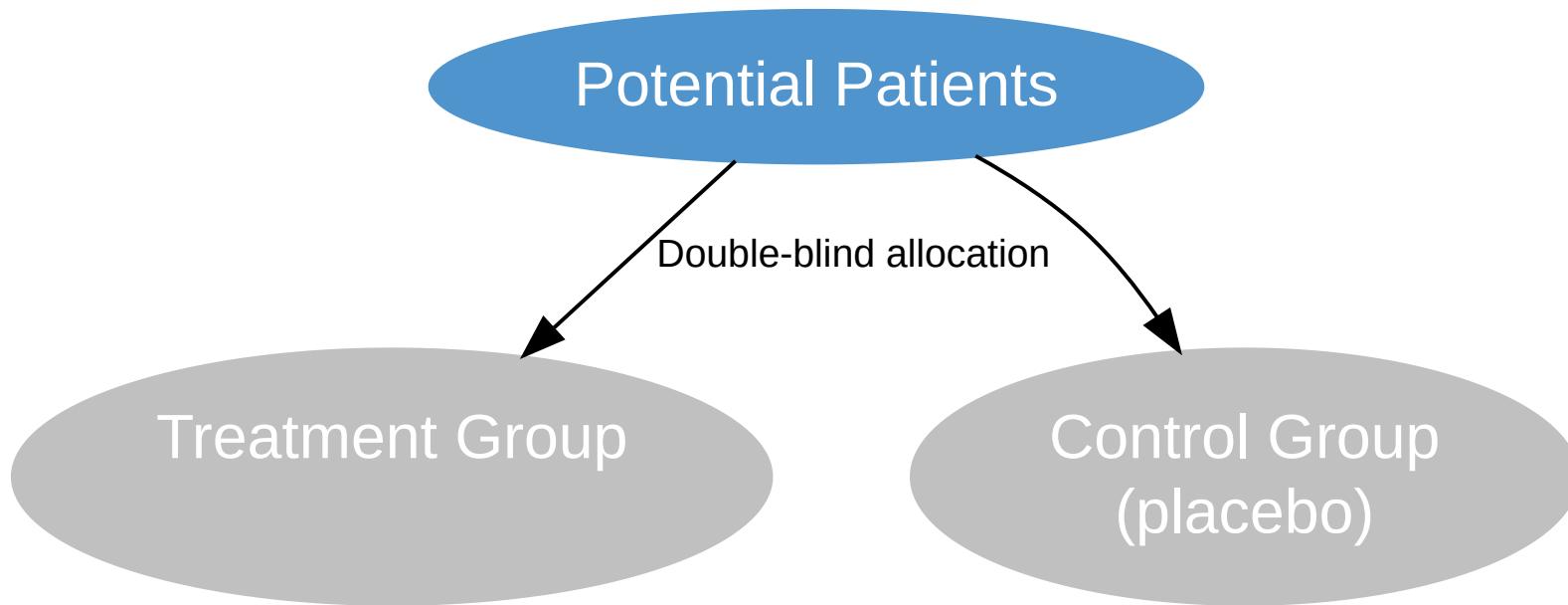
Problem3: Consent Bias

 **Consent bias** can occur when subjects choose whether or not they take part in the experiment.

This quickly raises many ethical questions.

- How can we avoid **consent bias**?
- Who determines who is part of each group?
- It may be unethical to withhold treatment for those in the control group or enforce treatment for those in the treatment group.

Summary: The best method of comparision



💬 Why is this the best design?



Statistical Thinking

Could the Roaccutane medical trial be designed as a randomised controlled double-blind experiment for teenagers?

For example: would it be ethical to randomly assign teenagers to either treatment or control (placebo)?

RCT Trial for Roaccutane

RCT Trial with 2 different brands of Roaccutane

A US study in 2013 was designed to determine the pharmacokinetics and bioequivalence of isotretinoin formulations (Roche & Dr Reddy's) after administration of single doses to normal, non-smoking, healthy males under fed conditions.

Study Type [1](#) : Interventional (Clinical Trial)
Actual Enrollment [1](#) : 26 participants
Allocation: Randomized
Intervention Model: Crossover Assignment
Masking: None (Open Label)
Primary Purpose: Treatment
Official Title: An Open Label, Randomized, Single Dose, Oral Bioequivalence Study of Isotretinoin Capsules 40 mg of Dr. Reddy's Laboratories Limited, India Comparing With That of ACCUTANE® Capsules 40 mg of Roche Laboratories Inc., Under Fed Conditions
Study Start Date [1](#) : May 2001
Primary Completion Date [1](#) : May 2001
Study Completion Date [1](#) : June 2001

 US Clinical Trials

Example of Data

The trial data was not available, so this is just for illustration.

```
data=read.csv("data/UStrial.csv")
dim(data)
```

```
## [1] 26 22
```

```
names(data)
```

```
## [1] "Subject.ID"      "Group"        "Pre.dose"      "X0.5.hours"   "X1.hour"
## [6] "X1.5.hour"       "X2.hours"     "X2.5.hours"   "X3.hours"     "X4.hours"
## [11] "X5.hours"        "X6.hours"     "X7.hours"     "X8.hours"     "X11.hours"
## [16] "X14.hours"       "X18.hours"    "X24.hours"    "X36.hours"    "X48.hours"
## [21] "X72.hours"       "X96.hours"
```

```
head(data,4)
```

```
##   Subject.ID Group Pre.dose X0.5.hours X1.hour X1.5.hour X2.hours X2.5.hours
## 1          1     T      1.2       1.6      1.8      1.9      1.6      2.2
## 2          2     T      1.4       2.0      2.2      2.2      2.6      3.0
## 3          3     T      1.5       1.6      1.3      1.0      1.4      1.9
## 4          4     T      1.6       2.0      1.8      2.2      2.7      2.7
##   X3.hours X4.hours X5.hours X6.hours X7.hours X8.hours X11.hours X14.hours
## 1      2.7     3.2     3.8     3.9     3.7     3.9     4.0     3.9
## 2      2.8     2.7     2.8     2.5     2.7     3.2     3.4     3.5
## 3      1.9     2.2     2.6     2.6     2.4     2.3     2.8     2.9
## 4      2.8     3.2     3.8     4.0     3.8     4.3     4.7     4.5
##   X18.hours X24.hours X36.hours X48.hours X72.hours X96.hours
## 1      3.9     4.0     3.9     4.2     4.5     4.2
## 2      3.9     3.6     3.6     3.5     3.6     3.9
## 3      3.2     3.3     3.3     3.0     3.3     3.6
## 4      5.0     4.7     4.5     4.3     4.4     4.1
```

Research continues

[J Clin Psychiatry](#). Author manuscript; available in PMC 2012 Feb 10.

PMCID: PMC3276716

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[J Clin Psychiatry. 2012 Jan; 73\(1\): 37–50.](#)

Published online 2011 Aug 23. doi: [10.4088/JCP.10r05993](https://doi.org/10.4088/JCP.10r05993)

Retinoic Acid and Affective Disorders: The Evidence for an Association

[J Douglas Bremner](#),¹ [Kirsty Shearer](#),² and [Peter McCaffery](#)²

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The publisher's final edited version of this article is available at [J Clin Psychiatry](#)

See other articles in PMC that [cite](#) the published article.

Abstract

Go to:

Objective

Isotretinoin (13-*cis*-retinoic acid, or 13-*cis*-RA) (Accutane), approved by the FDA for the treatment of acne, carries a black box warning related to the risk of depression, suicide, and psychosis. Retinoic acid (RA), the active form of vitamin A, regulates gene expression in the brain, and isotretinoin is its 13-*cis* isomer. Retinoids represent a group of compounds derived from vitamin A that perform a large variety of functions in many systems, in particular the CNS, and abnormal retinoid levels can have neurological effects. Although infrequent, proper recognition and treatment of psychiatric side effects in acne patients is critical given the risk of death and disability. This paper reviews the evidence for a relationship between isotretinoin, depression and suicidality.

Limitations to studies so far

"Studies performed to date have had limitations, including

- the use of retrospective databases with insufficient information,
- the lack of sufficient sample size to determine whether an effect on depression exists,
- lack of placebo controls and randomization, the lack of specific standardized assessments of depression and other behaviors.

Large placebo controlled trials assessing the effects of isotretinoin on depression would be a scientific advance, however the ethics of conducting such a trial when there is adequate aggregate information supporting a causal role of isotretinoin in the development of depression in some individuals, given the risks of the drug, is questionable."

 Journal of Clinical Psychiatry

Summary

The design of a statistical study is critical in order to obtain results that can be generalised. The best method for comparison is a controlled randomised double-blind trial, but this is often not possible.

Key Words

domain knowledge, psychosocial effects, evidence, reproducible research, treatment, control, placebo, confounding, historical control, contemporaneous control, bias, consent, randomised controlled trial, double-blind

Further Thinking

 RCT

Esther Duflo
Social experiments to fight poverty

