

BIOE 301: Lecture 21

Diffusion of Technology and Historical Precedents for Regulation

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April 9, 2008

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Review from Last Time

Errors Found in Clinical Trials

- Type I Error: (False Positive)
 - Mistakenly conclude there is a difference between the control and test groups, when in reality there is no difference
 - p-value = probability of making type I error
- Type II Error: (False Negative)
 - Mistakenly conclude that there is not a difference between the two groups, when in reality there is a difference
 - Beta = probability of making type II error

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Review from Last Time

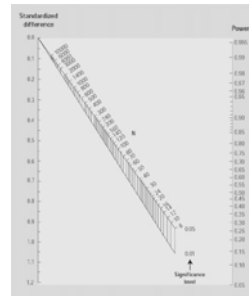
Sample Size Calculations

- Ensure differences between treatment & control group are real
- Choose our sample size:
 - Acceptable likelihood of Type I or II error
 - Enough \$\$ to carry out the trial

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Review from Last Time

Sample Size Calculations



Standardized Difference

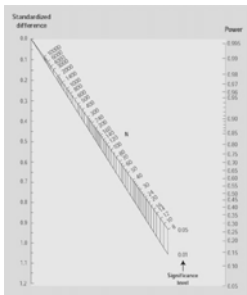
$$= \frac{(P_1 - P_2)}{\sqrt{p(1-p)}}$$

$$\bar{p} = \frac{P_1 + P_2}{2}$$

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Sample Size Calculations



Standardized Difference

$$= \frac{(P_1 - P_2)}{\sqrt{p(1-p)}}$$

Power

$$= 1 - \beta$$

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Sample Size Calculations: New Example

$$\text{Standardized Difference} = \frac{(P_1 - P_2)}{\sqrt{p(1-p)}}$$

$$\bar{p} = \frac{P_1 + P_2}{2}$$

$$\text{Power} = 1 - \beta$$

- Barrett's esophagus patients who present with cancer last 15 years

- Control group: Endoscopic surveillance every 1-3 years
- Test group: Prior laser ablation of Barrett's segment

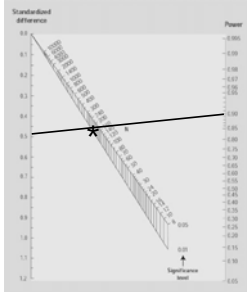
Control group: 50%
Test group: 25%

p-value = .01
Beta = .1

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Review from Last Time

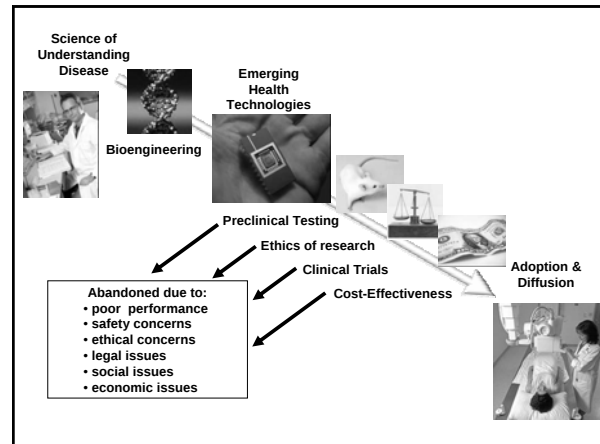
Sample Size Calculations: New Example Solution



$$\text{Standardized Difference} = \frac{(.5 - .25)}{\sqrt{0.375(1 - 0.375)}} = 0.516$$

$$\text{Power} = 1 - 0.1 = 0.9$$

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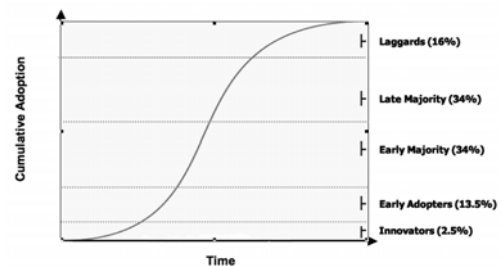


Agenda

- What is technology diffusion? Why is it important?
- Devices: Technology diffusion can happen quickly if the right regulations and resources are in place
- Drugs: Historically, slow diffusion and tragedy is what led to better regulation of drugs and devices

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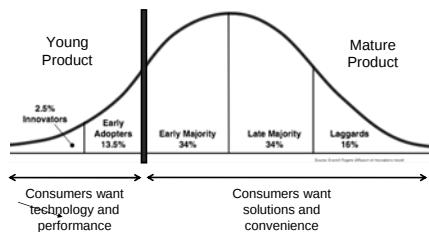
What is Technology Diffusion?



Garrity et al. J Med Internet Res 2006;8(2):e7

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How is Technology Diffused?



<http://mueller.educ.ucalgary.ca/TS2001/>
<http://www.speedofcreativity.org/2007/08/19/>

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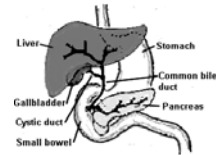
A Case Study

Cholecystectomy: Removal of the Gall Bladder

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The Gall Bladder

- Function:
 - Stores bile made by liver
 - After eating:
 - Gall bladder contracts
 - Secretes bile into duct which empties into small intestine
 - Aids in digestion
- Gallstones:
 - Liquid bile may precipitate into solid stones
 - 1/5 of North Americans and Europeans develop gallstones some point

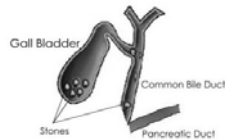


http://www.thaclinic.com/images/biliary_anatomy.gif

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Gallstones

- Symptoms
 - If gallstones block outflow of bile:
 - Abdominal discomfort
 - Pain
 - Heartburn
 - Indigestion
 - Acute inflammation



<http://www.qualitysurgical.com/gblad.jpg>

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Treatment of Gallstones

- Before 1990:
 - Open surgery to remove the gall bladder
 - Effective
 - Low mortality rate (0.3-1.5%)
 - 7 day hospital stay
 - 30 days lost time from work
 - Most common non-obstetric surgical procedure in many countries

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Laparoscopic Removal of Gall Bladder

- Patient receives general anesthesia
- Small incision is made at navel and thin tube carrying video camera is inserted
- Surgeon inflates abdomen with carbon dioxide
- Two needle-like instruments inserted; serve as tiny hands. Pick up gallbladder & move intestines around.

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Laparoscopic Removal of Gall Bladder

- Several instruments inserted to safely remove gallbladder & stones
- Gallbladder is teased out of tiny navel incision
- Entire procedure normally takes 30 to 60 minutes
- Puncture wounds require no stitches - navel incision is barely visible

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Laparoscopic Cholecystectomy



<http://www.lapsurgery.com/gallblad.jpg>

- http://www.laparoscopy.com/pictures/lap_chol.html

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Advantages/Disadvantages

- Benefits:
 - Ease of recovery
 - No incision pain as occurs with standard abdominal surgery
 - Up to 90% of patients go home the same day
 - Within several days, normal activities can be resumed
 - No scar on the abdomen
- Complications:
 - Complication rate is about the same
 - Nausea and vomiting may occur after the surgery
 - Injury to the bile ducts, blood vessels, or intestine can occur, requiring corrective surgery
 - 5 to 10% of cases, the gallbladder cannot be safely removed by laparoscopy

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An Important Innovator

Kurt Semm (1927-2003)

– Gynecologist

– 80 medical device inventions

- Electronic insufflator
- Thermocoagulation
- Loop ligator
- Laparoscopic suturing



– Allowed more complex procedures to be performed endoscopically – including the appendectomy

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Public Response

"He's gone absolutely crazy."

Was asked to undergo a brain scan by his colleagues

Lectures were greeted with laughter and derision

Surgeons saw no reason to change a well established working method into a complex technical matter

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Public Response

Semm:

"Both surgeons and gynecologists were angry with me. All my initial attempts to publish on laparoscopic appendectomy were refused with the comment that such nonsense does not and will never belong to general surgery."

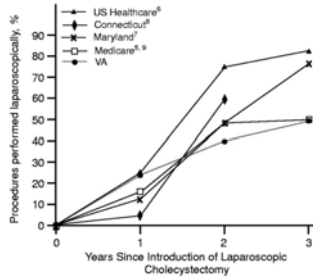
- Gynecologists have "surgeon envy"
- Semm is trying to enter into general surgery to bolster his "operation ego"

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Did this technology diffuse slowly or rapidly?

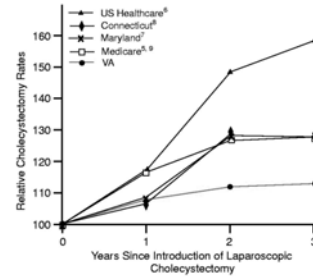
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Diffusion of the Technology



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Diffusion of the Technology



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Diffusion of the Technology

- No technique in modern times has become so popular as rapidly as laparoscopic cholecystectomy
- Semm
 - Displayed an ability to push his ideas through despite skepticism and suspicion
 - Without Semm, the laparoscopic revolution may have been postponed by many years

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Diffusion of the Technology

- Since its introduction in 1989:
 - Laparoscopic procedure has rapidly become the most widely used treatment for gallstone disease
- By 1992:
 - Laparoscopic cholecystectomy accounted for 50% of all cholecystectomies in Medicare populations
 - 75% to 80% of all cholecystectomies in younger populations

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Take Home Message

- Effective diffusion of reliable technologies lead to better results for patients
 - Rate of cholecystectomy increased dramatically
 - Associated with a 22% decrease in the operative mortality rate for cholecystectomy

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Strategies that Speed Up Diffusion

- Find sound innovations
- Find and support innovators
- Invest in early adopters
- Make activity of early adopters visible
- Trust and enable reinventions
- Create room for change
- Lead by example

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Agenda

Historically, slow diffusion and tragedy is what led to better regulation of drugs and devices

- Diffusion is slow: Vitamin C example
- Tragedy strikes, again, and again, and again

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Example: Vitamin C and Scurvy

Diffusion is historically slow....

- 1497
 - Vasco Da Gama lost 100 out of 160 crew members to scurvy sailing around Cape of Good Hope
- 1601:
 - British Navy Captain James Lancaster was in command of 4 ships traveling from England to India
 - Required sailors to take 3 tsp of lemon juice daily on 1 ship
 - The other 3 ships served as the control
 - Results:
 - 110/278 sailors died in control group
 - 0 deaths in the experimental group

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Example: Vitamin C and Scurvy

Diffusion is historically slow....

- 1747
 - British Navy physician James Lind repeated study with similar results
- 1865
 - British Navy finally adopted innovation, 264 years after first recorded evidence



Berwick DM. JAMA April 16, 2003 – Vol 289, No. 15

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Why did it take so long?

- Statistically significant studies
- Repeatable results
- Could not communicate results

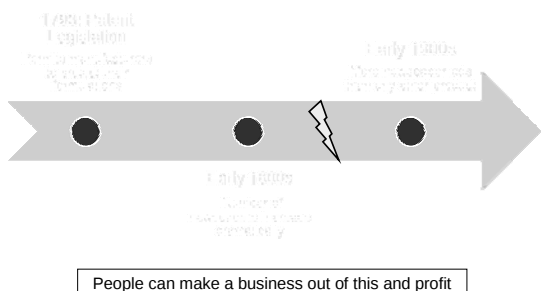


This changed with new forms of communication. Dietary supplements and drugs became more popular throughout history because of it.

http://www.tortdeform.com/archives/2007/10/in_the_news_2.html

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Popularity of Dietary Supplements



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Benefits of Dietary Supplements

- Vitamin C to prevent scurvy
 - Mid-18th century:
 - Scurvy killed more British sailors than war
- Folic acid to prevent neural tube defects
- Calcium to prevent osteoporosis
- Vitamin B₁₂ to prevent dementia
- Research in Alternative Medicine:
 - <http://nccam.nih.gov/>

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History of Dietary Supplements

Lydia Pinkham's Vegetable Compound

- "A Positive Cure," for "all those Painful Complaints and Weaknesses so common to our female population."
- 1914 AMA analyzed compound
 - 20% pure alcohol
 - 80% pure vegetable extracts



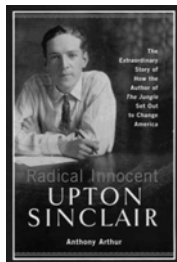
Many supplements laced with cocaine, caffeine, opium or morphine

http://www.realnews247.com/snow_white_witch.jpg

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History of Dietary Supplements

- 1906:
 - Pure Food and Drug Act
 - Reaction to "The Jungle" by Upton Sinclair
 - Permitted Bureau of Chemistry to insure that labels contained no false or misleading advertising



http://blogg.visir.is/kiljoker/2007/11/16/visdomsor9ac3%b0-2/honyarthur-340-copy_of_sinclairpg/

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Impact of Little Regulation

Sulfanilimide (1937)

- Antibiotic for streptococcal infections, used safely as a pill for years
- Most children can't swallow pills
- One company in Tennessee found they could dissolve drug in ethylene glycol (antifreeze)
- Tested for flavor, appearance, fragrance, NOT for toxicity



http://medgadget.com/archives/2006/10/antifreeze_prol.html

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Impact of Little Regulation

137 children died

- Severe abdominal pain, nausea, vomiting, convulsions

"Even the memory of her is mixed with sorrow for we can see her little body tossing to and fro and hear that little voice screaming with pain and it seems as though it would drive me insane."

» Letter to FDR, from woman describing the death of her child

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Impact of Little Regulation

137 children died

- Severe abdominal pain, nausea, vomiting, convulsions

1938

- Food, Drug, and Cosmetic Act
- Gave FDA authority it needed to regulate such products

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More History

- 1940s-1960s:
 - Line between foods and drugs was fairly clear
 - If manufacturers made a disease related claim for a supplement, FDA would go after them
- But then - 1970s:
 - Government started telling Americans to alter diets if they wanted to have longer, healthier lives
 - Heart disease, diabetes, cancers → eat less salt, fat; add fiber, eat more fruits & vegetables

The lines between food and drugs is a little unclear

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Today, supplements...

- CANNOT mention disease
- CAN make claims that food can affect structure or function of body
- Examples:
 - CANNOT say that a product reduced cholesterol but CAN say it maintains healthy cholesterol levels
 - CANNOT say echinacea cures disease, but CAN say it has natural antibiotic activities and is considered an excellent herb for infections of all kinds

The lines between food and drugs is a little unclear

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Impact of More Regulation: Echinacea

- One of the most commonly used cold remedies in US
- Clinical Trial:
 - 400 children with common colds over 4 months
 - Compared placebo to echinacea
 - Placebo worked just as well
 - Children taking echinacea were more likely to develop a rash



<http://www.kalix.com/store/images/208093.jpg>

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Impact of More Regulation: Ephedra

- Ephedra was the most popular supplement in US
- Brought in more than \$1B a year
- There were risks associated with ephedra use
 - Increased risk of heart attack, stroke, palpitations, anxiety, psychosis, death (when taken with caffeine)

- Public tragedy: Steve Belcher, Age 23
<http://www.npr.org/templates/story/story.php?storyId=1576453>
<http://www.npr.org/templates/story/story.php?storyId=1579643>



<http://www.mindritesports.com/category/baseball/>

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Today

- Congress
 - Considered several bills that would modify 1994 law so that many unregulated botanical supplements would be treated more like drugs than like foods
- Supplement manufacturers
 - Assault on first amendment

"We put disclaimers in our ads, and we give people the results of the studies and a money-back guarantee. What more could you want? Don't prevent people from using their judgment. Let them try it. If it doesn't work, they can return it. That's what's fair. That's what's American."

<http://www.theorator.com/bills108/hr4747.html>
http://www.thenhf.com/government_affairs_64.htm
<http://www.npr.org/templates/story/story.php?storyId=4169957>

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Misfortune, disaster, & tragedy

Lead to reforms in drug and device regulation

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“Take Aways”

- Strategies to speed up diffusion are important to disseminating new life saving technologies
- Historical precedents have set the tone for current regulation of drugs and dietary supplements
- It does not end here – more regulation is needed...

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Listen to for next time....

- NPR
 - <http://www.npr.org/templates/story/story.php?storyId=1581985>
 - There might be a quiz....hint hint



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