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Numeropharma: America's Powerful Legal Drug Culture and the Math Behind It

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Introduction

On March 14, 2010, thieves cut a hole in the roof of an enormous Eli Lilly warehouse located in Enfield Connecticut. After they climbed a rope into the warehouse and disabled the alarms, they stole an estimated $75 million dollars worth of prescription drugs. These were not "Robin Hoods" stealing antibiotics in short supply to treat a devastating epidemic. The stolen goods were the bestselling antidepressants Prozac and Cymbalta. Clearly, the thieves wanted to cash in on the billion-dollar-market for these drugs, perhaps using the latest consumer outlet: internet drug sales.

Every current measure of economic growth shows the tremendous increase in pharmaceutical use and consumption in post-World War Two America. Measured against the wider backdrop of post-war consumer culture in America, this industry is absolutely typical of our culture yet stunningly exceptional in its growth and power. The Kaiser Family Foundation regularly analyzes industry and government data for trends in prescription drug use and sales. Their report on the past 20 years in prescription drug trends shows an average annual spending growth rate in the double digits. This is steep even when compared with single-digit growth in other parts of the already-fast-growing healthcare sector. [1] Pharmaceuticals are not merely a multi-million industry or multi-billion one. This industry dwarfs almost all other industries. It competes with big oil and the (too-big-to-fail) commercial banks to be among the top three overall of the nation's most profitable industries. [2]

Healthcare is naturally a lucrative business. Health is one of the most important human needs along with food and shelter. What makes pharmaceuticals surpass housing and beat out agriculture is the centralized nature of the industry. The consumer protections implemented by the United States Food and Drug Administration throughout the 20 th century resulted in the creation of "Big Pharma". The FDA not only approves drugs for market but regulates the marketing of those approved drugs. This has contributed to the centralized nature of the pharmaceutical industry and has created defacto government approved monopolies.

The standard use of controlled clinical trials developed through FDA oversight of the drug industry. The successes of the FDA built a public faith in the role of "The Study", and as the use of "The Study" grew, so did the role of statistics. Statistics moved into an academically recognized field with "real math chops" during the

first half of the 20th century. The language of "The Study" and statistics have become an ubiquitous part of the modern consumer culture: economic statistics, weather statistics, sports statistics and the omnipresent medical studies, with the catch phrases "Four out of five doctors recommend..." and "Studies show...". Advertisers use the language of the pseudo-governmental "Study" to fuel demand for products that "The Study" recommends. Industry creates further demand for drugs and food products by designing studies to demonstrate a need. Their efforts are buoyed by the consumer society's infrastructure of mass marketing and the belief (in this case a literal belief) that a cure for all ills is through buying.

This unit will introduce students of high school statistics to the historical and contemporary role of statistics in the biopharmaceutical industry. This will be of particular interest to students who are pursuing careers in health or biomedical sciences. However, it is possible that this unit would be applicable to science and to political history classrooms, as much as to the math curriculum. As we look at a historical view of statistics and pharmaceuticals, we will see how the field of statistics is implemented in scientific research and discovery, in setting and enforcing governmental policies, and how that demand has transformed statistics into one of the most recognized and accepted forms of mathematics today.

While considering the role of statistics in developing and marketing pharmaceuticals, we will be looking at sampling methods and experimental design. We will discuss the role of random selection, and the advantages and potential biases of different sampling methodologies. We will describe the components of experiments graphically and verbally and analyze designs from the industry. Our purpose will be to understand the current application of statistics in the design and analysis of clinical trials. In particular, we will look at clinical trials as defined by the Food and Drug Administration (FDA). This is a valuable educational approach on two fronts. One is the acquisition of statistical skills through application-based learning. The other is to help students to perceive and value the role of statistics in their own contemporary culture.

Brief History of FDA Protections and the Birth of the Clinical Trial

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Beginning in the 19th century, the practice of medicine was licensed. The American Medical Association formed in 1847 and the US Pharmacopoeia was founded in 1820 [3] to create a formulary and official record of drugs. However, medical practice and drug production and distribution regulations varied from state to state. Many "quacks" existed who marketed ineffective and sometimes unsafe medicines. It is equally true that many fine remedies existed, remedies often culturally based: Native American, African American, British, Amish, and Chinese. Many medical practitioners used these remedies to great healing effect.

As the economy and infrastructure of the United States expanded in the late 19th and early 20th century, the FDA grew from a single chemist in 1862 who worked at the Department of Agriculture, to a full agency with a large mission. Charged with regulating the safety of foods and drugs produced and imported into the United States, the FDA took food as its primary focus at its beginning. Coming on the heels of revelations in Upton Sinclair's The Jungle [4], The 1906 Pure Food and Drug Act charged the FDA to regulate interstate transport and sale of unlawfully adulterated or inaccurately labeled foods and drugs. The act, however, was extremely vague and lacked enforceable language. Author of Inside the FDA, Fran Hawthorne writes: "... the law applied primarily to what was said on the label, not what was actually in the bottle. Government regulators were given no authority to look inside the container, let alone test the ingredients, to ensure the contents would not harm the public." [5]

The first regulations to require pre-market testing for safety came with the passage of the Food, Drug, and Cosmetic Act of 1938. President Roosevelt signed the law that required all drug manufacturers to show scientific proof that a drug was safe prior to being sold in the United States. This law followed the Sulfanilamide crisis of 1937, when a remedy laced with a toxic solvent killed 100 people, mostly children. The FDA was now charged with the evaluation of data related to the safety of products being developed.

The regulation that is responsible for the modern clinical trial model was the 1962 amendments to the Food and Drug act following the Thalidomide crisis. This story is proudly retold on the FDA website with the hero of the story, Frances Kelsey, as the human face for the critically important role that the government plays in protecting consumers. In September 1960, the drug company Richardson Merrill applied to the U.S. and Canada for the rights to market Thalidomide, a sleeping aid popular in Europe. Frances Kelsey's very first assignment at the FDA was to review the sedative that was also being marketed as a remedy for morning sickness in pregnant women. Frances Kelsey did not like the company's application, especially its lack of unbiased evidence. In a recent interview with the CBC, she said the "Claims were so obviously outrageous, I mean it was supposed to be perfect. It didn't have any ill effects" But she was also under " great pressure to approve it." [6] Since this was to be her very first approval, no one expected her to do very much with the application. In fact, she was given the file of a popular drug approved overseas as a way to learn the ropes.

Frances Kelsey used bureaucratic rules to delay approval. It is documented that drug representatives visited her no less than 50 times. Despite the pressure, she continued to delay, and her hunch paid off the following year. Articles began appearing in British journals reporting tingling and neuropathy, and then followed the reports of deformed babies. Eventually, over 10,000 thalidomide-affected births have been documented worldwide. These were horrifying, debilitating birth defects causing the limbs of these children to be truncated or missing completely.

In 1962 President Kennedy awarded Francis Kelsey the civilian Medal of Honor and the Kefauver-Harris amendments to the 1938 act were passed unanimously by Congress. The FDA now required scientific proof through well-controlled studies that drugs sold and manufactured in the United States be proven not only safe but also effective. This was evidence that Thalidomide lacked and Kelsey was so tenaciously demanding. This formalized, evidence-based approval process is why " the FDA today is considered the gold standard for approval. Again, Hawthorne: What the 1962 amendments essentially did was to codify Kelsey's courage and careful attention into law." [7] The regulation requiring pre-marketing studies for safety and efficacy have directly resulted in the formation of standards for clinical trials in the United States. The first clinical trials guidance documents came out in 1970, with additional changes in 1985 [8] . These guidance documents have largely been adopted as worldwide standards in the International Conference on Harmonization. [9]

Standards and Guidance for Clinical Trials

In order to ensure safety and efficacy of drugs, manufacturers must employ statistics in all phases of production. Drugs need to be safe. They need to have a positive effect on patients. They must be manufactured in a consistent way to ensure accurate dosages. No drug is without unintended or side effects. What matters is to have a positive benefit-to-harm ratio. Benefit must be weighed in terms of symptomatic relief, reduction in disease risk, complications or increased survival. Harm must be measured in terms of

unintended deleterious effects on patients. The balance of benefit to harm should be affected by what other drugs are available for the particular condition as well as the seriousness and urgency of the condition.

Prior to clinical studies, companies must do research to identify compounds and create a hypothesis against which they plan to test their drug. They must present meticulously planned studies and any research or prior animal testing in order to apply to do clinical trials in humans. Studies are generally considered Phase 1, 2, 3, or 4. Phase 1 studies are small and look at safety and metabolism in healthy patients. Phase 2 and 3 are clinical trials of patients who are being treated for the targeted conditions. With statistically significant success shown in these trials, a company may apply for a right to market the drug. After approval, Phase 4 consists of follow-up observational studies that look for rare adverse effects.

The FDA requires that a company present a prospectus with a hypothesis before any human testing can begin. An institutional review board must review this proposal for soundness. Not only does stating a hypothesis before beginning trials avoid fishing expeditions to find useful effects of drugs, it is a necessity in order to correctly design an experiment that effectively controls as much variability as possible.

There are several distinct types of study that can be performed for establishing benefits of a particular treatment. The most reliable is considered the double-blind, placebo-controlled, clinical trial. Clinical trials are prospective (forward moving) experiments that can establish cause and effect. Observational studies can show association or a relationship between variables, but are not accurate in demonstrating cause and effect. There must be comparison groups with manipulation of treatments in order to avoid mistaking the effects of confounding variables.

It is of paramount importance to randomize treatment groups of patients. Randomization is critical to establish equality among the treatment groups, to minimize the sources of variability that are not possible to be controlled for. Randomization reduces bias that researchers could intentionally or unconsciously weight the treatment groups. It is the best way to avoid systematic bias, and bias in an experiment can invalidate the results.

Blinding is a second feature of controlled clinical trials. When all parties involved in the treatment of the experiment (subjects, physicians, clinical staff) are not aware of which groups the subjects are assigned to, it is called single-blinding. This can help diminish "Hawthorne-effect" [10] where the knowledge that one is being studied can change the outcome of an experiment. Single-blinding can also mitigate "placebo effect", where patients improve on placebo, simply by feeling that they are being treated. Double-blinding, where all individuals involved in collecting and measuring the results of the treatments (subjects, physicians, clinical staff, researchers) do not know each individual subject's treatment assignment can lessen "ascertainment bias" where the hopes and expectations of subjects and researchers can sway outcomes. A famous National Institute of Health study of vitamin C's effect on the common cold showed that when participants (many of whom were NIH scientists) became curious and unblinded the study, they unconsciously underreported the duration of their symptoms and underestimated the length of their sickness. [11] This study showed that knowledge of treatment could affect both researchers and subjects in the interpretation of symptoms and disease markers.

Sample size is important in statistical theory as well as in practice. Statistics measures variability, and is most effective when given the opportunity to accurately measure the type of variability that exists in a population. Samples that are not sufficiently large cannot introduce the correct amount of actual variability and may under- or overmeasure the effects of a drug.

When clinical trials are not ethical or practical, observational studies or meta-analysis can be used to study safety and efficacy. These can be used to observe teratogenic effects, the effect on a fetus when a pregnant woman is given a drug. Although it would be unethical to test drugs on a fetus, records exist when a woman has been unintentionally treated with a compound during pregnancy, and those records may be used in an observational study.

Limits and challenges of FDA's policies

As the second century of the FDA begins, consumer protections in pharmaceuticals are firmly established and largely successful. Cases like thalidomide have demonstrated the need for a government agency to weigh the profit-motive against the protection of consumers. The establishment of the clinical trial created an industry of science-based companies and an infrastructure of academic and industrial links that are focused on deriving treatments for human illness. The combination of public and private interests creates both a profit-motive to grow and support the industry along with more altruistic motives of alleviating suffering.

By limiting the right to market drugs without their approval the FDA is equivalent to the Patent Office in its control of the industry [12] This control has centralized the power of the companies that hold these patents and created an enormous profit incentive and an accompanying drive to interpret statistics in favor of the products that the companies want to market. While that incentive is a legitimate and intended consequence of much legislation, it creates a strong temptation for inappropriate and misleading research, development and production of drugs.

There are two ways in which the approval process has been misused. One is simple deception to avoid potential losses by suppressing the negative findings during the trials process. The examples here are many and have led to the criticisms that the industry and the FDA are too close. Another is more vaguely unethical, and, in fact, a legal process by which these companies use federal money to produce less effective and costlier drugs whose only true beneficiaries are the shareholders of these companies.

When a company patents a successful drug, they can reap huge profits, by remaining the only source of this very much in-demand product. It is a monopoly that is accepted by the government as a trade-off for the humanitarian nature of the business to alleviate pain and suffering of patients. As the industry grew throughout the 1980's, further growth incentives were legislated to enhance the profits of these lucky few companies. Ostensibly, these incentives were to reward altruistic companies for furthering lifesaving research, in order to offset their financial risks in research and development. They were also intended to encourage the nascent bioscience industry. The meteoric growth of these industries shows just how successful these acts have been in encouraging work in developing pharmaceuticals. However, growth has been centralized, with more power in the hands of a few companies and an industry that has the power to influence those who try to control it.

In The Truth About the Drug Companies Marcia Angell, 20-year-veteran, and first woman editor of the New England Journal of Medicine, writes of the profit margins that zoomed in the 1980's following the enactment of the Bayh-Dole act in December 1980, " Before then it was a good business, but afterward, it was a stupendous one. From 1960 to 1980 prescription drugs were fairly static as a percent of the U.S. Gross Domestic product, but from 1980 to 2000 they tripled." [13] This act encouraged the use and commercialization of government-

funded research in order to spur research and create economic growth. It allowed NIH-funded researchers at universities to hold the title for their inventions. Previously, the government owned those rights. In turn the titleholders could sell the right to market the drug to pharmaceutical companies. This has become the dominant mode of research for these companies. Ironically, companies who have underpaid the NIH royalties on drugs they have licensed have charged the governments Medicare and Medicaid programs inflated prices on these same drugs. While there have been beneficiaries within universities and small biotech firms that have developed new technologies, an enormous amount of profit has gone to the licensors of these products, the Pfizers and Aventis, without their actually having to risk any capital on research and development.

The Hatch-Waxman act of 1984 sought to increase the production of cheaper generic drugs. In order to unburden the producers of generic drugs from their regulatory costs, this act allowed a streamlined approval process, where the generics could be approved on the basis of the clinical trials of the original drug. This was supposed to lower investment costs and in turn lower cost to the consumer. As a compromise to industry, name-brand drugs were given longer patents.

The clever producers of name brands have discovered ways to lower their overhead and extend their monopolies by using Hatch-Waxman. Angell writes that "in the five years 1998 through 2002, 415 new drugs were approved by the Food and Drug Administration (FDA), of which only 14 percent were truly innovative. A further 9 percent were old drugs that had been changed in some way that made them, in the FDA's view, significant improvements. And the remaining 77 percent? Incredibly they were all me-too drugs - classified by the agency as being no better than drugs already on the market for treating the same condition." [14] These products were either slightly chemically altered, or repackaged in new doses or levels of time release enough to claim a patentable product, not enough to require a full set of new trials. This practice is ethically challenging along several fronts. The financial resources of the NIH and these companies are NOT being spent discovering innovative treatments for challenging health problems, but are maximizing profits through copycat drugs.

An even darker side exists to the practice. The trialing process only requires that a drug be better than a placebo, but not better than existing treatments. Therefore the risk/benefit calculation is invalid. The copy may be better than no treatment and this benefit may outweigh the side effects, but is it better than another possible treatment? An example is Crestor, the cholesterol-lowering drug approved in 2003. Hawthorne says, "… the problem wasn't merely that Crestor might be redundant: The consumer advocacy group Pubic Citizen Watch charged that it actually caused worse side effects than the other statins, including kidney damage and severe muscle deterioration, and called for it to be banned." [15] There is no requirement for this side-by-side analysis to be made or to be reported.

This limitation of the trialing process can be outweighed by the prudence of the medical practitioners who prescribe and review medications. While drugs may be approved for sale, it is common practice for doctors and patients to decide which drug will be chosen for treatment. However, even this private arena is rapidly changing, as insurance and public/private pay options are reconfigured. The landmark prescription drug act of 2003 carried a provision that Medicare could not create a formulary or bargain with the drug companies for pricing. This is unheard of within the private insurance industry. All insurance carriers have formularies with tiered reimbursement for various levels of drugs and employ cost-saving practices such as substituting generics or even substituting completely different treatments for the same condition. How will these changes and the Health Care Act of 2010 affect the industry?

The evolution of statistics from government bureaucracy to mathematics

As we examine the growth of statistics in regulating and testing drugs, it is interesting and worthy to notice that the history of statistics itself is recent, and that the math co-evolved with the drug industry. Statistics is an infant among the ancient branches of mathematical study, yet it stands securely with its venerable peers among the four curriculum content strands in the state of Connecticut mathematics framework:

1. Algebraic Reasoning (Al-Jabr was written in ancient Persia)
2. Numerical and Proportional Reasoning (Incan and Mayan cultures explored the use of zero; there are ancient Arabic, Egyptian, Roman, and Hindu numerical systems.)
3. Geometry and Measurement Working with Data (Geometry has roots in ancient Egypt; Pythagoras wrote theorems in ancient Greece)
4. Probability and Statistics (The first time that statistics appeared in academia was the biostatistics program at John Hopkins University in 1918. [16])

Statistics developed from three disparate fields; political science, astronomy and gambling. [17] From politics comes the name. This terminology persists in governmental bureaus of Vital Statistics. The name shares a Latin root with state, and is related to the notions of state as a condition of matter or body, state as in a body politic, and status. My 1947 edition of the Oxford English Dictionary gives the mid-century definition of statistic as "pertaining to status" and statistics as "that branch of political science dealing with the collection, classification, and discussion of facts bearing on the condition of a state or community. " [18] The estimation of errors in measurement was an important pursuit in astronomy, and provided the basis for quantifying variability, which is the heart of statistical inference. Thirdly, the mathematical studies of chance in gambling throughout the 17th and 18th centuries provided the mathematical bases for many of the central theories in statistics. These fields began to come together as a recognized academic discipline in the earlier part of the 20th century.

The American Statistical Association (ASA) was founded in 1839, not as an academic pursuit, although erudite members of their Boston society founded it. The original members were graduates of Ivy League colleges and, as such, were all men. They had expertise in medicine, law and education. Their concerns were chiefly vital statistics, and their process was to generate and collect writings on statistical matters. These were articles concerned with public health issues, preventative medicine, and population and labor statistics.

As statistical study began to move into academia during the early twentieth century it was still considered vital statistics and focused on public health. During this period, mathematicians in the United States, Europe and Russia were building on theories of probability, and through the 1920s to '40s an expansion of these mathematical proofs led to a body of work in mathematical statistics with a focus on formal probability theory. Princeton University was a base for many mathematical statisticians and the theoretical frameworks developed in the middle of the 20 th century by these academics gave sound basis to the field as accepted math practice. [19] Samuel Wilks and Henry Rietz split from the ASA to found the Institute of Mathematical Statistics and publish a separate journal, "Annals of Mathematical Statistics", to distinguish it from the practical application-oriented work. However, Wilks circled around to focus on practical applications. He influenced the great John Tukey, whose boxplot (first appearing in 1977) is one of the most familiar graphs to

high school students today.

Current theory in statistics pedagogy emphasizes the applications of statistics and limits the focus on formal proof or derivation. [20] This would not be possible without the formal mathematical proofs of the 1930s and 1940s. However, the fact that statistics no longer needs to "prove itself" is a result of the immense growth in the use of this math. Textbook author and distinguished professor of statistics at Purdue University, David S. Moore cites the 1996 joint recommendations of the MAA (Mathematical Association of America) and ASA in his argument for an application, process-based pedagogy for introductory statistics. That statement called for three basic reforms:

1. Emphasize the elements of statistical thinking
2. Incorporate more data and concepts, fewer recipes and derivations. Whenever possible, automate computations and graphics.
3. Foster active learning

Moore points out that the increase of computerized calculations and data organization allows a student to have less calculation skills while their exposure to a greater number of real world applications requires a higher level of inference and statistical analysis. There also needs to be a focus on ethics and a grasp of good experimental design and data production. He would replace the study of formal probability with these areas of content. [20]

It is important that our students learn through applications. This will prepare them best for the statistical questions that arise in their lives and studies. Many applications for statistics exist in the clinical trials and pharmaceutical industry, so it is a rich area to draw studies from. In addition, the notion of clinical trials has arisen within the political and scientific history of the United States pharmaceutical industry. This makes the immersion of statistical study in this area so rewarding.

Lessons

Sampling Methods and Experimental Design

Whether in an AP course or in an introductory high school course in Statistics, production of data is an important component. Students need to understand what samples are and how samples can be used to make inferences about a population. Sampling methodologies are an important subject, each type should be understood along with along with their potential sources of bias. Random selection is a core principle in the creation of a statistically useful sample.

The importance of randomization extends to treatment assignments in experimental design. Random assignment avoids bias that can be a fatal flaw in drawing conclusions from a study or experiment. The correct design of an experiment in clinical practice requires a statistician. While scientists and medical doctors are often carrying out the experiment, without the correct underlining design, analysis is not meaningful. Therefore the topic of experimental design is essential to learning statistics and to understanding the process

of how a drug gets to market.

Students will follow a topic outline similar to College Board's suggested syllabus [21] where students spend about two weeks looking at randomization, sampling and experiments. The following are three examples of lessons that incorporate pharmaceutical industry applications with the development of proficiency in analysis and design of experiments.

LESSON 1

The history and use of Sampling Methods

Resources

The First Measured Century (Book and Video)

http://www.pbs.org/fmc/lessons/lesson4.htm [22]

Random Rectangles [23]

Teachers can adapt the lesson plan from the one on the PBS website. In my class I will use the video segment and worksheet and then use random rectangles activity to draw samples. This is an excellent overview of the concepts of sampling. It introduces samples, populations and bias in sampling through a 20th century example of the failure of a biased sample to predict accurately.

OBJECTIVE

Students will identify samples and populations. Students will compare sampling methodologies and analyze sampling methods for bias.

ASSESSMENT/PRODUCT

Worksheet analysis of video segment. Dot Plots of random rectangles. Written analysis of sampling methods.

OPENER

Discussion: How do we decide what products to buy? What is safe and effective? What do statistics in the news tell us? Who do you trust?

PROCEDURE

Watch Gallup segment from "The First Measured Century."

Students will take notes and complete the accompanying worksheet. Class discussion on bias will follow. Give examples in sampling methodologies (SRS, cluster, stratified, systematic). Create a class list of potential for bias in sampling methodologies.

Using "Random rectangles" from "Activity Based Statistics."

Students will use their judgment to select five rectangles that best represent the scope of the rectangles on the page. Students average their rectangles and add their mean to the class dotplot on the board.

Students will use randomization to select five rectangles on the page.

Teacher demonstrate randint command on TI-84 (MTH>PRB #5 randint)

Using randint, students select 5 rectangles and find their mean and add to second class dotplot.

Class will verbally analyze, discuss, compare/contrast the two dot plots looking for center and spread.

LESSON 2

Elements of an experiment

OBJECTIVE

Students will correctly identify the elements of a well-designed experiment and know how to describe and diagram an experiment.

ASSESSMENT/PRODUCT

Students will read a prose description of an experiment and sketch the design.

OPENER

Discussion of confounding factors, causation, controlling treatments in a study. There are many examples to use. I use the example of gastric freezing from "Statistics through Applications" [24] This example couples two experiments, one with a faulty design and a reworking of the experiment with a significantly different outcome. The first design did not use a placebo-controlled group and so did not have a comparison group with which to measure placebo effect. It was difficult to determine if the positive reports of pain relief were due to placebo or actual relief. In the second trial 160 ulcer patients received a balloon treatment for pain relief; 82 received a freezing solution in the balloon, 78 received a body-temperature balloon. The first treatment group reported a 34% rate of improvement, the second showed a 38% rate of improvement. The placebo worked even better than the treatment.

There is lots to discuss here: placebo effect, placebo-control groups, placebos that are not "sugar pills". In terms of consumer awareness, we can discuss the potential benefits and dangers to the consumer, the role of the individual's right to choose treatments, informed consent of subjects, methods of blinding, and the medical profession's decision on how best to treat based on financial or ethical reasons.

PROCEDURE

Working in groups, students should read the study. Students should have index cards with the titles:

Experimental Question

Subjects

Response variable

Students should arrange the cards logically and write information from the study prose on the correct index card.

Using the Gastric Freezing example we can repeat this by adding the secondary study, which used a placebo-controlled group. We will add these index cards into the set.

Factors

Levels

Once the students have arranged and discussed the design, the class should work to draw these designs, with each student producing their own, which includes indications of randomizing, indications of factors and levels. Students should read a follow-up experiment and analyze it in a prose segment as an assessment.

LESSON 3

Bringing a drug to the market: Need, treatment, safety, efficacy

OBJECTIVE

Students will look at the history of clinical trials and look at a study involving a specific drug.

ASSESSMENT/PRODUCT

Students will research a current drug and describe the protocol for clinical trials. Students may also read and respond to excerpts from "The Treatment." [25]

OPENER

Discussion: How do we treat disease? Where do treatments come from? How do we know that they are safe? What are the ways in which drugs are tested and sale of drugs controlled?

Listen to excerpts from CBC program on Thalidomide.

Discussion on Safety and efficacy (What experimental designs are needed to study each?)

Discussion of Phase 1, Phase 2, Phase 3, Phase 4 trials.

PROCEDURE

Students will use clinicaltrials.gov website to investigate clinical trials ongoing or completed.

An excellent starting point is to look at the clinical trials search for trials: http://clinicaltrials.gov/ct2/search

The top right hand side of each page gives a link to the glossary, which can be helpful when interpreting the information.

Students can input their city name (works well for New Haven) or a disease of interest.

Once a study is chosen, students can look at it in tabular view (use tabs at top of page)

This view lays out the WHO, WHAT, WHEN, WHERE, HOW of a study.

Students can scroll down below the study description to find the Study Phase, type, design, condition and

treatment.

Alternately teacher can give out fact sheets about a trial accessed from the website: http://clinicaltrials.gov/

Appendix: District Standards

The curriculum standards addressed in the unit are contained in the fourth strand of the Connecticut Department of Education's Mathematics Curriculum Framework:

Working with Data: Probability and Statistics

Data can be analyzed to make informed decisions using a variety of strategies, tools and technologies.

In addition, this unit addresses the following standards recommended by the National Council on the Teaching of Mathematics (NCTM)

understand the differences among various kinds of studies and which types of inferences can legitimately be drawn from each (We will look at surveys, experiments and observational studies and examine cases where we can draw inferences about causation, and where we can draw inferences about population proportions and means.)

know the characteristics of well-designed studies, including the role of randomization in surveys and experiments

use simulations to explore the variability of sample statistics from a known population

construct sampling distributions to understand how sample statistics reflect the values of population parameters

use sampling distributions as the basis for informal inference

evaluate published reports that are based on data by examining the design of the study, the appropriateness of the data analysis, and the validity of conclusions

Works Cited

Angell, Marcia. The Truth About the Drug Companies: How They Deceive Us and What to Do About It. New York: Random House, 2004. This is an excellent, readable, critique of Big Pharma by Angell, a 20 year veteran of the New England Journal of Medicine.

Angell, Marcia . "The Truth About the Drug Companies." The New York Review of Books" July 15, 2004. A synopsis of the above book in article form.

Bakhai, Ameet, and Duolao Wang. Clinical Trials -- A Practical Guide to Design, Analysis, and Reporting. 1 ed. London: Remedica

Publishing, 2006. Dense and more information than is needed for this unit.

Brody, Howard. Hooked: Ethics, the Medical Profesion, and the Pharmaceutical Industry. 1 ed. Lanham: Rowman & Littlefield Publishers, Inc., 2007. This book gives an intricate critique of the interplay between medical profession and Pharma. More than is necessary for this unit, but contains a lot of excellent examples.

Caplow, Theodore, Louis Hicks, and Ben J. Wattenberg. The First Measured Century: An Illustrated Guide to Trends in America 1900-2000. Washington D.C.: American Enterprise Institute Press, 2000. PBS documentary with accompanying video and website has great resources for classroom use.

Chance, Beth L., J. Barr Von Oehsen, and Allan J. Rossman. Workshop Statistics: Discovery with Data and the Graphing Calculator (Key Curriculum Press). 3 ed. New York, NY: Wiley, 2008. This is a classroom statistics text with many medical examples.

Furberg, Bengt. All that glitters is not gold: What clinicians need to know about clinical trials. second edition ed. New York, NY: Dr. Potata, 2007. This is designed for medical professionals to examine and analyze clinical research. It is a wonderful, readable resource about the mechanics of clinical trials.

Gladwell, Malcolm. "The Treatment." The New Yorker, May 17, 2010. This is an excellent article on bringing a drug to market from the entrepreneur's point of view.

Gnanadesikan, Mrudulla, Richard L. Scheaffer, Ann Watkins, and Jeffrey Witmer. Activity-based Statistics. 2nd ed. Emeryville, CA: Key College, 2004. This textbook is a staple for the high school statistics classroom.

Hawthorne, Fran. Inside the FDA: The Business and Politics Behind the Drugs We Take and the Food We Eat. New York, NY: Wiley, 2005. This is a readable and comprehensive guide to the history of the Food and Drug Administration and the development of Big Pharma.

Hunter, Patti Wiger. "Foundations of Statistics in American Textbooks: Probability and Pedagogy in Historical Context." From Calculus to Computers/MAA Notes 68 (2005): 165-180. This journal has interesting articles on math pedagogy.

Kelsey, Frances. "Thalidomide." The Current. CBC, CBC.CA, April 27, 2010. The famous Frances Kelsey, now a nonagenarian, recounts her refusal to approve Thalidomide for sale in the United States in this CBC interview. This was produced in Canada, so it has the added insight of a country who did approve Thalidomide.

The Henry J Kaiser Family Foundation. " Prescription Drug Trends Fact Sheet-May 2010 Update." Kaiser Family Foundation. http://www.kff.org KFF maintains excellent fact sheets on the drug industry.

Mason, Robert L.. "Home | American Statistical Association." Home | American Statistical Association. http://www.amstat.org (accessed April 26, 2010). Why? Just for geeks.

Moore, David S. "New Pedagogy and New Content: The Case of Statistics." International Statistical Review 65, no. 2 (1997): 123-137. http://www.jstor.org/satble/1403333 (accessed April 24, 2010). This article was quoted and responded to by several authors. It gives a good argument for an application-driven statistics classroom, and the author lives up to his own challenge with the next book.

Moore, David S., Daren S. Starnes, and Dan Yates. Statistics Through Applications. Second Edition ed. New York: W. H. Freeman, 2009. Here is an application-driven statistics textbook, designed for the non-AP level classroom.

Senn, Stephen. Statistical Issues in Drug Development (Statistics in Practice). 2 ed. New York: Wiley-Interscience, 2008. Most of this book is overkill for this unit. It does have a nice math history overview.

The Shorter Oxford English Dictionary (2 Vol. Set; Thumb Indexed Edition). 1933. Reprint, Oxford : Oxford University Press, 1947 Again, for geeks.

"U S Food and Drug Administration Home Page." U S Food and Drug Administration Home Page. http://www.FDA.gov (accessed April 3, 2010). The FDA provides wonderful public resources, including lots of history.

Notes

[1] Kaiser Family Foundation, "Prescription drug trends September 2008", http://www.kff.org/rxdrugs/3057.cfm (accessed June 7, 2010).

[2] Based on quote from Marcia Angell, The Truth About the Drug Companies ,3, updated with Fortune 500 annual ranking of America's largest corporations, http://money.cnn.com/magazines/fortune/fortune500/2006/performers/industries/return_on_revenues/index.html (accessed on May 20, 2010)

[3] U.S. Pharmacopeia, http://www.usp.org/aboutUSP (accessed on May 20, 2010)

[4] FDA history part 1 www.fda.gov

[5] Fran Hawthorne, Inside the FDA: The Business and Politics Behind the Drugs We Take and the Food We Eat, 40.

[6] Frances Kelsey, "Thalidomide." The Current. CBC, CBC.CA, April 27, 2010.

[7] Fran Hawthorne, Inside the FDA , 44.

[8] Fran Hawthorne, Inside the FDA , 46.

[9] http://www.fda.gov/regulatoryinformation/guidances/ucm122049.htm

[10] Bengt Furberg, All that glitters is not gold, 13.

[11] Bengt Furberg, All that glitters is not gold , 51.

[12] Marcia Angell, The Truth About the Drug Companies , 9.

[13] Marcia Angell, The Truth About the Drug Companies , 1.

[14] Marcia Angell, The Truth About the Drug Companies , 75.

[15] Fran Hawthorne, Inside the FDA , 274.

[16] The first 160 years American Statistical Association http://www.amstat.org (accessed April 26, 2010) and Johns Hopkins School of Public Health http://www.biostat.jhsph.edu/research/publication/handbook.shtml (accessed June 26, 2010)

[17] Stephen Senn, Statistical Issues in Drug Development (Statistics in Practice) chapter 2

[18] The Shorter Oxford English Dictionary (2 Vol. Set; Thumb Indexed Edition). 1933. Reprint. Oxford : Oxford University Press, 1947. Print, 2007.

[19] For more on history of statistics see:
Stephen Senn, Statistical Issues in Drug Development (Statistics in Practice). Chapter 2

[20] Patti Wiger Hunter, "Foundations of Statistics in American Textbooks: Probability and Pedagogy in Historical Context." From Calculus to Computers/MAA Notes 68

[21] David S. Moore, "New Pedagogy and New Content: The Case of Statistics." International Statistical Review 65, no. 2 (1997), 128.

[22] apcentral.collegeboard.com/apc/public/.../ap06_stat_syllabus2.pdf (accessed July 3, 2010)

[23] http://www.pbs.org/fmc/lessons/lesson4.htm The first Measured Century.

[24] Mrudulla Gnanadesikan, Richard L. Scheaffer, Ann Watkins, and Jeffrey Witmer, Activity Based Statistics 82.

[25] David S. Moore, Daren S. Starnes, and Dan Yates, 260-261.

[26] Malcolm Gladwell "The Treatment".