



2nd Annual Venable Advertising Law Symposium
**Substantiating Structure/Function and
Health Claims after POM**

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Events Leading up to POM

Well, maybe





Events Leading Up To POM

- Old Definition has been around for awhile
 - “tests, analyses, research, studies or other evidence based on the expertise of professionals in the relevant area, that has been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the profession to yield accurate and reliable results.”
- But the FTC started losing contempt cases.



Events Leading Up To POM

- New Definition in Nestle/Iovate Case
- “at least two adequate and well-controlled human clinical studies of the product, or of an essentially equivalent product, conducted by different researchers, independently of each other, that conform to acceptable designs and protocols and whose results, when considered in light of the entire body of relevant and reliable scientific evidence, are sufficient to substantiate that the representation is true.”

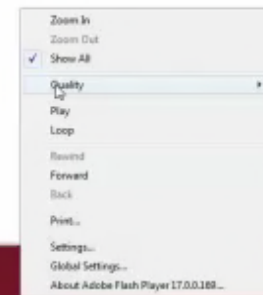


Events Leading Up To POM

- Initially limited to specific claims at issue in case
 - Nestle – Reduce duration of acute diarrhea
 - Iovate – Weight loss
 - Dannon – Transit time

Events Leading Up To POM

- But then came POM



POM Case

Cheat death.

The antioxidant power of
pomegranate juice:



- Treats, prevents, reduces risk of heart disease, ED and prostate cancer.
- FTC experts said 2 RCTs for HD, 1 for ED and prostate cancer.
 - Commission fenced in with 2 RCTs for any food, drug or dietary supplement for any disease claim.

Cheat death.

POM Wonderful. The Antioxidant Superpower.

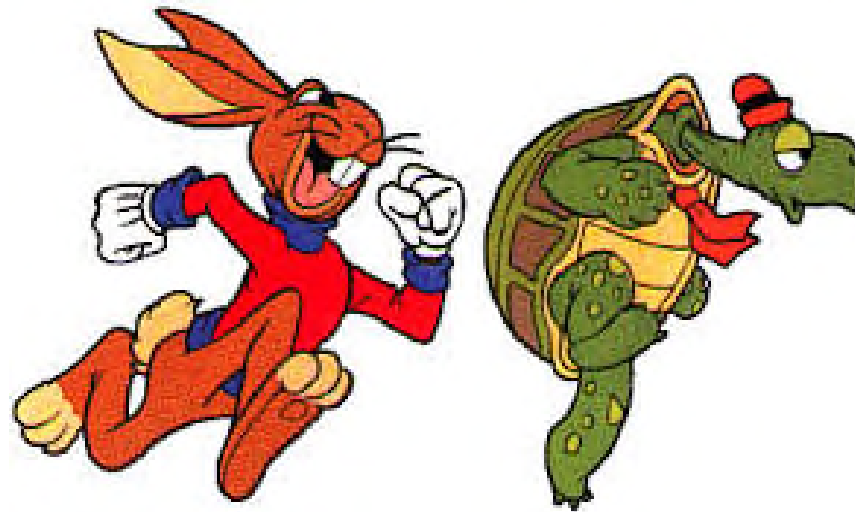


"...Natural Fruit Product with Health Promoting
Characteristics." – FTC Judge

[Learn More](#)



- Comm. Ohlhausen favored 1 study not 2 requirement.
- She was the tortoise and not the hare in this case





POM DC Circuit Decision

- DC Circuit opinion rejecting the FTC's 2 study requirement signals there is still room for flexibility in how one substantiates these types of claims
- There has been a push of late to go even further and question traditional thinking on issues such as statistical significance
- My colleagues will address this next



The FTC Substantiation Standard Competent and Reliable Scientific Evidence

“[T]ests, analyses, research, studies, or other evidence based on the ***expertise of professionals in the relevant area***, that has been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the profession to yield accurate and reliable results”

The FTC has specifically stated “[a] guiding principle for determining the amount and type of evidence that will be sufficient is what ***experts in the relevant area*** of study would generally consider to be adequate”



Statistical Significance Is Not a Requirement for Meeting Competent and Reliable Standard

- FTC dietary supplement advertising guide provides no requirement for statistical significance
- Statistical significance doesn't necessarily mean clinically meaningful benefits and vice versa (*see* FTC Guide)
- Scientific studies when viewed by **EXPERTS** in the field, rather than **lawyers**, clearly demonstrate clinically meaningful benefits to consumers



Expert in a Relevant Area

- Professionals in ***relevant area*** of expertise are professionals who specialize in the claims being made
- The courts require that these expert opinions be considered for determining the amount and type of evidence that will be sufficient to meet the competent and reliable standard



Pom Wonderful v. FTC

- Decision was based on experts' views of the studies, not on the studies themselves
- Court made clear the decision is relevant only to disease claims and request for injunctive relief
 - Court intimated a different decision if the claims were different: structure/function claims v. direct disease claims
 - “The Commission declined to address the level of support required for general health or nutritional claims.” (opinion at 23)



Statistical Significance versus Clinically Relevant

- Statistical significance simply indicates the probability of incorrectly rejecting a true null hypothesis. Never meant to be a rigid standard.
 - Is the 95% Confidence Level an Arbitrary Number?
- Can a study fail to reach statistical significance but still be considered clinically relevant?
 - Statistical significance does not give any indication of the magnitude or clinical importance of the difference.



Statistical Significance versus Clinically Relevant

- The issue is applying statistical significance in a rigid manner
 - Studies that are statistically non-significant are ignored even though there is a true treatment effect – generally due to small sample size
 - Studies that show small difference can reach statistical significance by increasing the number of subjects in a study even though the results provide little value to the patient
 - Commercial speech concerns – 1st Amendment. Throwing the baby out with the bathwater.



Statistical Significance versus Clinical Outcome

- **Question:** What to do with clinical trials where positive clinical outcomes are observed but do not have statistical significance? Is there no value with data that shows $p > 0.05$?
- **Question:** What other methods are there that determine efficacy, other than p -values?
- **Question:** How does one proceed with new and statistically significant and unexpected results that are primary end point but in a subgroup that was not previously identified?



Statistical Significance versus Clinically Relevant

- Clinically relevant relevance is a change in an individual's clinical status that is regarded as important
 - **Minimal clinically important difference** (also known as **MCID**) attempts to define the smallest change in a treatment outcome that a patient would identify as important
 - Requires a paradigm shift
 - More consistent with 1st Amendment concerns than statistical significance




Consideration Points

- Statistical Significance versus Clinically Relevant
 - Is evidence-based science really about the 95% confidence level?
 - 95% confidence level merely validates the extreme results while ignoring the clinical results
 - Lawyers prefer bright lines because it is easier to prove their case
 - Experts may disagree on the clinical relevance of a clinical trial
 - First Amendment would permit the claim as being non-deceptive if it is clinically relevant

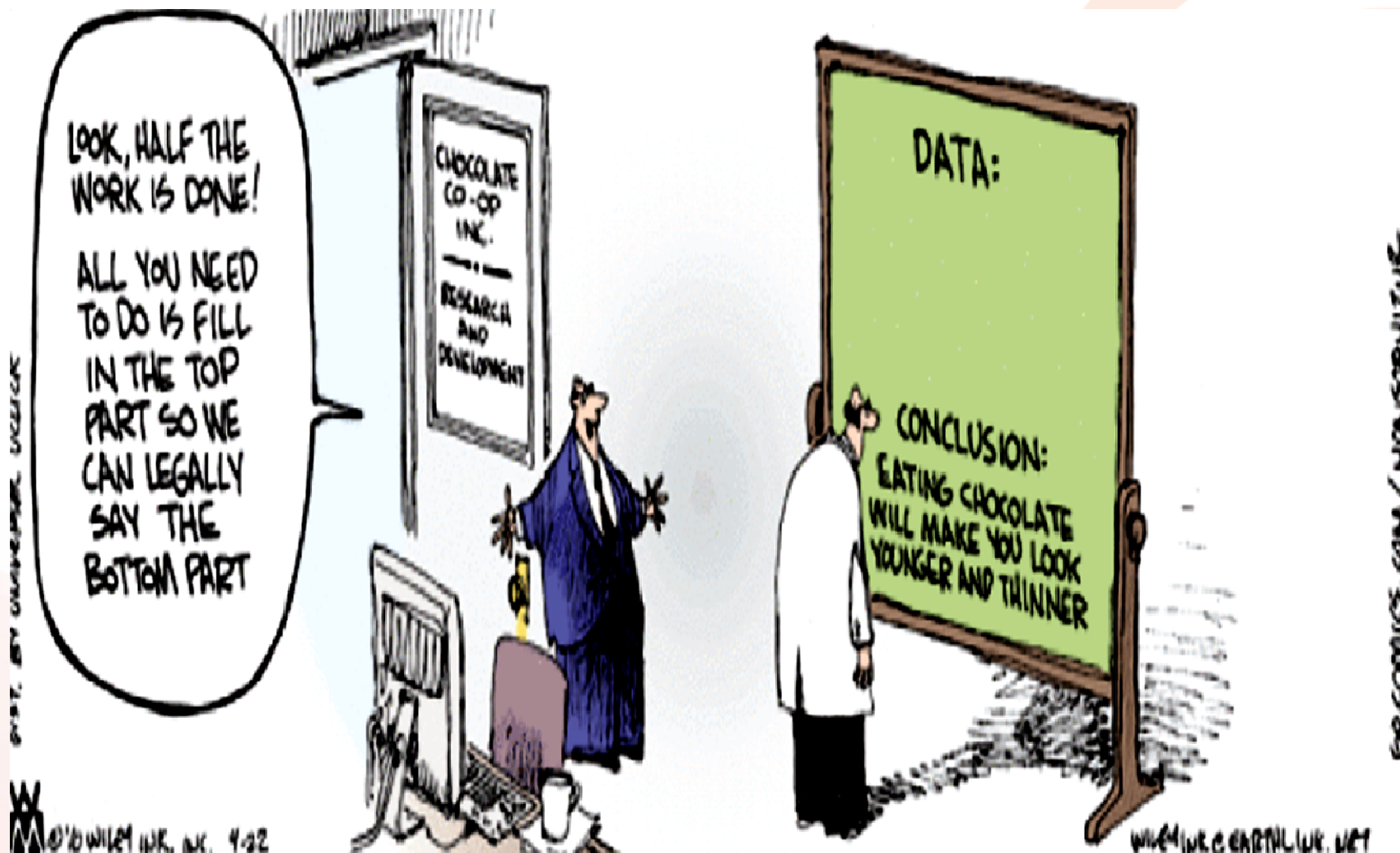


Our Mission



*If we are to bring credibility
to the dietary supplement industry, we
must design and conduct our clinical
studies with scientific integrity .*

Burden of Proof for your claim is with YOU



Levels of Evidence





STUDY DESIGN IS KEY!!!

The Randomized Double-Blind, Placebo-Controlled Trial the Gold standard for evaluating claims

- ✓ **Controls for confounding**
- ✓ **offers the strongest evidence of causal relationship**

Clinical Trial Check List

Claim

- Target population
- Study Design
- Endpoints
- Duration of Study
- Statistical analysis

Protocol-ICH

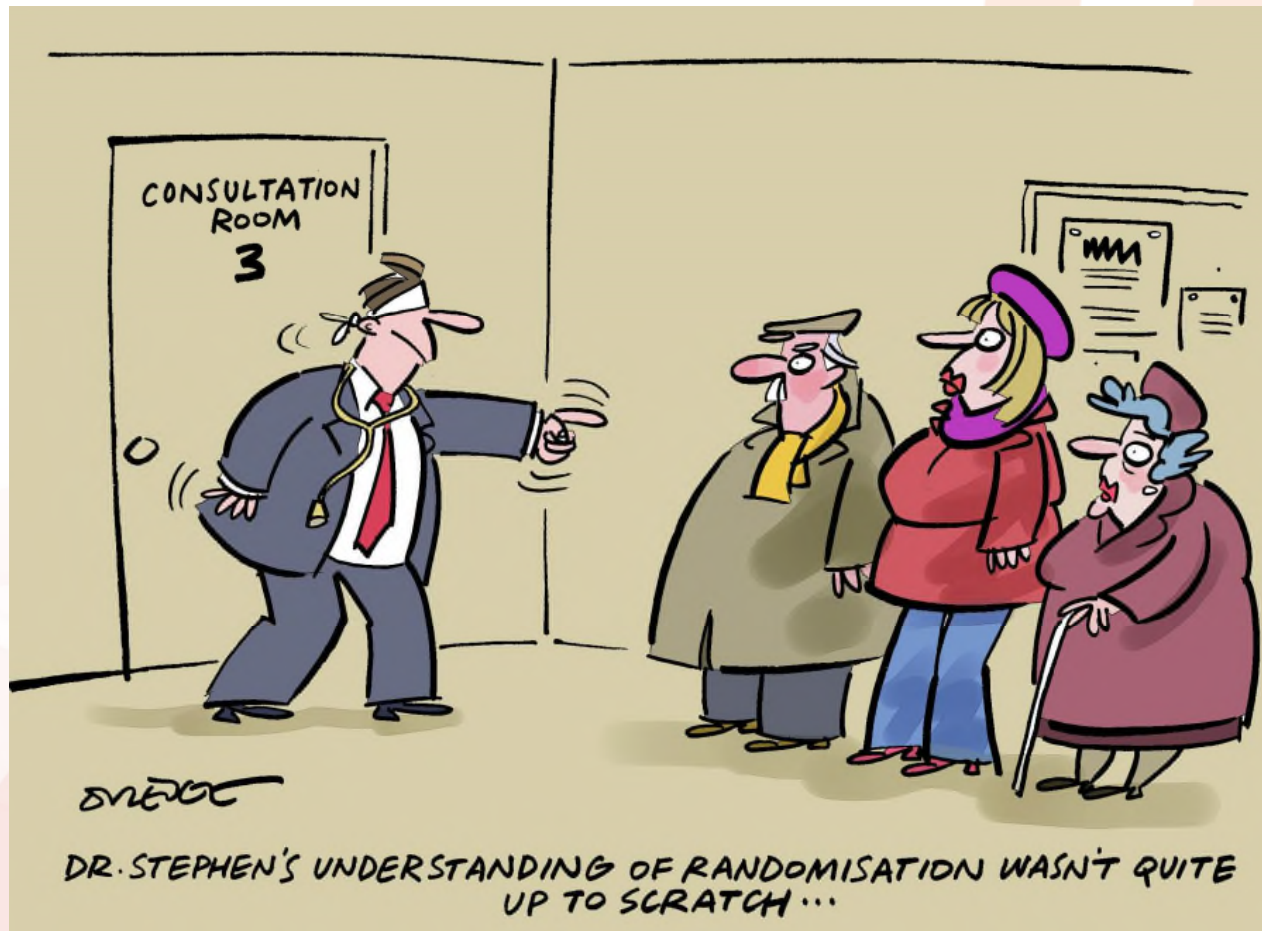
Final Report (Consort 2010)

- Subject disposition
- All Results
- Adverse events



Key components of the design of an RCT
intended to minimize bias:

Randomization



Key components of the design of an RCT intended to minimize bias:

➤ BLINDING




Fig. 3 A double-blind placebo-controlled clinical trial for CAM therapies.

Key components of the design of an RCT intended to minimize bias:

➤ Allocation concealment

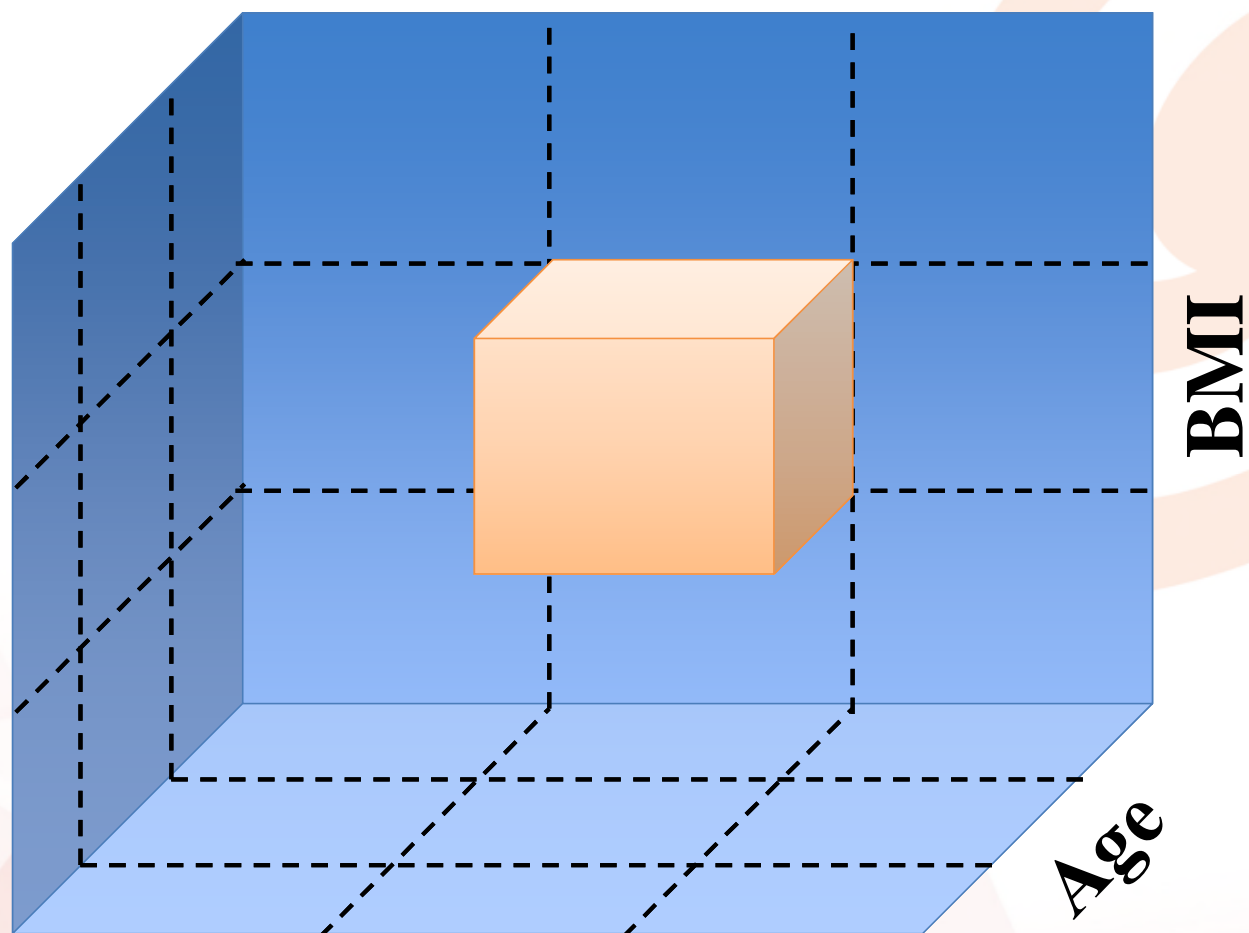




Additional components of the design required for claim substantiation:

- Sample size calculation
- Appropriate surrogate markers
- Subject disposition
- Appropriate control group

Choosing your Population



Glucose/SBP/Menopause

Animation Credit: Scott Martling



Challenges



Limiting Confounding Factors



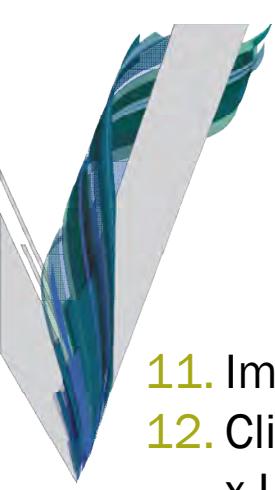
Efficacy Study Design for a Probiotic on Healthy People with Occasional Diarrhea – Inclusion Criteria

1. Male or female between 18-65 years of age (inclusive)
2. If female, subject is not of child bearing potential. Female subjects of childbearing potential must agree to use a medically approved method of birth control and have a negative urine pregnancy test result.
3. BMI 18.5-35.0kg/m²
4. Subjects must have < 3 bowel movements per week for at least 2 weeks (but for not more than 12 weeks) prior to randomization (confirmed at screening and baseline) and the presence of at least one other bowel symptom of constipation in at least 25% of defecations;
 - a. Hard stools. or complete lack of loose or watery stools
 - b. straining during defecation
 - c. feelings of incomplete evacuation
 - d. abdominal discomfort
 - e. bloating/distension
 - f. Subjects may be OTC laxative users for occasional constipation but should not be using prescription medication
5. Healthy as determined by laboratory results, medical history and physical exam
6. Subjects must agree not to use any other products to treat their constipation during the run-in to the study (7 days prior to baseline) or during the course of the study except as a rescue medication.
7. Agrees not to change current dietary habits (with the exception of avoiding pro- and prebiotics) and activity/training levels one week prior to randomization and during the course of the study
8. Has given voluntary, written, informed consent to participate in the study



Efficacy Study Design for a Probiotic on Healthy People with Occasional Diarrhea – Exclusion Criteria

1. Women who are pregnant, breastfeeding, or planning to become pregnant during the course of the trial
2. Subjects currently under a doctor's care and treatment for constipation
3. Subjects that have a history of chronic constipation (defined as <3 bowel movements per week for more than 3 months) due to any underlying cause (IBS, functional constipation [chronic constipation], IBD, ulcer, etc.) based on self-report, physical examination, or documented medical history
4. Subjects who have severe abdominal pain as the predominant constipation symptom as determined by the Principal Investigator.
5. Subjects who have a history of colorectal cancer, anal abscess, anal fistula, anal fissure, anal stenosis, gastric retention or obstruction, bowel resection, rectocele, or colostomy
6. Subjects with known renal or hepatic insufficiency
7. Subjects with gastrointestinal bleeding or acute infection
8. Subjects who plan to regularly use laxatives, other than the study supplements, during the treatment period (use as a rescue medication is permitted).
9. Subjects currently taking or taken within 7 days of randomization a concomitant medication that causes constipation which in the Principle Investigator's opinion may impact the study results.
10. Any non-gastrointestinal disease/complication that, in the investigator's opinion, may affect subject safety or confound the evaluation of the study endpoints

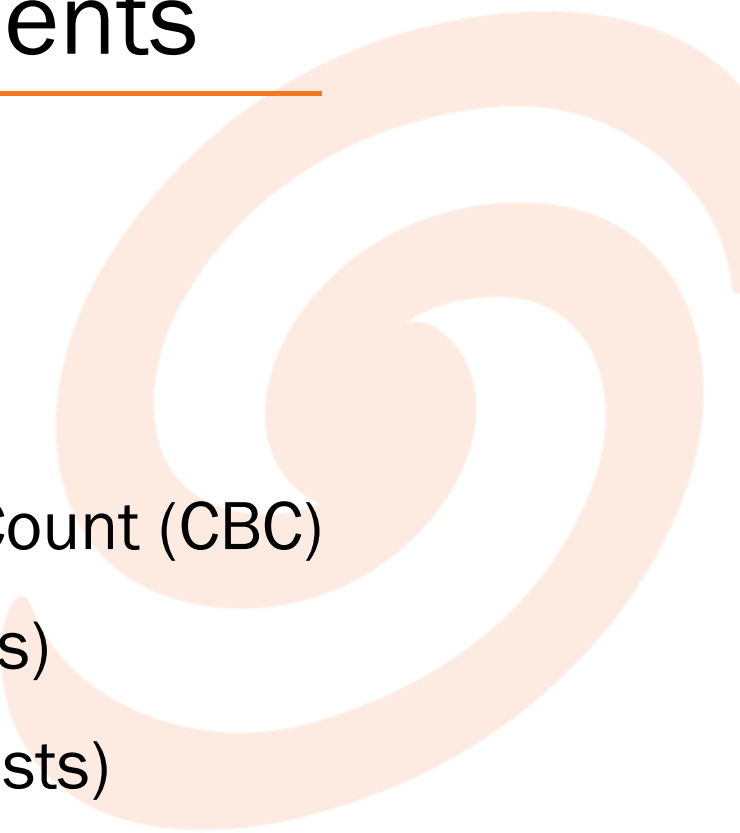


Efficacy Study Design for a Probiotic on Healthy People with Occasional Diarrhea – Exclusion Criteria (contd)

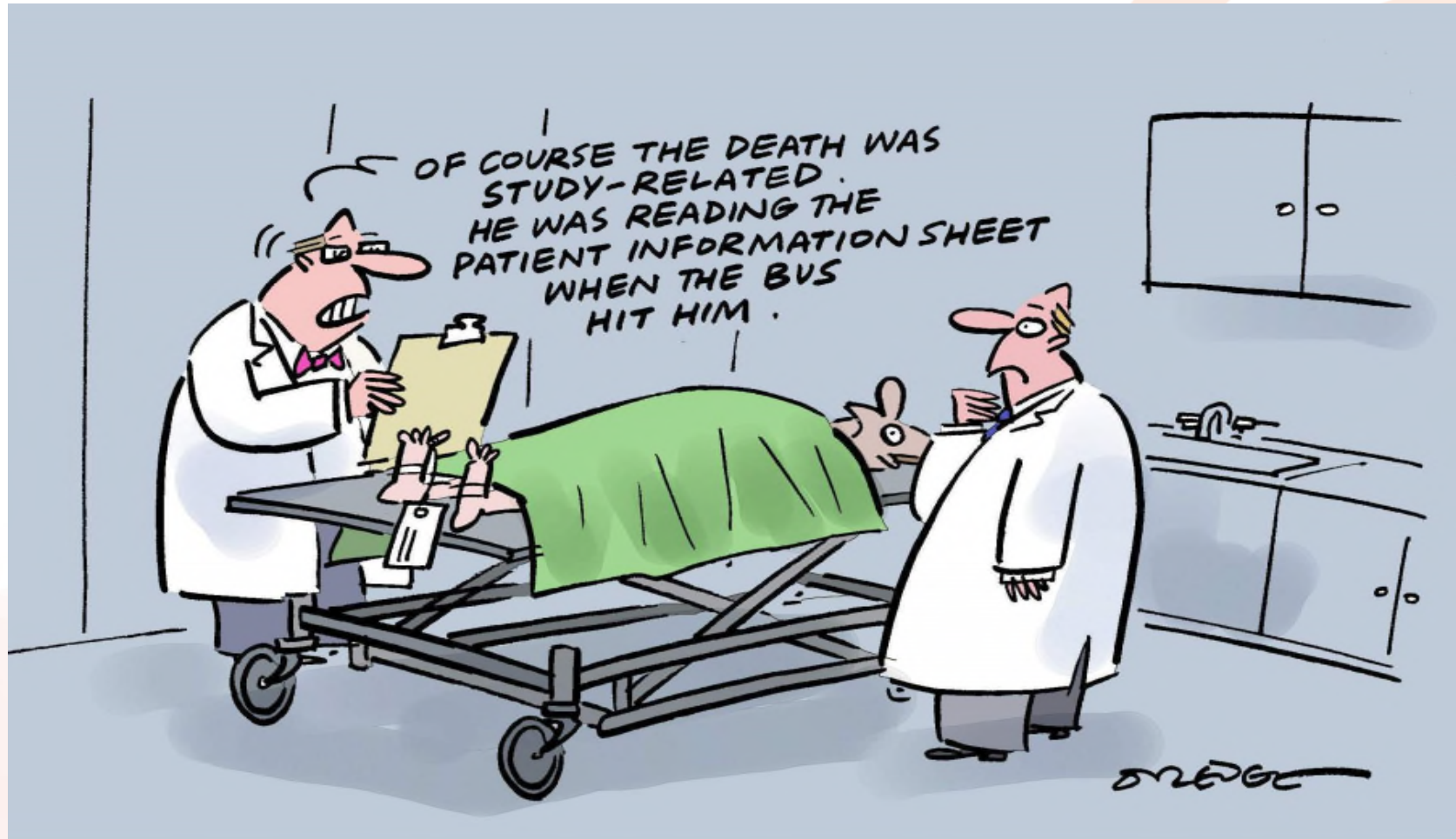
11. Immunodeficiency
12. Clinically significant abnormal laboratory results at screening (e.g. AST and/or ALT > 2 x ULN, and/or bilirubin > 2 x ULN; serum creatinine > 1.5 x ULN; hemoglobin < 140 g/L for males and < 123 g/L for females)
13. Abdominal surgery within 6 months of randomization
14. Participation in a clinical research trial within 30 days prior to randomization
15. Change in anti-psychotic medication within 3 months of randomization
16. Allergy or sensitivity to study supplement ingredients
17. Use of pre- and probiotics within 3 weeks prior to randomization
18. Alcohol abuse (>2 standard alcoholic drinks per day) or drug abuse within the past 6 months
19. Individuals who are cognitively impaired and/or who are unable to give informed consent.
20. Any other condition which in the Investigator's opinion may adversely affect the subject's ability to complete the study or its measures or which may pose significant risk to the subject



Safety Measurements

- ✓ Vital Signs
 - ✓ Hematology, Complete Blood Count (CBC)
 - ✓ Liver function tests (put in tests)
 - ✓ Kidney function tests (put in tests)
- 

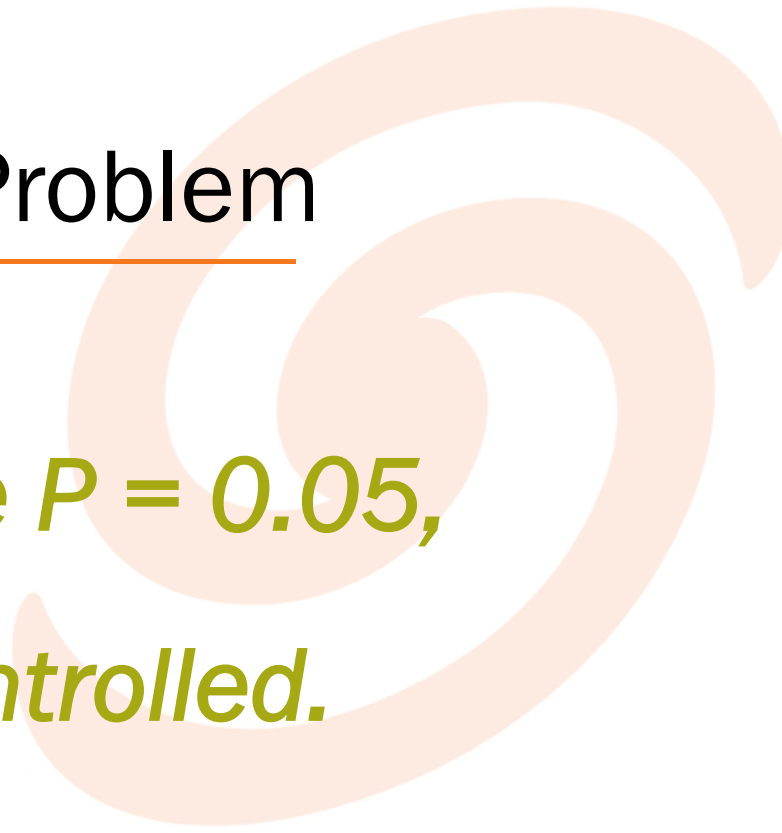
Adverse Events





Houston, We Have a Problem

*Regulators want to see $P = 0.05$,
with type 1 error controlled.*



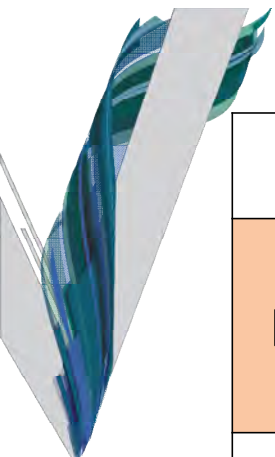
EBM versus EBN

Parameter	Drugs	Nutrients
Essentiality	None	Essential
Inadequacy results in disease	No	Yes
Homeostatically controlled by the body	No	Yes
True placebo group	Yes	No
Baseline “status” affects response to intervention	No	Yes
Systemic function	Isolated	Complex networks
Targets	Single organ/tissue	All cells/tissues
Effect size	Large	Small
Side effects	Large	Small
Nature of effect	Therapeutic	Preventative

Heaney, 2008, Shao and Mackay, 2010

The incredible shrinking population


	Hypertension Spectrum			
	“Healthy”		Pre-clinical	“Diseased or Unhealthy”
	Normal laboratory values	Pre-hypertension	Moderate Hypertension	Hypertension
Blood pressure (BP)	<120 mm Hg	Systolic BP 120-139 mm Hg Diastolic BP 80-89 mm Hg	Systolic BP 140-159 mm Hg Diastolic BP 90-99 mm Hg	Systolic BP ≥ 160mm Hg Diastolic BP ≥100 mm Hg



	LDL Cholesterol Spectrum		
Risk Category	LDL Goal	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)	LDL Level at Which to Consider Drug Therapy
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 mg/dL	100 mg/dL	130 mg/dL (100-129 mg/dL: drug optional)*
2+ Risk Factors (10-year risk 20%)	<130 mg/dL	130 mg/dL	10-year risk 10-20%: 130 mg/dL 10-year risk <10%: 160 mg/dL
0-1 Risk Factor**	<160 mg/dL	160 mg/dL	190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

Diabetes Spectrum

	Diabetes Spectrum		
	“Healthy”	Pre-clinical	“Diseased or Unhealthy”
	- Normal laboratory values	Elevated biomarkers but not to the level of “diseased”	- Biomarkers reach level defined as disease
Fasting Blood glucose	70 to 99 mg/dL (3.9 to 5.5 mmol/L)	100 to 125 mg/dL (5.6 to 6.9 mmol/L) Impaired fasting glucose (pre-diabetes)	126 mg/dL (7.0 mmol/L) and above on more than one testing occasion (Diabetes)
OGTT (Sample drawn 2 hours after 75g glucose beverage)*	Less than 140 mg/dL (7.8 mmol/L)	From 140 to 200 mg/dL (7.8 to 11.1 mmol/L) Impaired fasting glucose (pre-diabetes)	Over 200 mg/dL (11.1 mmol/L) on more than one testing occasion (Diabetes)



Absence of statistical significance in the presence of clinical significance

- With 1% ↓ in LDL-C, there is 2% ↓ in heart disease rates^a
- With 10% ↓ in total cholesterol, there is 30% ↓ in coronary heart disease^b
- For each 1mg/dL ↑ in HDL-C, there is 2 -4% ↓ in coronary heart disease^c
- Achieving clinical significance for important risk markers is of great value for health promotion

a. Gotto et al Circulation. 2002; 105: 893-898

b. Cohen JD. American Journal of Clinical Nutrition 1997;102:23-5

c. Toth. Circulation.2005; 111: e89-e91

Statistical Significance

- P-value was never meant to be used the way it is used today. Currently, P-value encourage muddle-thinking
- Statistical significance is no indicator of practical relevance. The question we should be asking is “how much of an effect is there”, not “is there an effect”



STATISTICAL ERRORS

P values, the 'gold standard' of statistical validity, are not as reliable as many scientists assume.

BY REGINA HUIZZO

For a brief moment in 2010, Matt Motyl was on the brink of scientific glory: he had discovered that extremists quite literally see the world in black and white.

The results were “plain as day”, recalls Motyl, a psychology PhD student at the University of Virginia in Charlottesville. Data from a study of nearly 2,000 people seemed to show that political moderates saw shades of grey more accurately than did either left-wing or right-wing extremists. “The hypothesis was sexy,” he says, “and the data provided clear support.” The P value, a common index for the strength of evidence, was 0.01 — usually interpreted as “very significant”. Publication in a high-impact journal seemed within Motyl’s grasp.

But then reality intervened. Sensitive to controversies over reproducibility, Motyl and his adviser, Brian Nosek, decided to replicate the study. With extra data, the P value came out as 0.59 — not even close to the conventional level of significance, 0.05. The effect had disappeared, and with it, Motyl’s dreams of youthful fame.

It turned out that the problem was not in the data or in Motyl’s analyses. It lay in the surprisingly slippery nature of the P value, which is neither as reliable nor as objective as most scientists assume. “P values are not doing their job, because they can’t,” says Stephen Ziliak, an economist at Roosevelt University in Chicago, Illinois, and a frequent critic of the way statistics are used.

For many scientists, this is especially worrying in light of the reproducibility concerns. In 2005, epidemiologist John Ioannidis of Stanford University in California suggested that most published findings are false; since then, a string of high-profile replication problems has forced scientists to rethink how they evaluate results.

At the same time, statisticians are looking for better ways of thinking about data, to help scientists to avoid missing important information or acting on false alarms. “Change your statistical philosophy and all of a sudden different things become important,” says Steven

Goodman, a physician and statistician at Stanford. “Then ‘laws’ handed down from God are no longer handed down from God. They’re actually handed down to us by ourselves, through the methodology we adopt.”

OUT OF CONTEXT

P values have always had critics. In their almost nine decades of existence, they have been likened to mosquitoes (annoying and impossible to swat away), the emperor’s new clothes (fraught with obvious problems that everyone ignores) and the tool of a “sterile intellectual rake” who ravishes science but leaves it with no progeny. One researcher suggested rechristening the methodology “statistical hypothesis inference testing”, presumably for the acronym it would yield.


The irony is that when UK statistician Ronald Fisher introduced the P value in the 1920s, he did not mean it to be a definitive test. He intended it simply as an informal way to judge whether evidence was significant in the



Paradigm shift from Proof of Efficacy to Proof of Probable Harm

- Developing biomarkers and global indices for the dietary supplement industry
- Endpoints that can capture multiple effects across different organ systems and tissues
- Minimally Clinically Important improvement (MCII) or difference (MCID)
- subject related outcome measures (PRO Instruments)

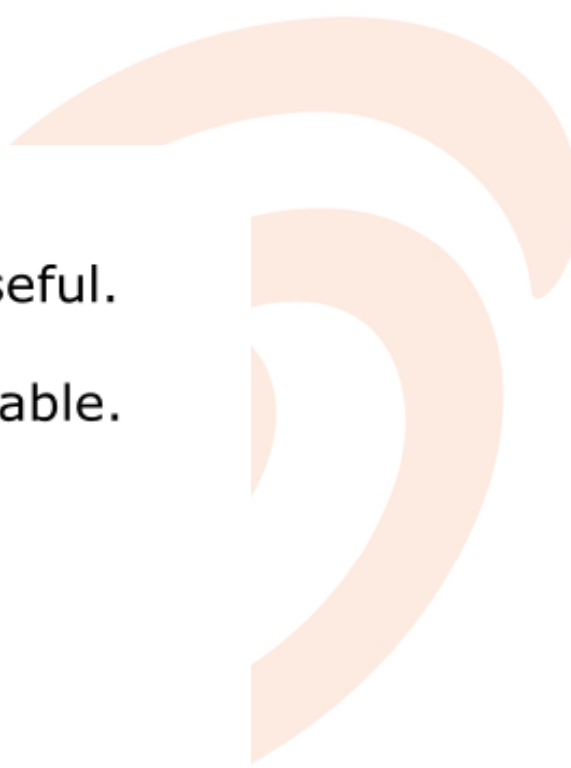
Heaney , *et al.* (2011). EBN (Evidence-Based Nutrition) Ver. 2.0 *Nutrition Today*



Congressman,
there are other methods
that could provide some
useful evidence.



I don't need useful.
I need indisputable.



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