

4.46: Cancer Monologue and Lecture #5 from VP's Class on How to Appraise Medical Literature

Season	4
Type	Plenary Session
Status	Complete

We Discuss:

- Introduction [0:00]
 - Foreign policy [4:00]
 - When are randomized trials necessary? [9:31]
 - Randomized trials of parachutes [26:19]
 - Parachute pt. 2 [33:00]
 - Pragmatic trials and sham surgery [37:00]
 - Cost [45:30]
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Plenary Session 4.46 Show Notes

Overview

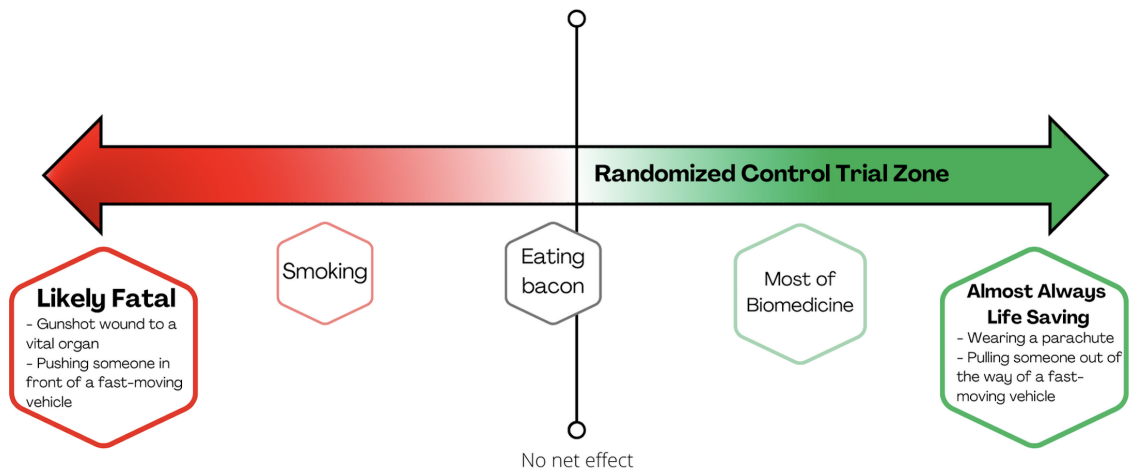
Monologue with VP and Dr. Timothee Olivier

- **Introduction [0:00]**
 - Dr. Olivier is a practicing oncologist at the Hôpitaux Universitaires de Genève
 - He is a visiting scholar at University of California San Francisco

- His research interests span medicine, oncology, and public health policy
- **Foreign policy [4:00]**
 - OncoAlert's Virtue Signaling Hurts Cancer Patients
 - Substack article by VP
 - Do we really want sanctions being placed by random doctors?
 - As a physician, you have a loyalty to your country, but a commitment to mankind that transcends nations

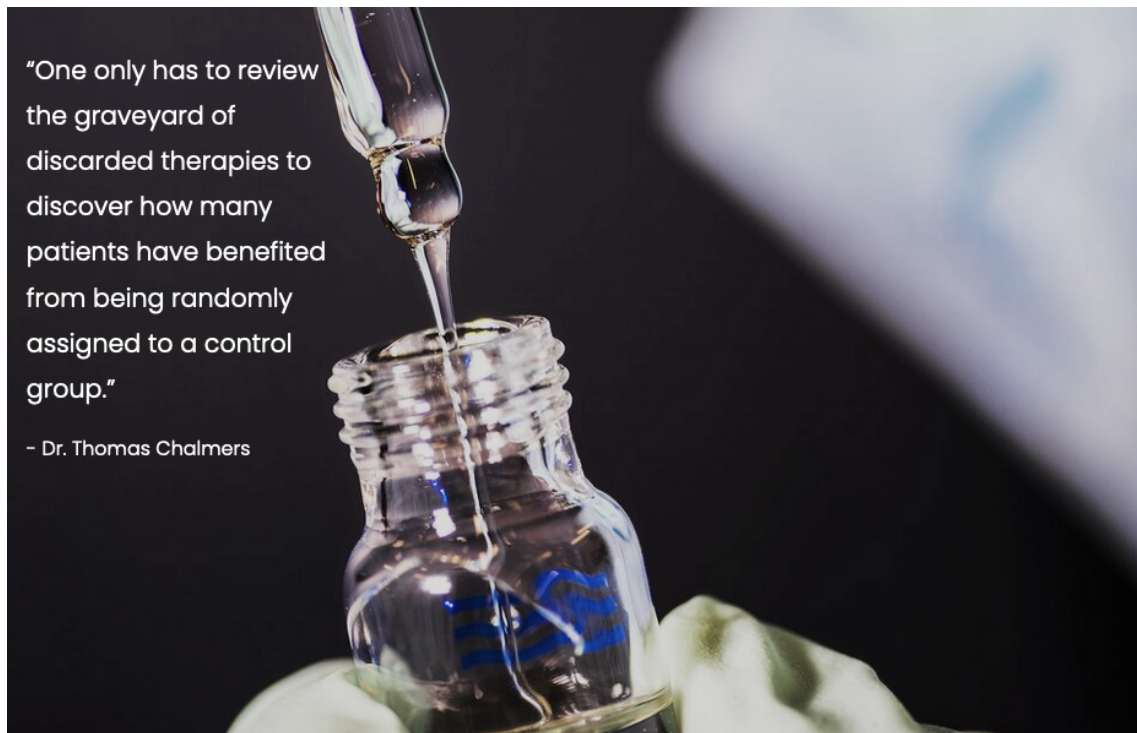
“Even if our government chooses to place sanctions, I think that's one thing, but for an average sort of professional association or doctor to place their own sanctions on a cancer patient in Russia – I think is just bizarre.” - VP

- The European Society of Cardiology were also not permitting Russian experts to present papers at their meeting
- Citizens may express their support for their government or offer feedback to it
 - However, arbitrary abolition of Russian cultural elements may do more harm than good.
- **When are randomized trials necessary? [9:31]**
 - Powell K, Prasad V. Where are randomized trials necessary: Are smoking and parachutes good counterexamples? *European Journal of Clinical Investigation*. 2021



Powell & Prasad

o Randomization concepts



Source

1. The RCT Zone

- The need for randomization in biomedicine

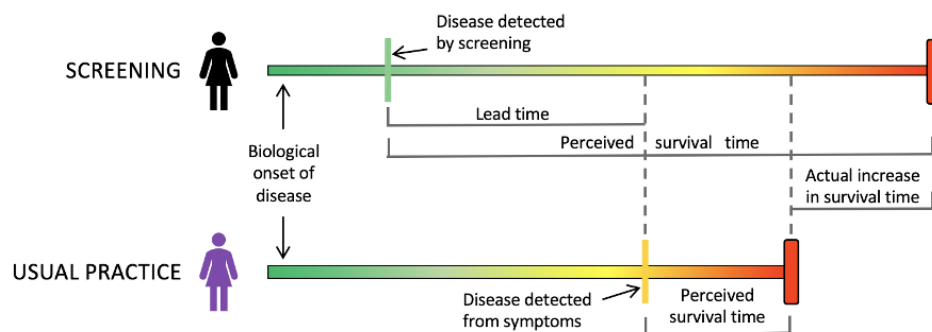
- Almost no medical interventions are at the parachute level; the vast majority of what biomedicine provides is at the modest, moderate effect size level.
 - Biomedical interventions often deal with human optimism and profiteering, which may produce an erroneous estimate of the impact
 - Only well conducted RCTs can determine if the effect is good or negative, and whether the intervention is worthwhile.

2. What are the benefits of randomization?

a. Randomization distributes both known and unknown confounders and equilibrates outcomes distributions

i. What is time zero?

1. Lead time bias in the context of screening



Source

ii. Multiplicity

1. The bulk of our practices, at least the ones that have been reviewed, may not have as large an impact that people believe (or an effect at all)
2. Additionally, observational studies are upwardly biased, favoring benefit above reality

• **Randomized trials of parachutes [26:19]**

- Smith and Pell's original publication made fun of evidence-based medicine supporters and their insistence on conducting randomized trials for everything.
 - They do this by claiming, "Did you know that using a parachute when you fall from an aircraft is not subjected to randomized trials?" As a result, we have no way of

knowing for certain if it works/s!

- However, randomized trials are clearly not required for intervention with a large and readily apparent effect size, such as a parachute
 - When contrasted to medicine, where therapies have an impact size of 10-15%, this is a straw man comparator

“Can anyone really say that taking a statin pill is an obvious benefit... You really need huge sample sizes to see that difference” - VP

- Appendectomy



“Not long ago, many predicted that randomized studies of appendectomy vs high-dose antibiotics for appendicitis would never be conducted. And, although there is considerable leeway in interpreting the findings, there is no doubt that we have conducted at least four such randomized studies” - Powell & Prasad

- Safety and efficacy of antibiotics compared with appendectomy for treatment of uncomplicated acute appendicitis: meta-analysis of randomised controlled trials.
Varadhan et al., *BMJ*, 2012

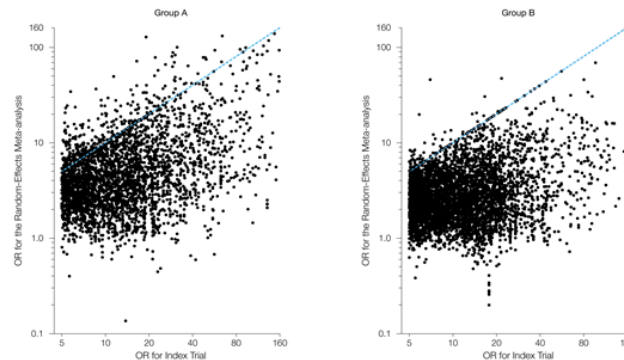
- Pooled analysis



“Additional evidence supporting this claim comes from Pereira and colleagues, who found only one intervention among 80,000 practices consistently had a large effect (defined as an odds ratio of ≥ 5) on mortality in their search of Cochrane reviews, which was a 40% reduction in the risk of death associated with extracorporeal oxygenation for severe neonatal respiratory failure. Although these risk differences of up to 40% are massive, a 99% absolute risk difference has yet to be discovered in medicine, tempering the parachute analogy and bolstering the need for randomized evidence.” - Powell & Prasad

- Pereira TV, Horwitz RI, Ioannidis JPA. Empirical Evaluation of Very Large Treatment Effects of Medical Interventions. *JAMA.* 2012

Figure 2. Treatment Effects in Index Trials vs the Meta-analysis of All Trials on the Same Topic (Under a Random-Effects Model).



Pereira et al.



“However, is a randomized trial necessary for every intervention? Glasziou and colleagues tackled this question by developing a model to assess when well-designed observational evidence for treatments is sufficient enough to eliminate the need for randomized trials, such as insulin for diabetes or liver transplantation in end-stage liver disease” - Powell & Prasad

- Glasziou P, Chalmers I, Rawlins M, McCulloch P. When are randomised trials unnecessary? Picking signal from noise. *BMJ* 2007
- Mentioned literature
 - Smith G C S, Pell J P. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. *BMJ* 2003
 - Yeh R W, Valsdottir L R, Yeh M W, Shen C, Kramer D B, Strom J B et al. Parachute use to prevent death and major trauma when jumping from aircraft: randomized controlled trial. *BMJ*
- **Parachute pt. 2 [33:00]**
 - Hayes MJ, Kaestner V, Mailankody S, **Prasad V.** Most medical practices are not parachutes: a citation analysis of practices felt by biomedical authors to be analogous to

parachutes. *CMAJ open*

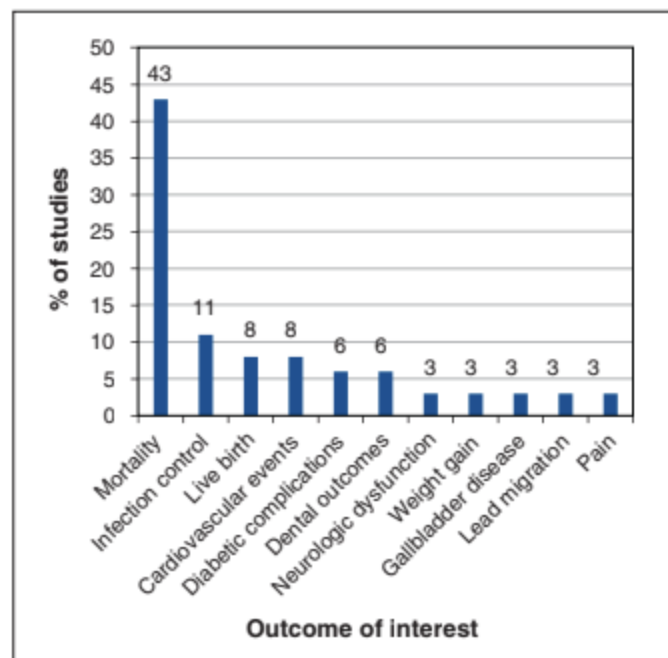


Figure 2: Outcome of interest for medical practices analogized to parachutes.

Hayes et al.

- **Pragmatic trials and sham surgery [37:00]**

- Prasad V., Cifu A. The Necessity of Sham Controls *The American Journal of Medicine*

“So people who say it's unethical to do the study, I would argue back, it's unethical *not* to do this study, you're playing Russian roulette, and you could be harming hundreds of 1000s of people. It's something you don't know that works.” - VP

- **Cost [45:30]**

- A conventional randomized control trial can cost \$2,000 per patient
 - However, if done correctly, the cost may be significantly reduced

“The reason it's expensive is that we have, again, just like United Airlines, we've added all this *stuff*” - VP

- Speich B, von Niederhäusern B, Schur N, et al. Systematic review on costs and resource use of randomized clinical trials shows a lack of transparent and comprehensive data. *J Clin Epidemiol.* 2018



*“The median costs per recruited patient were USD **409** (range: USD 41-6,990). Overall costs of an RCT, as provided in 16 articles, ranged from USD 43-103,254 per patient, and USD 0.2-611.5 Mio per RCT but the methodology of gathering these overall estimates remained unclear in 12 out of 16 articles (75%).” - Speich et al.*

Plenary Session is a podcast on medicine, oncology, & health policy.

Host: Vinay Prasad, MD MPH from University of California, San Francisco.

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