JUMP START

Energize your Research in Parenteral Nutrition

JUMPstart Virtual Meeting

Basic module JUMPstart 2021: Day 1 Presentation slides

January 30, 2021

Introduction

Dear JUMPstart participants,

We are happy to share with you the presentation slides for the Basic module. In this document, you will find the content presented in the live meeting on Saturday January 30. For your convenience, the slide numbers in this booklet correlate with those you will see in the live meeting.

Some slides (indicated by the  icon) will not be shown in the live session but are available for further information within this booklet.

Please feel free to use this document to take notes and refer back to.

Please do not share or reproduce any of the content within this booklet.

If you have any questions please contact: JUMPstart@fresenius-kabi.com.

Meeting agenda: Saturday, Jan 30, Part I

Time (GMT)	Session	Lead
Part I: A bird's eye view - Getting the big picture of study design		
13:05	Introduction to clinical research (Part I)	Prof. Mette Berger
13:20	Introduction to clinical research (Part II)	Prof. Bob Martindale
13:40	Q&A	
13:50	Defining the trial participants I	Prof. Olav Rooyackers
14:10	Defining the trial participants II	Prof. Mette Berger
14:25	Discussion	
14:35	**Break (20 minutes)**	

Meeting agenda: Saturday, Jan 30, Part II

Time (GMT)	Session	Lead
14:55	Welcome back	Prof. Mette Berger
15:00	**Bubble discussions**	All
Part II: Down to the nitty gritty - Running a clinical study in detail I		
15:15	From evidence gap to archiving: Life cycle of a CT	Prof. Ho-Seong Han
15:35	Discussion	
15:45	Statistics in planning and evaluating CTs – Part 1	Prof. Tim Friede
16:15	Discussion	
16:25	Statistics in planning and evaluating CTs –Part 2	Prof. Tim Friede
16:55	Close of Day 1	Prof. Mette Berger Dr. Anke Wenn

CT, clinical trial

Contents: Day 1

Part I: A bird's eye view - Getting the big picture of study design

Part II: Down to the nitty gritty - Running a clinical study in detail I

Part I: A bird's eye view - Getting the big picture of study design

Introduction to clinical research Part I

Prof. Mette Berger

FRESENIUS KABI
caring for life

JUMPstart Training Program

Introduction to clinical research

Why training matters?

Clinical study design impact on results

Prof. Mette M Berger, M.D., Ph.D

Basic Module: Running a clinical trial; Day 1, Part I: A bird's eye view - Getting the big picture of study design

This extended version contains the slide set as presented by Prof. Mette Berger and additional content marked with this icon:

Murphy's law

adage in Western culture

« Whatever can go wrong will go wrong, and at the worst possible time, in the worst possible way »

or

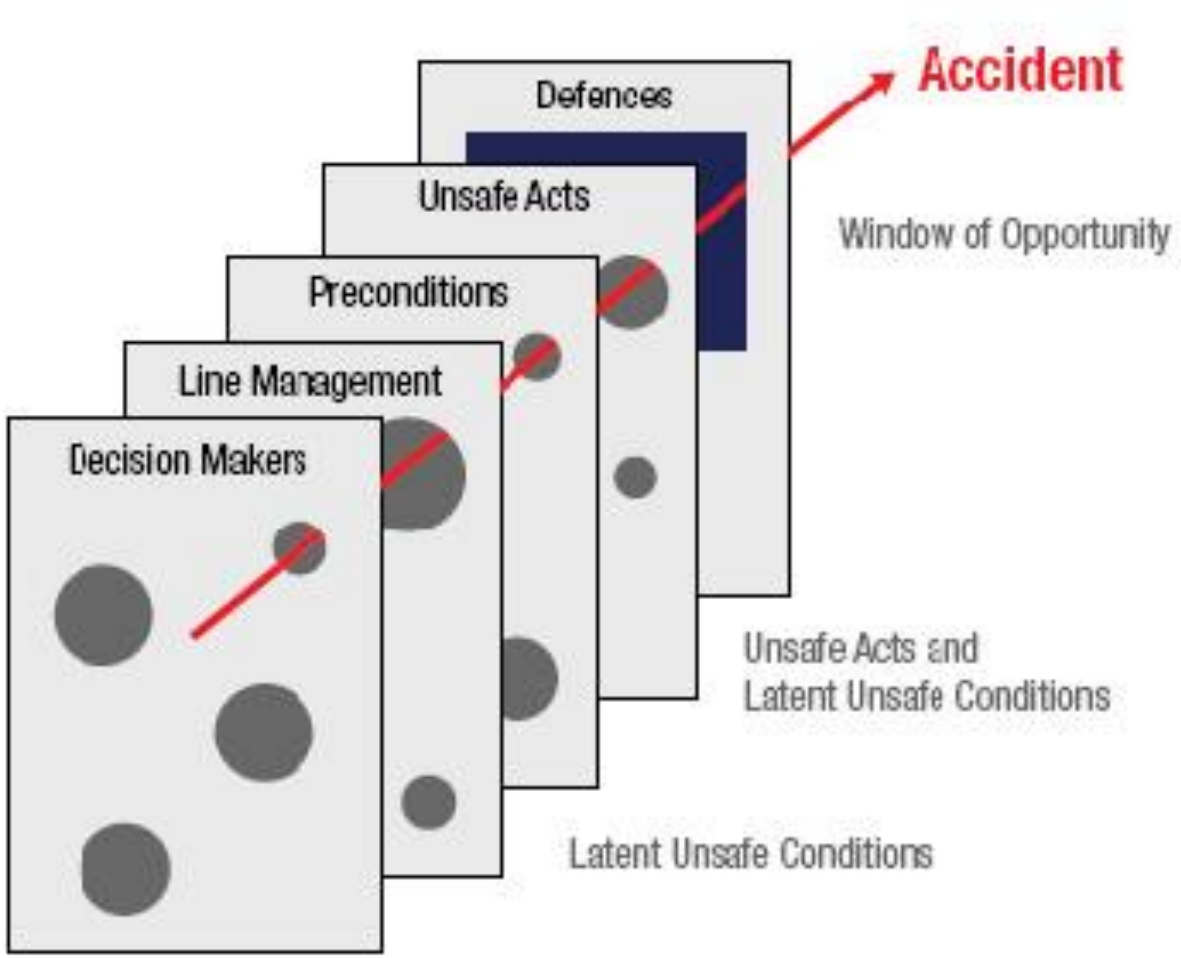
« If anything can go wrong, it will, and usually at the most inopportune moment ».

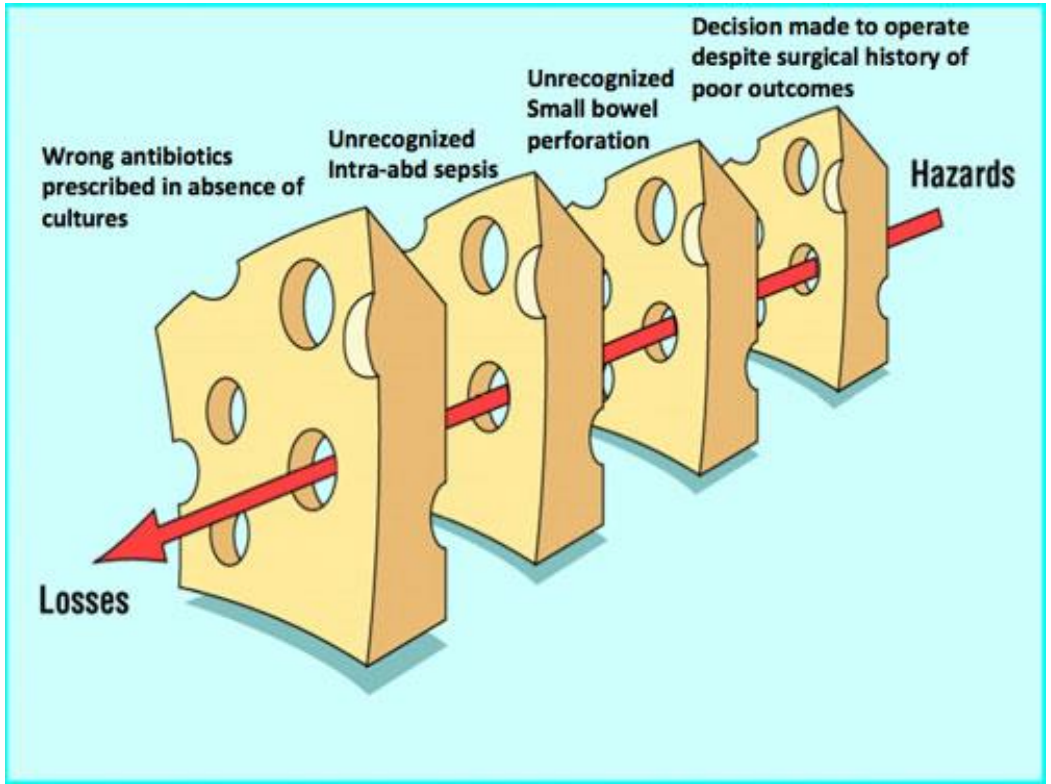
Flanagan's Precept = addendum to Murphy's Law is « Murphy was an optimist »

Edward Aloysius Murphy Jr. (January 11, 1918 – July 17, 1990) - American aerospace engineer who worked on safety-critical systems

The Swiss Cheese model: Model of Accident Causation

James Reason 1990





Problems that may occur and compromise the study

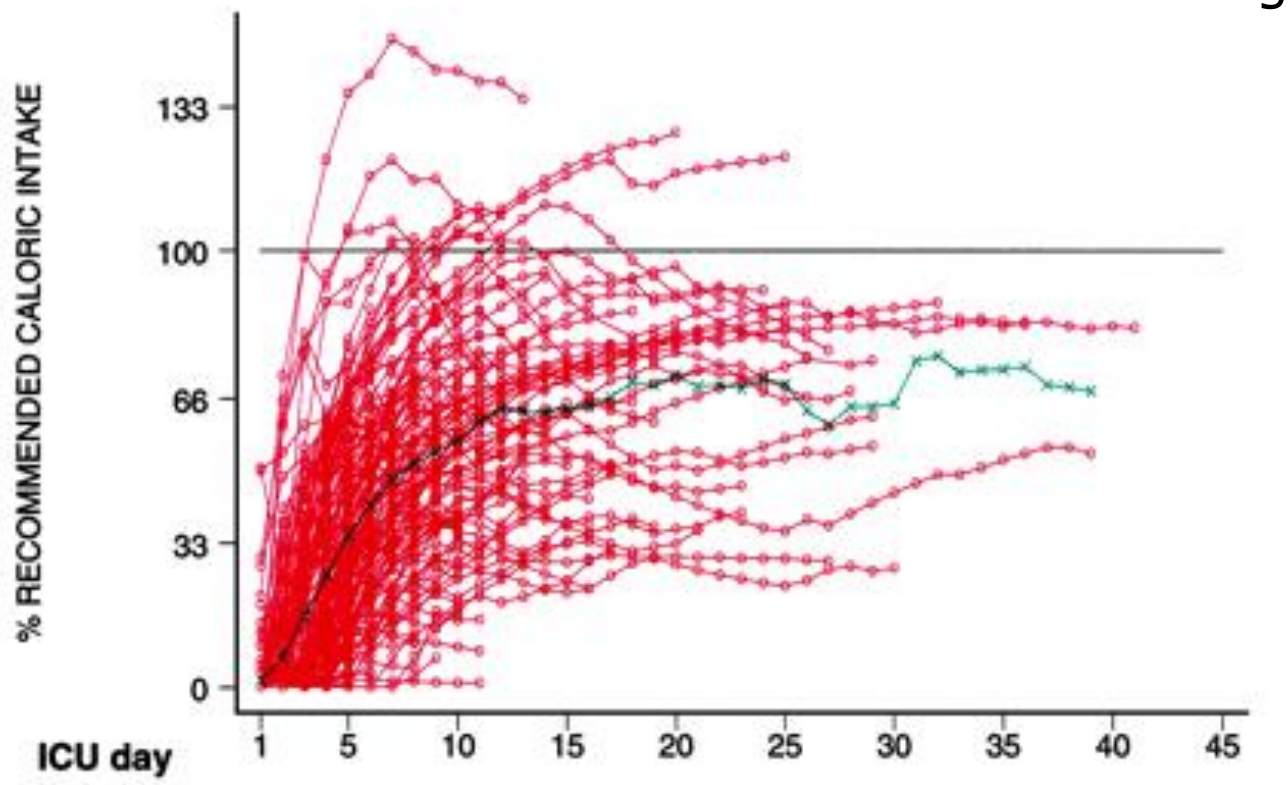
- Design issues:
  - Asking the right question
  - Choice of the design (2x2 factorial…, before after…)
  - Defining adequate endpoints (cave composite)
  - Optimal population definition (representative?)
  - Optimal control solution
- Realisation issues
  - E.g.: not delivering the what was intended
  - Loss to follow up, etc.
- Co-investigator skills and presence
- Sampling & laboratory problems

Typical example of fooling

Caloric Intake in Medical ICU Patients

Krishnan et al, Chest 2003: 124:297

Best outcome in 33-65% of ACCP targets



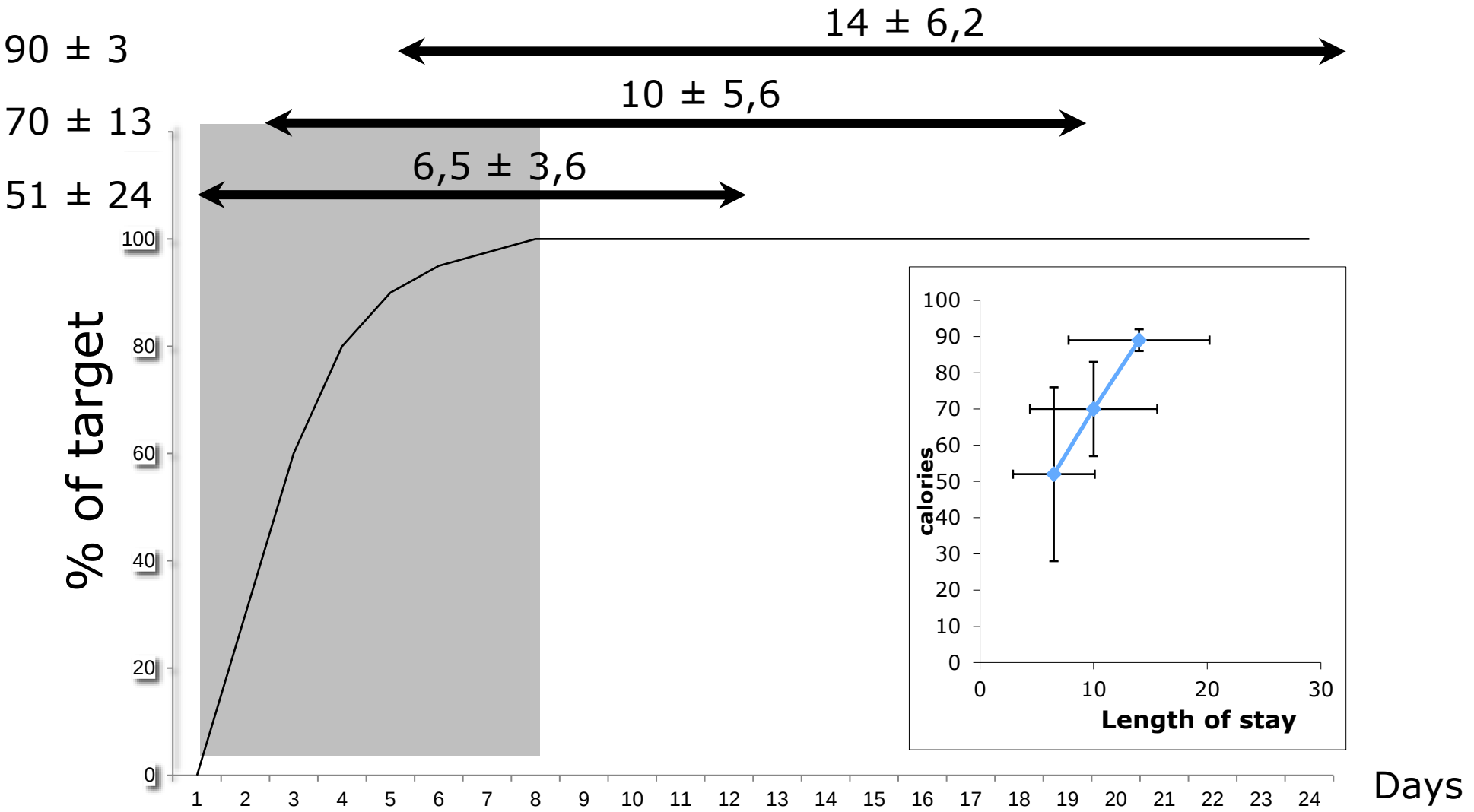
# Participants	187	186	95	45	26	16	5	3	1	0

A mixture of very different patients
Short stayer overwhelm the picture: have the best outcome

Cumulative average caloric intake since ICU admission for 187 patients (55 yrs). Horizontal line at caloric intake represents 100% of the target caloric intake ← ACCP guidelines (27.5 kcal/kg)

Conclusion: ACCP targets overestimate needs, since moderate caloric intake (ie, 33 to 65% of targets; approx. 9-18 kcal/kg/day) was associated with better outcomes

Don’t get fooled (1)

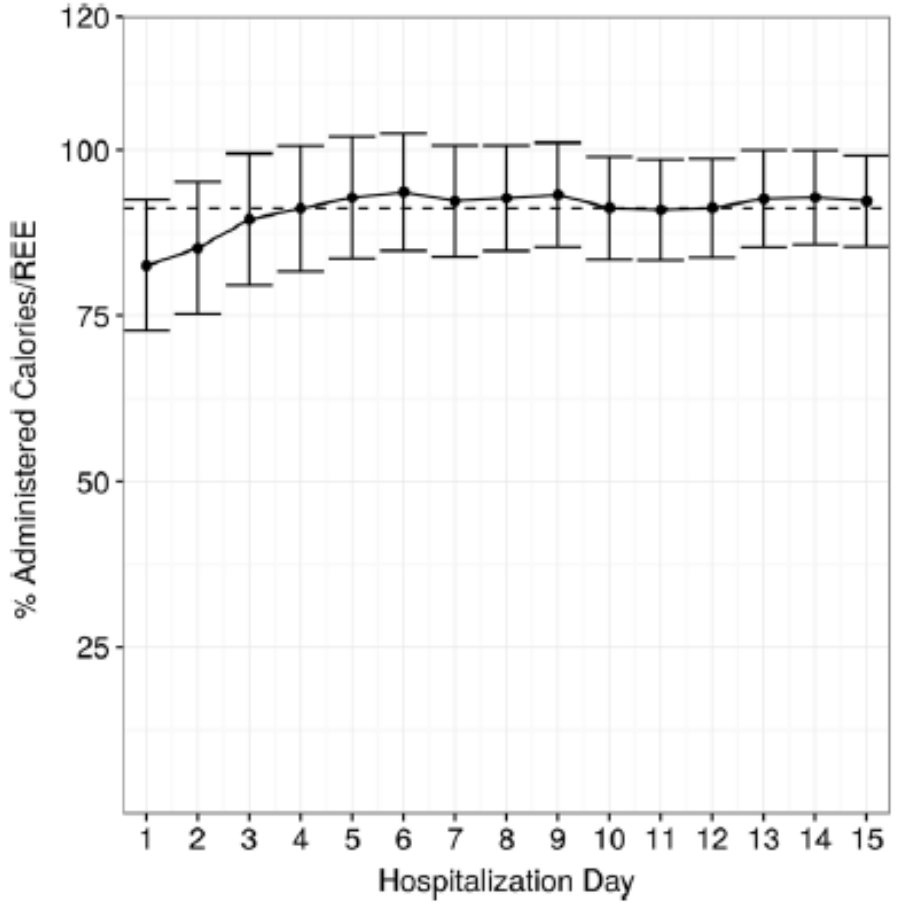


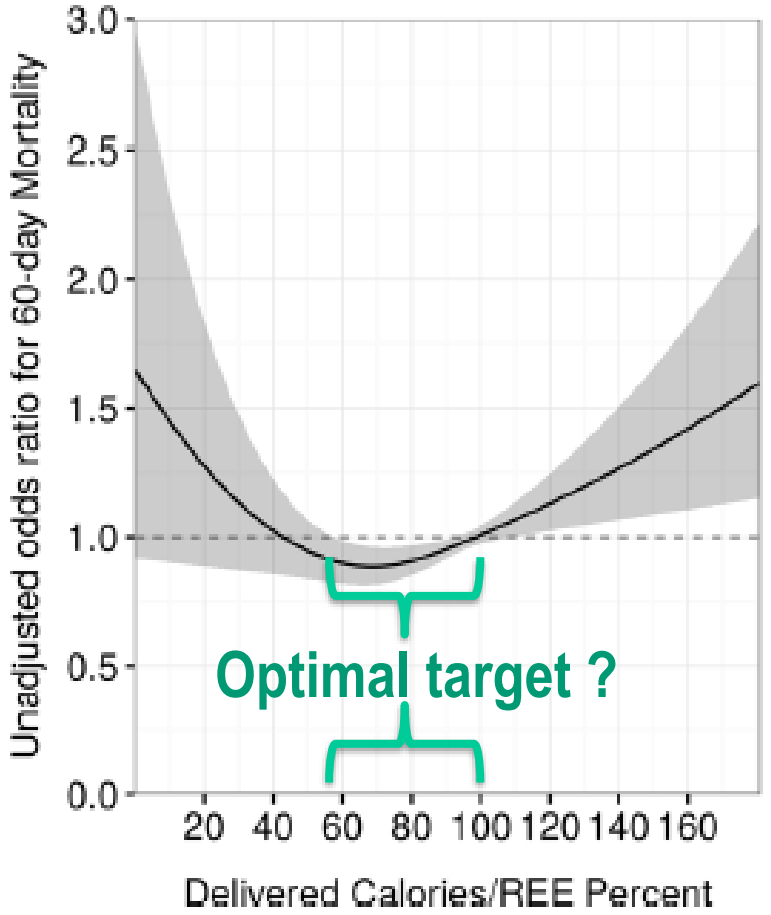
Why do patients stay shorter? Less severe → they do better

Courtesy Pr E.Fontaine

Resting energy expenditure, calorie and protein consumption in critically ill patients: a retrospective cohort study

Zusman et al, Crit Care 2016: 20: 367





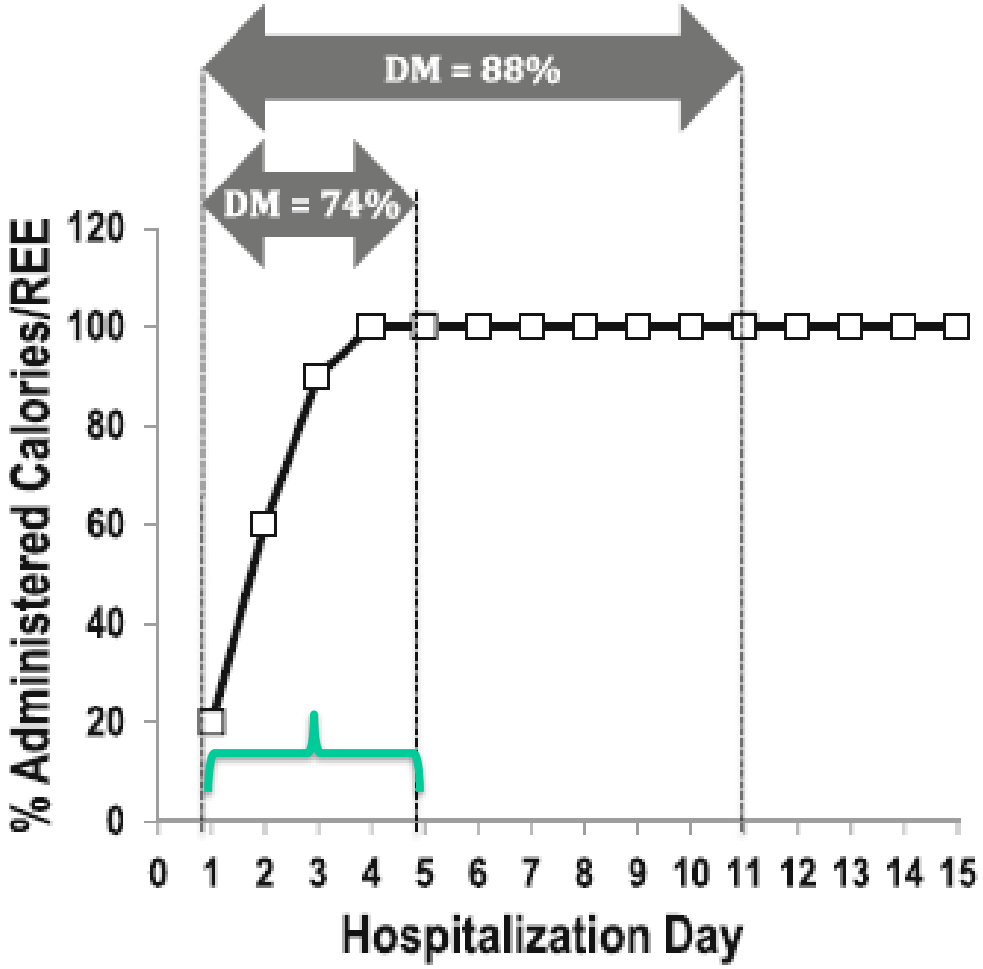
1171 patients had IC measurements, → 5012 IC measurements.

Median age 58 (IQR 34) yrs - **Median LOS was 5 (IQR 10)** days

Median LOS for those remaining in the ICU for >96 hours was 11 (IQR 13) days

Mean Energy delivery value by LICU

Berger et al. Crit Care (2017) 21:39



Example of calories administered to a patient.

The daily mean (DM) of calories is 74% if the patient leaves the ICU at day 5 but 88% if the patient leaves at day 11.

The only way to make the mean unaffected by the length of stay is to calculate the mean only once the delivered calories have reached a plateau

Inappropriate control solution

Trial examples

-OMEGA (low protein supplements)

-Omega-3 trials – fat 52% as control

-NOURISH – carbs versus high protein + vit + HMB

Mode of administration

complicates outcome analysis

- OMEGA – bolus feeding (vs continuous) → vomiting

Enteral Omega-3 Fatty Acid, γ-Linolenic Acid, and Antioxidant Supplementation in Acute Lung Injury

Rice et al, JAMA 2011, 306: 1574

- **OMEGA study**, multicenter RCT: **272 adults** within 48 hours of developing **ALI** (P/F<300) requiring mechanical ventilation
- **2-daily enteral supplements** of n-3 PUFAs, γ-linolenic acid, and AOXs compared with an isocaloric control - bolus
- The study was stopped early ← futility
- 2-daily n-3 supplements did not improve I-ary endpoint despite an 8-fold ↑ plasma EPA

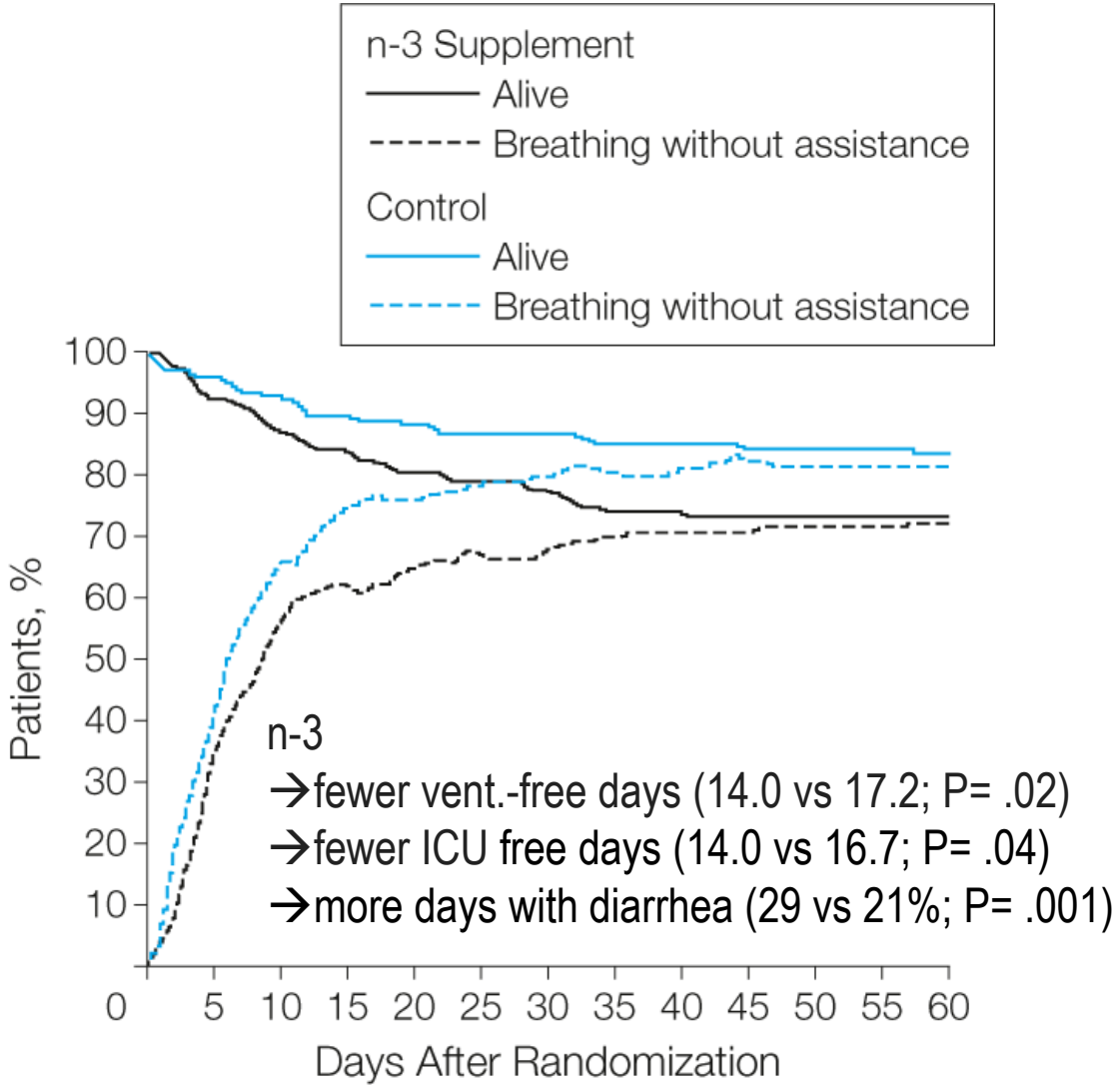
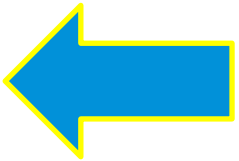


Table 1. Daily Nutrients in Omega-3 (n-3) vs Control Supplements

Nutrient	n-3 (240 mL)	Control (240 mL)
Energy, kcal	480	474
Protein, g	3.8	20
Carbohydrate, g	4.2	51.8
Fat, g	44.6	22
EPA	6.84	0
DHA	3.40	0
GLA	5.92	0
Vitamin C, mg	1000	76
All-natural vitamin E, IU	440	12
Beta-carotene, mg	4.8	0
Zinc, mg	24.2	5.6
Selenium, µg	85.2	18
LCarnitine, mg	180	38
Taurine, mg	350	138

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GLA, γ-linolenic acid.

Rice et al, JAMA 2011



5 x more protein in the control group !!!

Underfeeding in both groups
Bolus feeding

Comments to OMEGA & EDEN Trophic trials

Low severity illness of a young patient population

(52 yrs, P/F < 300!, obese BMI 30)

Both groups hypocaloric : proteins maintained in one group

Bolus EN is not standard in first days of ICU

Lipid bolus via gastric or postpyloric access → ↑incidence of diarrhea in study group, potentially resulting in malabsorption (F,W,M, 2012)

The success of 2×2 factorial design depends on the low interactions between the 2 interventions. Which is probably not the case (low-caloric EN)

Felbinger, Weigand & Mayer JAMA 2012;307:144

NOURISH

ONS Composition & Product Intake

Deutz et al, Clin Nutr 2016

Variable	Placebo ($n = 309$)	HP-HMB[b] ($n = 313$)
Mean age (SD), y	78.1 (8.6)	77.7 (8.2)
Male, *n* (%)	149 (48.2)	149 (47.6)

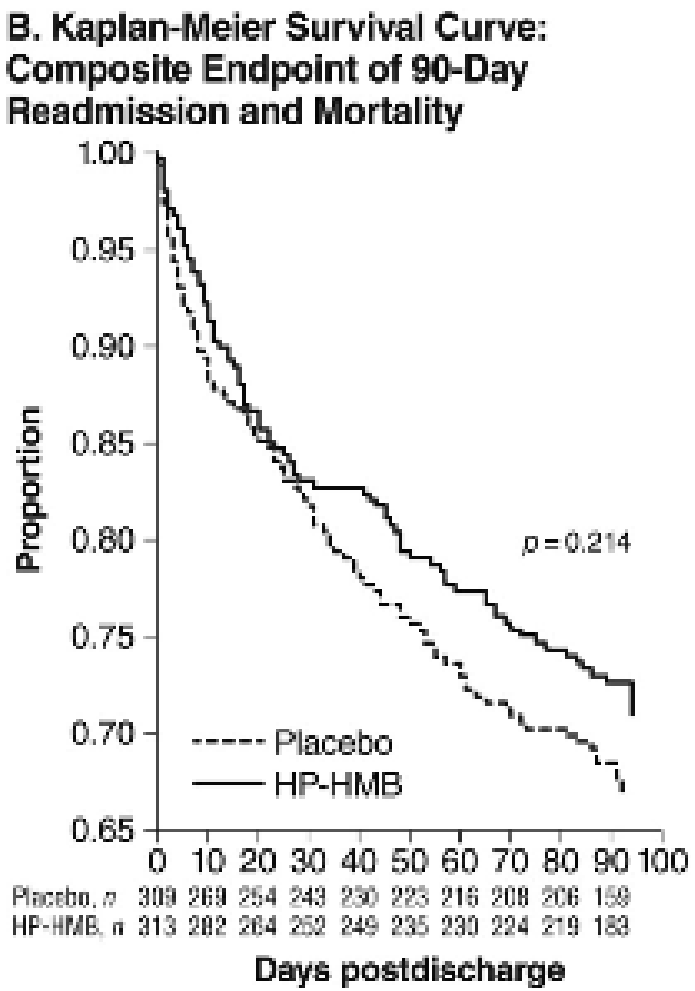
Supplementary Table 5. Study Product Intake Based on Paks per Day[a]

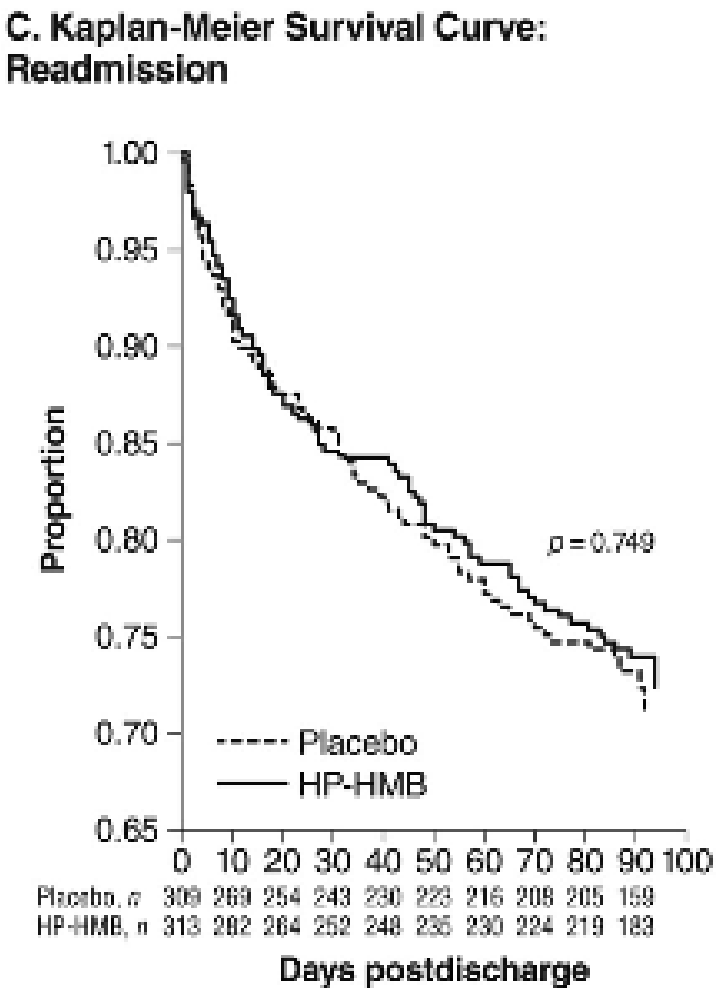
Adherence	Placebo	HP-HMB
In hospital		
n	309	311
Intake, Paks/day, mean (SE)	1.45 (0.03)	1.46 (0.03)
Percent of expected intake, mean (SE)	72.68 (1.49)	73.15 (1.45)
Discharge through 10 days post-discharge (or readmission/death)		
n	227	242
Intake, Paks/day, mean (SE)	1.69 (0.03)	1.65 (0.03
Percent of expected intake, mean (SE)	84.70 (1.56)	82.44 (1.59)
Discharge through 30 days post-discharge (or readmission/death)		
n	231	243
Intake, Paks/day, mean (SE)	1.57 (0.04)	1.54 (0.04)
Percent of expected intake, mean (SE)	78.36 (1.86)	76.86 (1.77)

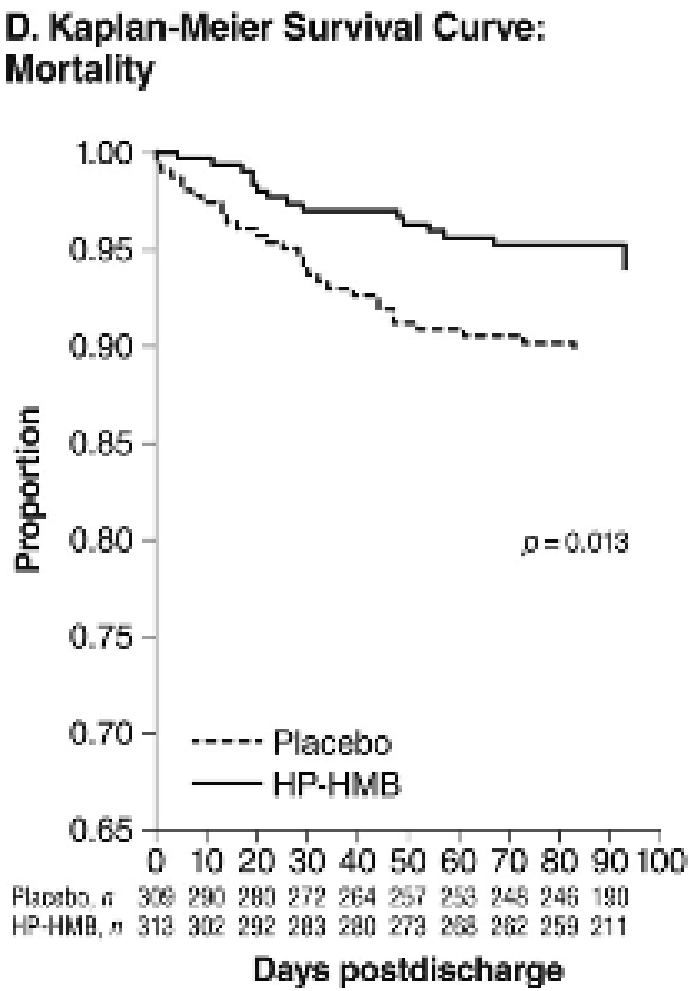
[a]Patients were encouraged to take 2 Paks per day.
HP-HMB, high-protein beta-hydroxy-beta-methylbutyrate; SE, standard error.

		HP-HMB	Placebo	RDA
Volume	mL	237	237	
Energy	Kcal	350	48	
Protein	g	20	–	
Fat (corn oil and canola oil)	g	11	–	
Linoleic acid	g	3	–	
Carbohydrate	g	44 / 45	12	
Fructo-oligosaccharide	g	3 / 2	–	
Sugar	g	20	12	
Ca-HMB	g	1.5	–	
Vitamin A (palmitate)	IU	1000	–	3000
Vitamin D_3	IU	160	–	600
Vitamin E	IU	30	–	15
Vitamin K_1	mcg	20	–	120
Vitamin C	mg	60	10	90
Folic acid B9	mcg	200	–	400
Vitamin B_1	mg	0.38	–	1.2
Vitamin $B_{2\text{ - riboflavin}}$	mg	0.43	–	1.3
Vitamin B_6	mg	0.5	–	1.7
Vitamin B_{12}	mcg	3	–	2.4
Niacin B3	mg	5	–	16
Pantothenate	mg	2.5	–	5
Biotin	mcg	75	–	30
L-carnitine	mg	43	–	
Choline	mg	83	–	
Sodium	mg	240	–	
Potassium	mg	560	–	
Chloride	mg	150	–	
Calcium	mg	500	–	1200
Phosphorus	mg	350	–	700
Magnesium	mg	100	–	420
Iron	mg	4.5	–	8
Zinc	mg	15	–	11
Manganese	mg	0.5	–	2.3
Copper	mg	0.5	–	0.9
Iodine	mcg	25	–	150
Selenium	mcg	30	–	55
Chromium	mcg	30	–	30
Molybdenum	mcg	30	–	45

NOURISH - HMB – composite primary endpoint: ns (readmission+ mortality) while mortality significantly reduced p=0.013







A PERSONAL EXPERIENCE OF MURPHY'S LAW

SPN - Combined EN + PN strategy

Heidegger et al, Lancet 2013; 381: 385

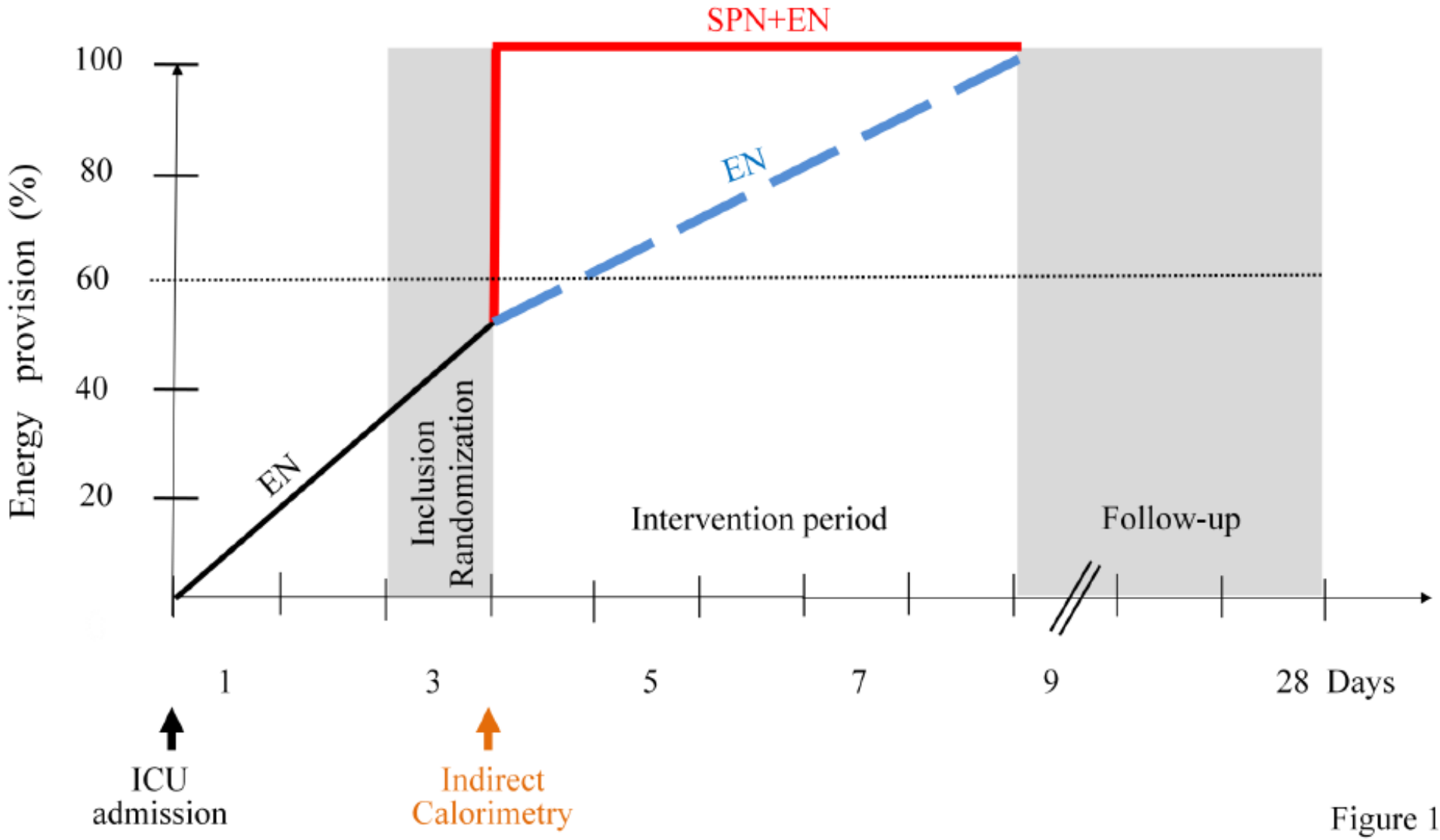
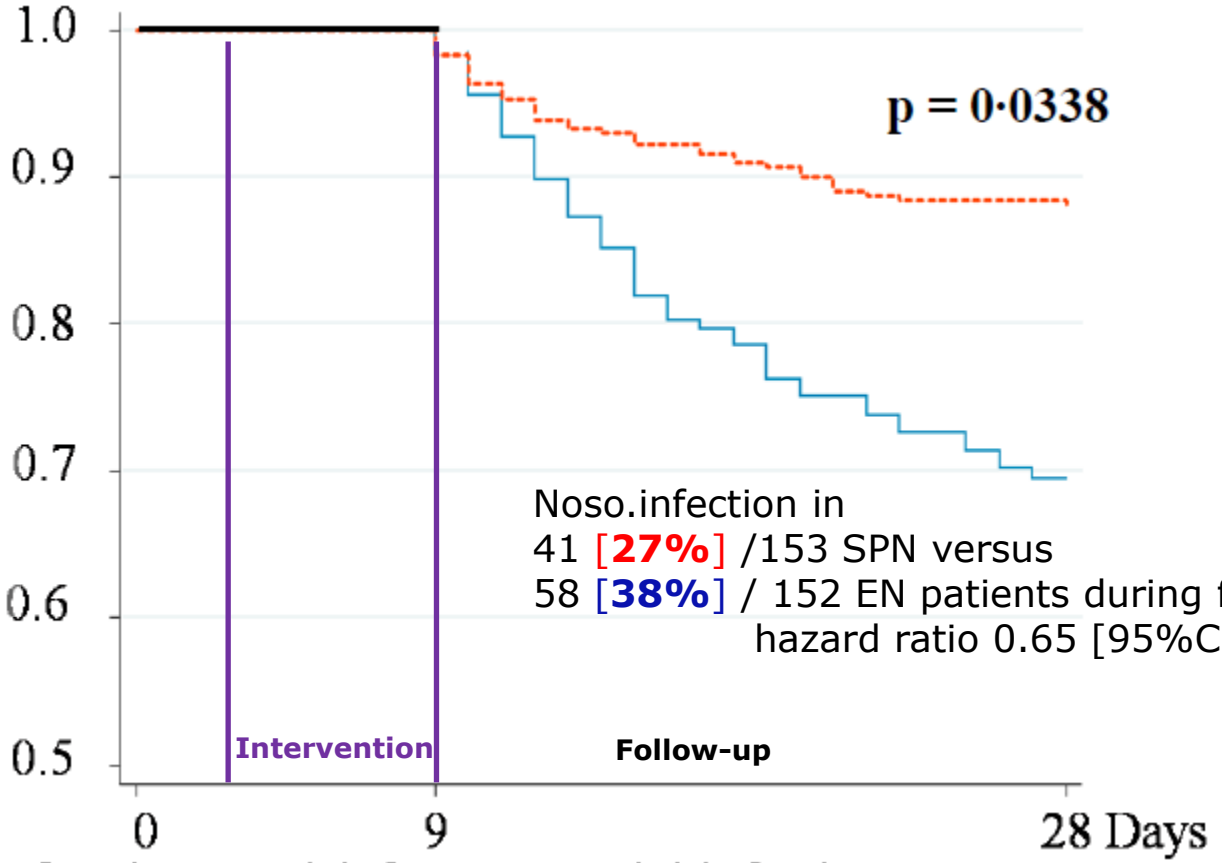


Figure 1

Optimization of energy provision with SPN improves the clinical outcome of critically ill patients: a randomized controlled clinical trial

Heidegger et al, Lancet 2013; 381: 385

Was criticised for not showing similar infections rates during intervention (published in original Table 3 ☺)
Time to effect of nutrition intervention?



Noso.infection in
41 [**27%**] /153 SPN versus
58 [**38%**] / 152 EN patients during follow up
hazard ratio 0.65 [95%CI 0.43–0.97]

Number of patients at risk for nosocomial infections

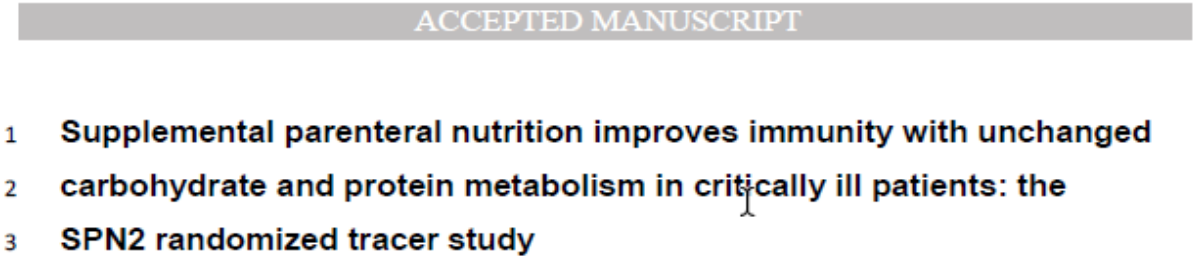
SPN	153	148	99
EN	152	147	71

ACCEPTED MANUSCRIPT

1 **Supplemental parenteral nutrition improves immunity with unchanged**
2 **carbohydrate and protein metabolism in critically ill patients: the**
3 **SPN2 randomized tracer study**

ClNu online 5 Nov 2018
Clin Nutr 2019; 38: 2408

- Study project: 2012
- Study funding: 2013
- Submission of protocol to Ethics: 13 SEP 2013
- Ethics Approval: 5 DEC 13
- Study screening – started in May 2014
- 1st inclusion+ consent: 20th May: after D4 study patient transferred and lost on D5, 22nd May
- 2nd inclusion + consent 4th June 2014
- Last 28th inclusion: 22nd April 2016
- Additional laboratory determinations → March 2018


ACCEPTED MANUSCRIPT

1 **Supplemental parenteral nutrition improves immunity with unchanged**
2 **carbohydrate and protein metabolism in critically ill patients: the**
3 **SPN2 randomized tracer study**

ClNu online 5 Nov 2018
Clin Nutr 2019; 38: 2408

Collaborators:

0) Principal investigator MMB reduced her activity at CHUV -1.NOV13
1) Dietician: after training on MetaVision and protocol, nearly fainted in the ICU upon attempting ventilator connection – decided she could not work in the ICU
2) 1st Physician – AN – 1.4.2014 start 100%: but pregnancy with complications → progressive reduction of activity, and stop may 2015. Payment prolonged for stilling – short of money
3) Study nurse – CP from the CRC – 15.1.2015: 125 CHF/hour – helped through study
4) 2nd Physician – NJR – nov 2014: not trained in research, was working in private practice. Accepted to work for no money – but training
5) HPLC apparatus at Physiology institute : 6 months delay in tracer determinations

How to avoid these problems?

Interdisciplinary discussions during protocol development

Initial trophic feeding v. full enteral in patients with acute lung injury: the EDEN trial

Rice et al, JAMA 2012, 307: 795

Aim: To determine if initial lower-volume trophic EN would increase ventilator-free days and decrease gastrointestinal intolerances compared with initial full enteral feeding.

Patients: 1000 adults within 48 hours of developing acute lung injury (P/F < 300) requiring mechanical ventilation

Results: Both groups underfed - The full-feeding group received about 1300 kcal/d vs. 400 kcal/d (P < .001).

Ventilator-free days ns (14.9 vs 15.0d) Infections ns

60-day mortality ns (23.2% vs 22.2%).

Full-feeding group more vomiting (2.2% vs 1.7%: P = .05), Higher GRV (4.9% vs 2.2%; P < .001), and constipation (3.1% vs 2.1%; P = .003). Mean plasma glucose & insulin administration higher in full-feeding

Mean age 51 yrs, well nourished BMI 29.3

Introduction to clinical research Part II

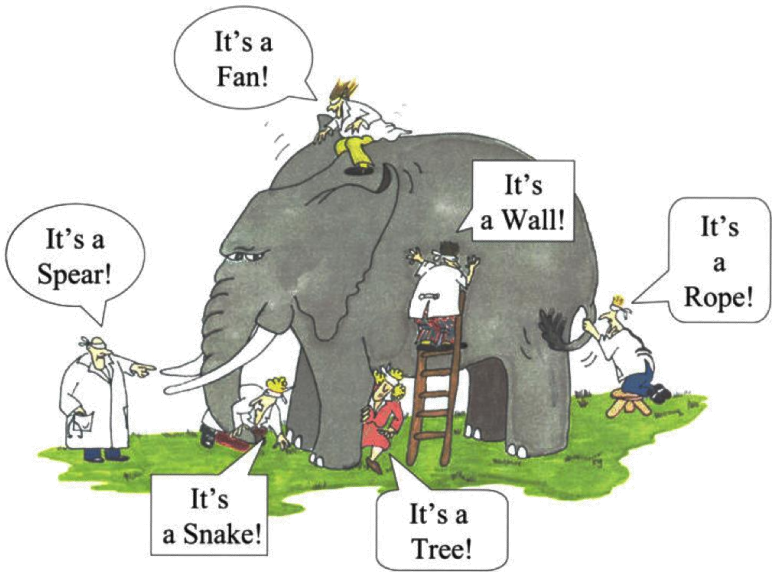
Prof. Bob Martindale

FRESENIUS KABI
caring for life

JUMPstart Training Program

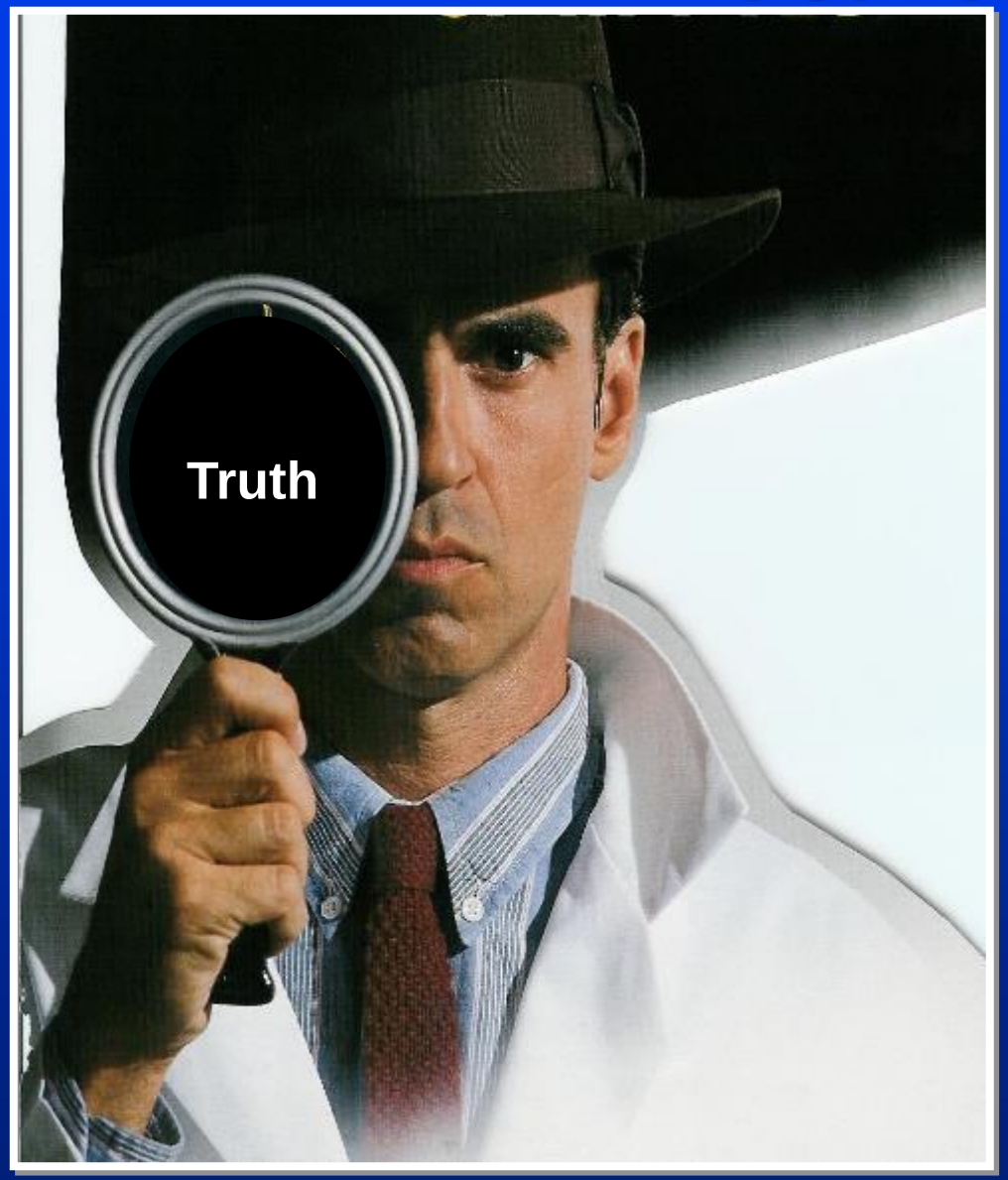
Introduction to Clinical Research Part II
The Big Picture: Observational Cohort Studies and Surveys

Prof. Bob Martindale MD PhD



Basic Module: Running a clinical trial; Day 1, Part I: A bird's eye view - Getting the big picture of study design

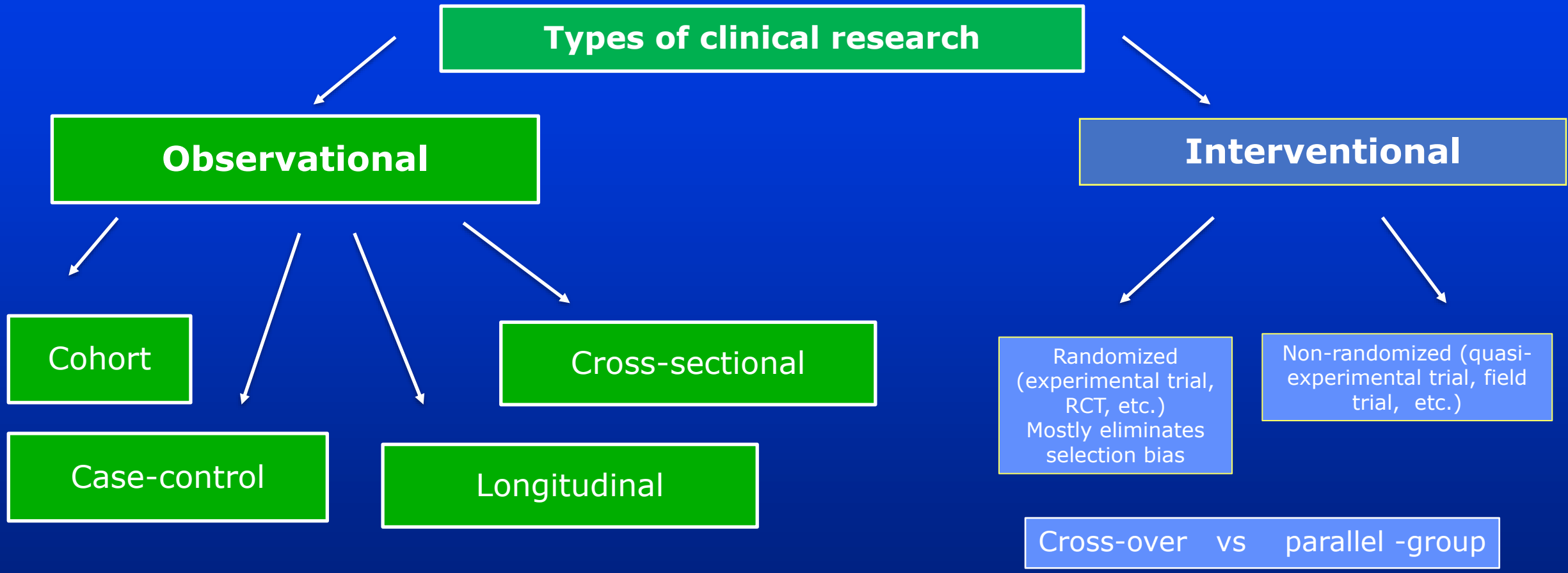
Searching for the Truth



Are observational cohort studies the answer ?

Clinical Study design

What are the most common type of studies performed?

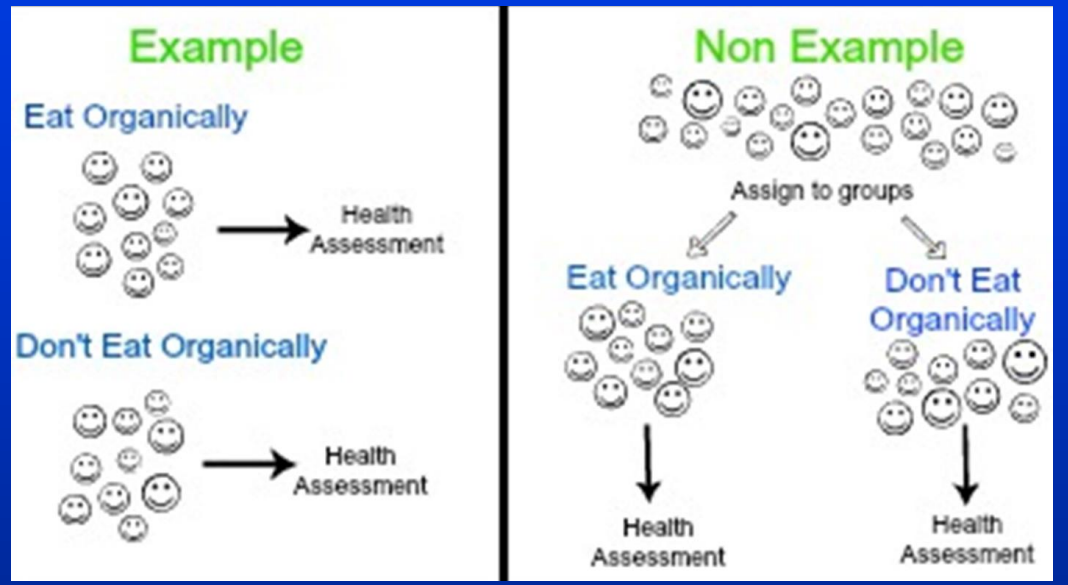


Definition: ob·ser·va·tion

The action or process of observing something or someone carefully in order to gain information.

Observational trials

- **Good for defining associations**
- **Cannot prove causation**
- **Excellent for hypothesis generations**
- **Observational studies make up approximately 8 of 10 clinical studies**



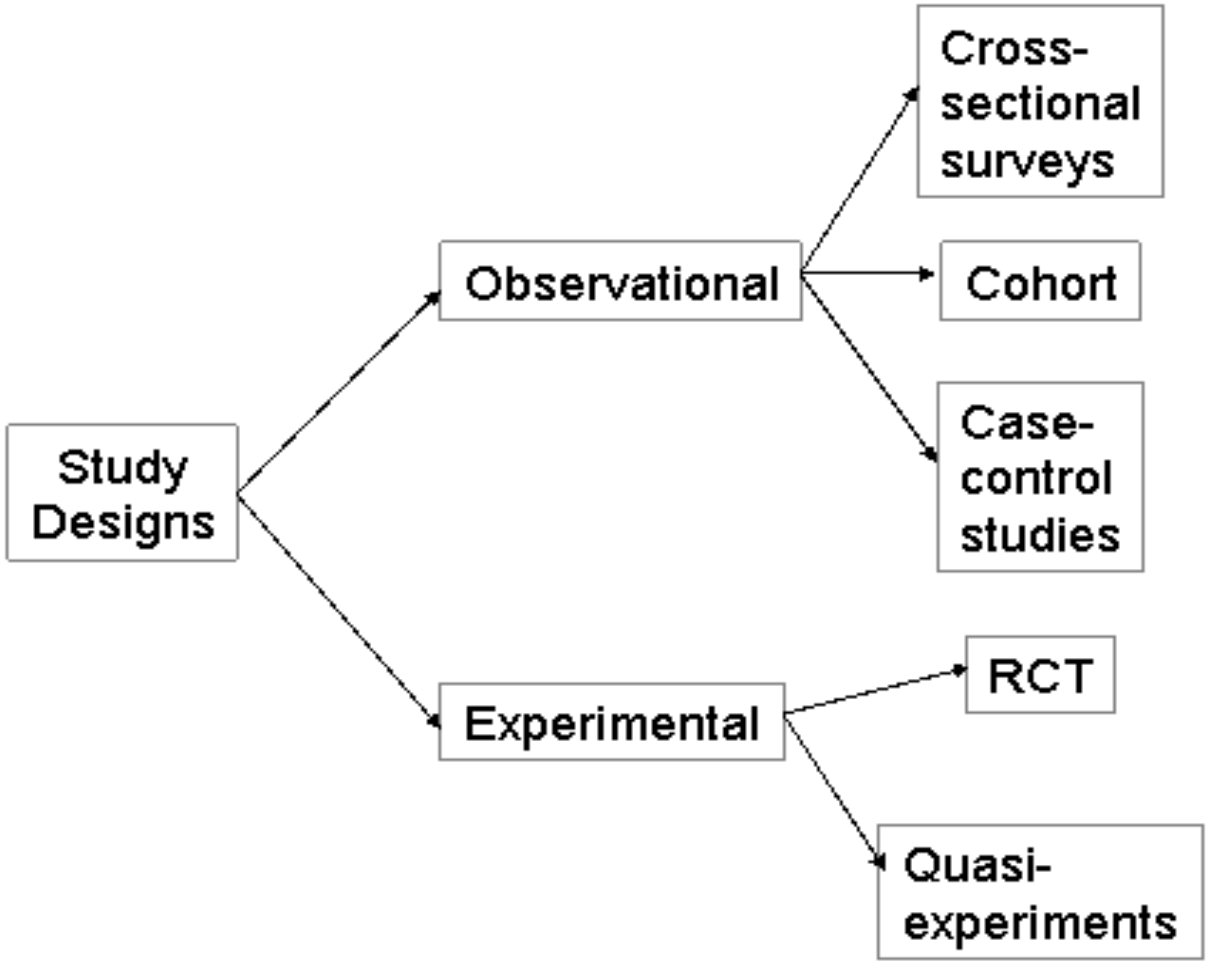
Vandenbroucke JP et al Int J Surgery 2014

Observational Studies: Realities

- Association can never prove causation
- Various methodologic biases can influence conclusions made in both RCTs and observational studies
- Subgroup analyses ***cannot*** prove hypotheses although they can generate them
- $P < 0.05$ is not the same as truth
- The failure to find a difference does not mean that no difference exists (type II error)
- Common errors with observational trials
  - occur when multiple analyses are performed
  - when trials are prematurely stopped for perceived benefit when there was no a priori plan to do so
  - small papers with dramatic results that are selectively published

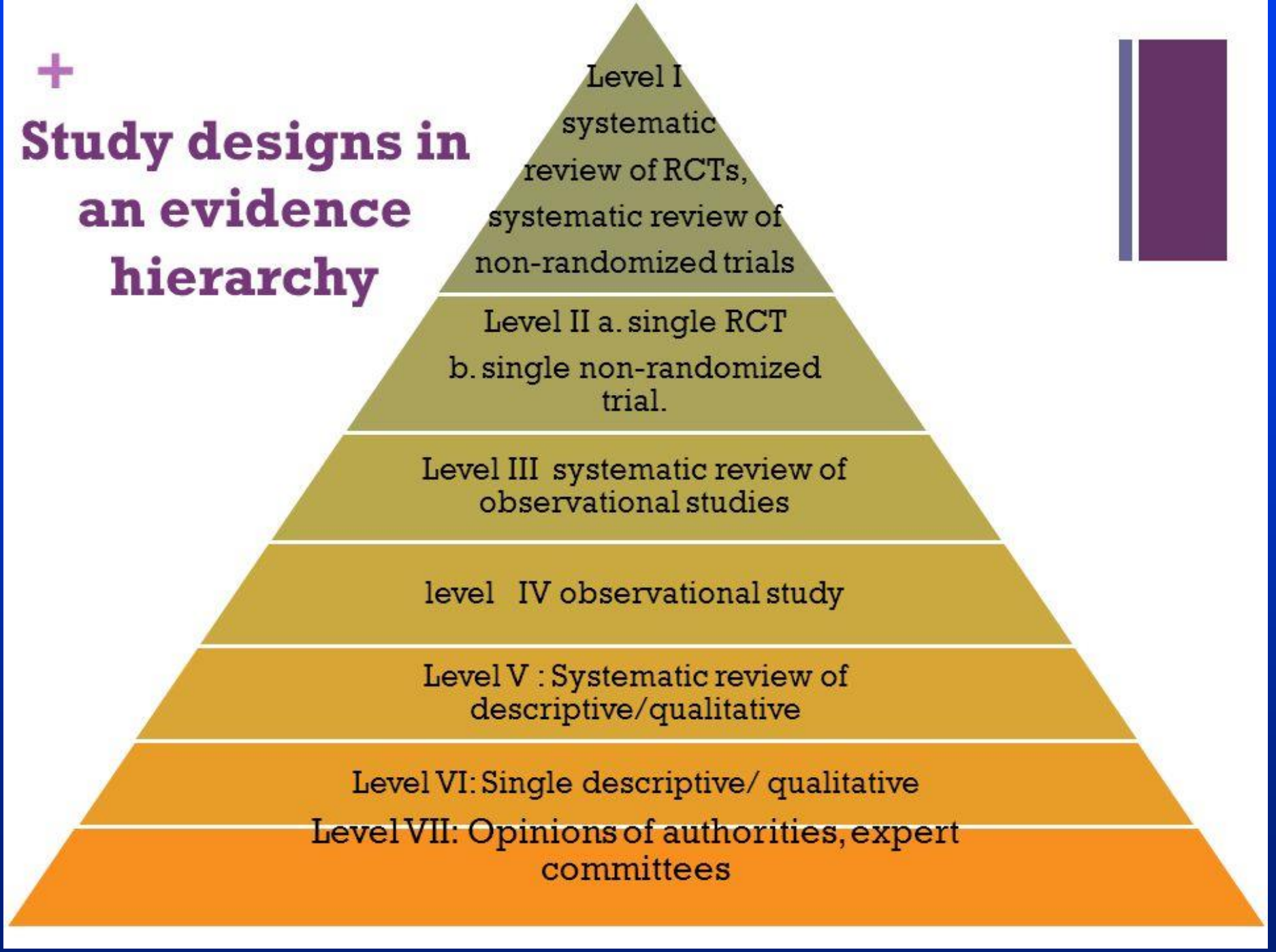
REFERENCE: Koretz R *Nutr Clin Pract.* 2019;34:60–72

Pro and Con of Study Designs

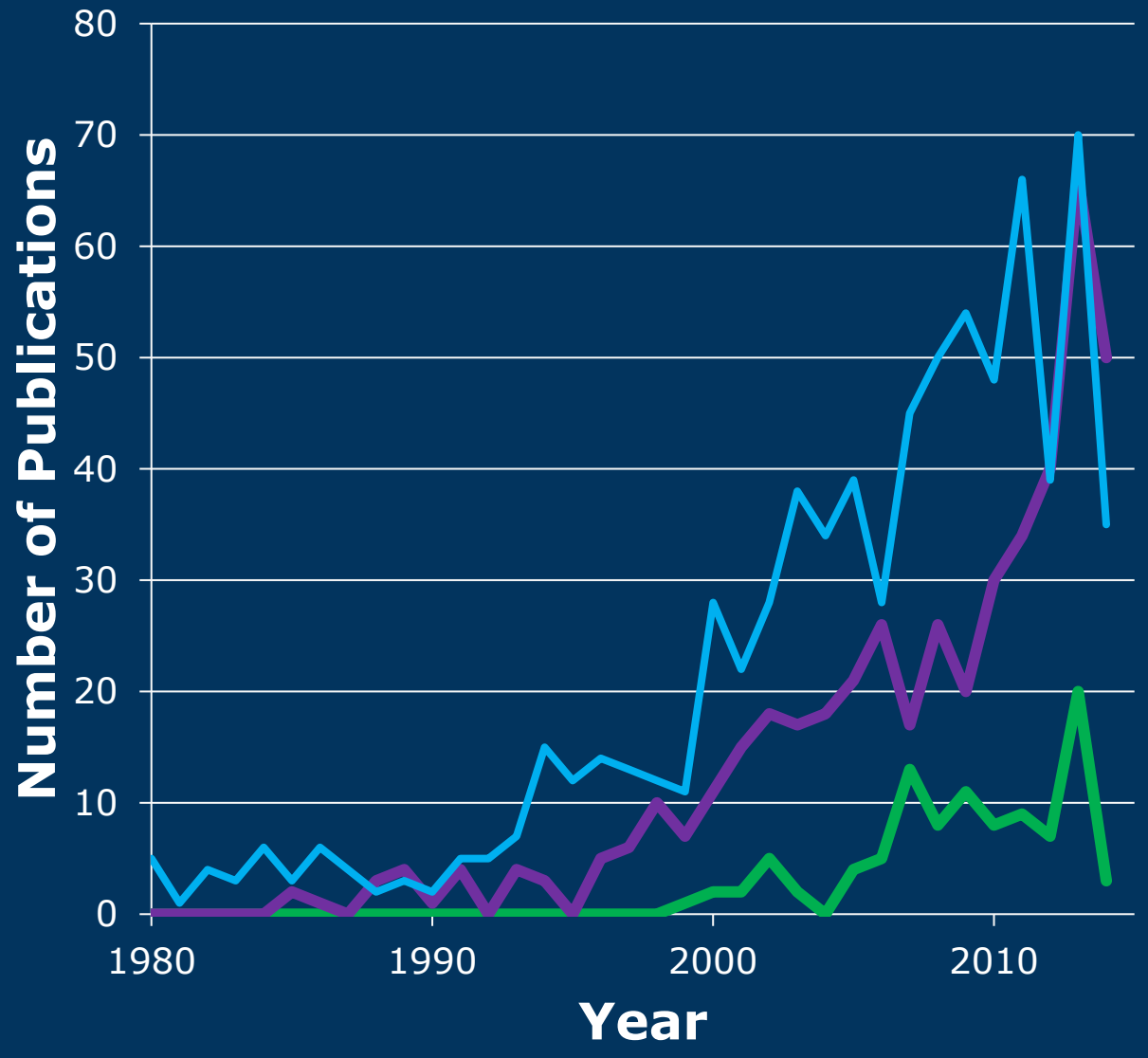


Advantages	Disadvantages
Quick; can cover whole population, giving representative information whether or not people are seeking care	Based mainly on self-report (biases?); diagnostic information usually inaccurate; can't establish causal sequence
Prospective, so can establish causal sequence; can estimate incidence	Time-consuming; costly; attrition of cohort?
Relatively cheap way of focusing on causal factors	Requires recall of past events (inaccurate?); controls not equivalent to cases
Controls for all main forms of bias; good for both etiological and evaluative research	Ethical concerns in etiological applications; Often uses selected populations: issue of generalizability?
May be more practical than RCT: can use "natural experiments"	Allocation bias often significant (exp'tal and control groups not equivalent)

Study designs in an evidence hierarchy



Ventral hernia publications by level of evidence



Level 4 N=757

Level 2 and 3 N=1

Level 1 (n=100)

Liang M, Martindale R 2016

Pitfalls of Observational Trails

- Principal disadvantage of a cohort design is lack of randomization
- Potential for confounding bias
  - Any study can change subjects habits etc
- Loss to follow-up which may result in selection bias
- No widely accepted guidelines in methods to assess consistency and arrive at actionable conclusions

Morton JC et al J Clin Epidem 2016
Stoto M et al eGEMS Chapter 2 Design of Observational Trials 2017
Laura Lee Johnson, in Principles and Practice of Clinical Research, Design of Observational Studies 2018

Questions to Consider When Choosing Data for an Observational Study

- Do the data contain a sufficiently long duration of follow-up after exposures?
  - example: following the effects of smoking on heart disease?
- Is there a complete dataset from all appropriate settings of care to comprehensively identify exposures and outcomes?
  - example: in SARS CoV-2 viral infections, what about asymptomatic patients ?
- Are there sufficient historical data to determine baseline covariates?
  - example: Is there historical information available to estimate differences expected ?

- **Greater Nutrient Intake Is Associated With Lower Mortality in Western and Eastern Critically Ill Patients With Low BMI: A Multicenter, Multinational Observational Study. Compher C, …. Heyland D et al JPEN 2019;43:63-69**
- **BACKGROUND:**
- **Little is known about the impact of feeding adequacy by NUTrition Risk in the Critically Ill (NUTRIC) groups in critically ill patients with body mass index (BMI) <20. Our purpose was to assess whether adequacy of protein/energy intake impacts mortality in patients with BMI <20 in Western/Eastern intensive care units (ICUs) and high/low NUTRIC groups.**
- **METHODS:**
- **Data from the International Nutrition Survey 2013-2014 were dichotomized into Western/Eastern ICU settings; BMI <20 or ≥20; and high (≥5)/low (<5) NUTRIC groups. Association of BMI <20 with 60-day mortality was compared in unadjusted and adjusted (Western/Eastern, age, medical/surgical admission, high/low NUTRIC group) logistic regression models. The impact of adequacy of protein/energy on 60-day mortality relationship was tested using general estimating equations in high/low NUTRIC groups, in unadjusted and adjusted models.**
- **RESULTS:**
- **Western (n = 4274) patients had higher mean BMI (27.9 ± 7.7 versus (vs) 23.4 ± 4.9, P < 0.0001) than Eastern (n = 1375), respectively. BMI <20 was associated with greater mortality (adjusted odds ratio [OR] 1.30, 95% confidence interval [CI] 1.07-1.57), with no interaction between BMI group and Western/Eastern ICU site. Among patients with BMI <20 and high NUTRIC score, 10% greater protein and energy adequacy was associated with 5.7% and 5.5% reduction in 60-day mortality, respectively. Results were not significantly different between Western and Eastern ICUs.**
- **CONCLUSIONS:**
- **The benefit of greater protein/energy intake in high-NUTRIC patients was observed regardless of geographic origin or low BMI, suggesting a consistent response to nutrition support in this group.**

Discussion Questions

- Can the association of BMI < 20 and increase mortality be made ?
- Are western or eastern ICU populations equal and does it matter for this trial ?
- What are the uncontrolled variables that may be confounding and may nullify the conclusions
- Are the data sufficiently granular for the purpose of the study?
- Are there a sufficient number of exposed individuals in the dataset?

- **Are all low-NUTRIC-score patients the same? Analysis of a multi-center observational study to determine the relationship between nutrition intake and outcome. Chourdakis M et al Clinical Nutrition 2018**

- **BACKGROUND:**
- **The NUTrition Risk in the Critically Ill (NUTRIC) scoring system is a tool useful, discriminating critically-ill patients benefiting from optimal nutrition intake (>80% of prescription). Recent recommendations advocate for withholding artificial nutrition among low-NUTRIC patients, however, we hypothesized that some low-NUTRIC patients would show an association between nutrition intake and outcome.**

- **METHODS:**
- **Patients were selected from the 2013-2014 International Nutrition Surveys when ICU length of stay (LICU) ≥72 h, baseline mNUTRIC score ≤4 and had at least three evaluable nutrition days (N = 2781). Proportion of prescription received during evaluable days was associated to 60-day hospital mortality by a logistic regression modelling. A priori, we expected that the association between proportion of prescription received and mortality might differ according to: LICU, BMI and prior unintentional weight loss or reduced oral intake.**
- **RESULTS:**
- **A total of 2781 patients fulfilled the inclusion criteria and participated in the study. Ten percent of the sample had a BMI <20 kg/m^{2}and 20% experienced either unintentional weight loss during the last 3 months, or reduced food intake over the last week. Sixty-day hospital mortality was 15% and median LICU reached 11.3 [6.3-21.7] days. Mean total prescription received by any means of nutritional support during the first 12 evaluable days was 57.4 ± 28.1% for energy and 53.7 ± 29.2% for protein. In the pooled, subgroup and sensitivity analyses, no significant associations were identified.**

- **CONCLUSION:**
- **Low-NUTRIC (≤4) patients demonstrate a prolonged length of stay in ICU, while experiencing significant mortality and a high prevalence of malnutrition risk factors. Although improvements in mortality were not achieved with increased nutritional intake, this should not be construed as a rationale for withholding artificial nutrition among this patient group.**

Discussion Questions to Consider

- What is the difference between the study and target population demographics and distributions of comorbid illnesses?
    - Will these differences affect the interpretation and generalizability of the results?
- Are the key variables available to define an analytic cohort
    - the study inclusion and exclusion criteria?
- Are the key variables available for identifying important subpopulations for the study?

Randomized controlled trials vs. observational studies: why not just live together?

David Faraoni[1] and Simon Thomas Schaefer[2*]

BMC Anesthesiology 2016

RCT's (efficacy studies)

1) Prospective protocol with strict inclusion and exclusion
2) Well defined intervention
3) Predefined endpoints

Down side:

- cost
- may not represent "real world"

Observational trials (effectiveness studies)

1) Sometimes the only option
   - ethical or cost issues
2) Less restrictive inclusion / exclusion makes conclusions generalizability "reflecting real world"
3) Sophisticated statistics can help
   - multivariable logistic regression
   - propensity matched analysis

Concepts in Making a Good Survey

- Start with straightforward material
- Shorter is better
  - ideal is less than 30 questions
- Logical order of progression
- Clear and precise language
  - Avoid jargon / technical terms
- Use response scales
  - response scales capture direction and intensity of attitudes.
  - avoid branching questions
- Ensure respondents meet criteria
- Avoid leading and biased questions
- Time to respond
- Reminders to complete
- Test your survey

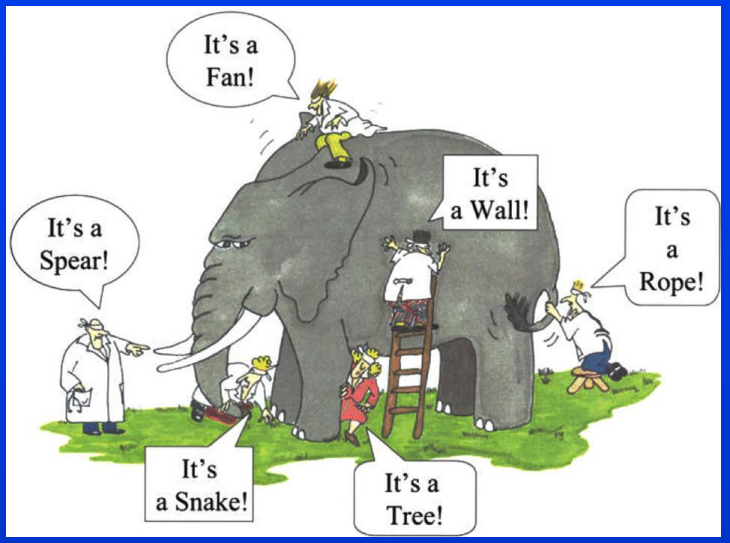
Types

- multiple choice
- side by side matrix
  - avoid if possible
- rank order question
- constant sum question
- image type question
- open ended question

SUMMARY:

Observational Cohort Trials

Take Home Messages



1) Valuable at discovering trends and possible relationships

2) NOT possible to demonstrate causal relationships

3) Caution: even "unobtrusive" observational studies can influence the subject outcome

Defining the trial participants

Prof. Olav Rooyackers

FRESENIUS KABI
caring for life

JUMPstart Training Program

Casting show: Defining the participants

Prof. Olav Rooyackers, Ph.D

This extended version contains the slide set as presented by Prof. Olav Rooyakers and additional content marked with this icon:

Basic Module: Running a clinical trial; Day 1, Part I: A bird's eye view – getting the big picture of study design

FRESENIUS KABI
caring for life

Agenda

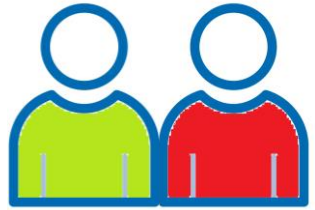
This segment of the training program will cover:

- Inclusion and exclusion criteria and outcome parameters (Olav)
- …for healthy volunteers (Olav)
- …for ICU patients (Mette)

Inclusion and exclusion criteria

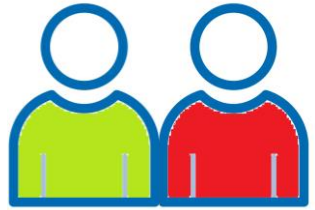
Inclusion and exclusion criteria are defined as the key selection criteria of the intended population that the investigator will use to answer his or her research question.

Inclusion criteria



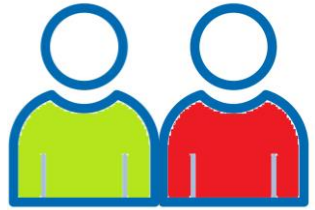
- The central defining elements of the target population
- Well-defined inclusion criteria are critical to the study’s success
- Include demographic, anthropometric, clinical, and geographic characteristics

Exclusion criteria



- Characteristics of the potential trial subject who meets all of the inclusion criteria but present with additional elements that may interfere with the success of the study or increase the risk for the subject.
- Like:
  - confounding comorbidities,
  - an increased risk for adverse events
  - skew results by having a high likelihood of being lost to follow-up, missing scheduled visits

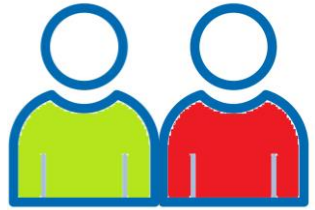
Inclusion and exclusion criteria



A study's results are **externally valid** if the observations and results can be transmitted to the entire target population (not just the study population) by:

reducing bias related to your selection process and typical patient population, mimic clinical practice, reduce drop-outs or general attrition

Inclusion and exclusion criteria



*(Note: **Internal validity** deals with the minimization/avoidance of any bias in comparing treatments that are attributable to trial design, conduct, or analysis.)*

Primary and secondary outcome parameters

Outcome measures are the most important dependent variables that are to be examined in the study.

Primary endpoints represent the highest priority parameters. Secondary outcome measures support the interpretation of the study with respect to effectiveness and safety and are inferior in hierarchy to primary endpoints.

Primary outcome parameters

The primary outcome measure is set before the study commences:

- ✓ Prevents the practice of cherry-picking significant and welcomed results and presenting them as the primary endpoint.
- ✓ The primary outcome measure is used to perform sample size calculations.

Primary outcome parameters

How is the primary outcome measure set?

- ✓ by questions asked
- ✓ based on consensus opinion by investigator and clinical team
- ✓ based on previous, similar studies
- ✓ study sponsors
- ✓ regulatory authorities after seeking scientific advice

Primary and secondary outcome parameters

Primary outcomes are set before the study starts to protect against **type I errors** (the risk of a false positive).

When setting *α* (alpha) for statistical significance to $p < .05$, we expect to observe that out of 100 times the study is performed, 95 times the "effect" will occur. In 5 attempts, the result may be the opposite by chance, and the effect is NOT observed.

A type I error occurs, when we observe an effect that is not really there.

Primary and secondary outcome parameters

Type II errors are also avoidable if primary outcome measures are defined in advance because sample sizes can be calculated. If a trial fails to show that a treatment is effective, then one of two situations has occurred:

a. The treatment is **in**effective.

b. The treatment is effective, **but** the study failed to identify a statistically significant effect because the sample size was too small. This is a false negative or type II statistical error due to low power.

KAROLINSKA
Universitetssjukhuset

Karolinska Universitetssjukhuset Huddinge
Anestesi- och intensivvårdskliniken

HÄLSOKONTROLL
Intervju- och undersökningsformulär

Personnummer……..
Namn:……
Adress:……..
Postnr:…… Tel.nr:……

Förekommer det eller har det förekommit följande sjukdomar?	**Nej**	**Ja**	**Kommentar**
Astma eller annan lungsjukdom			
Hjärt-kärlsjukdom			
Högt blodtryck			
Struma eller annan sköldkörtelsjukdom			
Diabetes			
Lever-eller njursjukdom			
Sjukdom i nervsystemet			
Allergi/överkänslighet (beskriv symptom)			
Överkänslighet mot läkemedel			
Smittsam sjukdom t.ex. MRSA, HIV, TBC, VRE, hepatit			
Annan sjukdom			
Har du besvär med något av följande?			
Psykisk sjukdom			
Andfåddhet eller bröstsmärta			
Bensvullnad			
Ökad blödningsbenägenhet			
Aktuell medicinering eller naturläkemedel (senaste 2 månader)			
Har du besökt läkare de sista två åren?			
Har du varit intagen på sjukhus?			
Har du varit sjukskriven de senaste två åren?			
Känner du dig för närvarande fullt frisk?			
Äter du specialkost? Om ja, detaljera			
Är du blodgivare? Om ja, senaste donation?			

Är du gravid?			

Sida 1

KAROLINSKA
Universitetssjukhuset

Karolinska Universitetssjukhuset Huddinge
Anestesi- och intensivvårdskliniken

HÄLSOKONTROLL

Intervju- och undersökningsformulär

Personnummer……
Namn:……
Adress:……
Postnr:…… Tel.nr:……

Förekommer det eller har det förekommit följande sjukdomar?	**Nej**	**Ja**	**Kommentar**
Astma eller annan lungsjukdom			
Hjärt-kärlsjukdom			
Högt blodtryck			
Struma eller annan sköldkörtelsjukdom			
Diabetes			
Lever-eller njursjukdom			
Sjukdom i nervsystemet			
Allergi/överkänslighet (beskriv symptom)			
Överkänslighet mot läkemedel			
Smittsam sjukdom t.ex. MRSA, HIV, TBC, VRE, hepatit			
Annan sjukdom			
Har du besvär med något av följande?			
Psykisk sjukdom			
Andfåddhet eller bröstsmärta			
Bensvullnad			
Ökad blödningsbenägenhet			
Aktuell medicinering eller naturläkemedel (senaste 2 månaderna)			
Har du besökt läkare de sista två åren?			
Har du varit intagen på sjukhus?			
Har du varit sjukskriven de senaste två åren?			
Känner du dig för närvarande fullt frisk?			
Äter du specialkost? Om ja, detaljera			
Är du blodgivare? Om ja, senaste donation?			
Är du gravid?			

Personal details

Common diseases

Common symptoms

Allergies/diet/general health/pregnancy

KAROLINSKA
Universitetssjukhuset

Jag är medveten om att lämnande av ofullständiga eller felaktiga uppgifter kan göra att jag riskerar att utsättas för onödig risk/fara.

……
Ort, datum: Underskrift

Försöksledare
Professor Jan Wernerman
Tel: 08-585 86 395

KAROLINSKA
Universitetssjukhuset

Hälsoundersökning av försöksperson

Studie:_____

Namn Försöksperson:_____

Längd:……cm	Vikt:……..kg	Uppmätt: Ja / Nej		
		Normal	Ej normal	Ej utfört
BT: …../……mm Hg; Puls: ……..slag/min				
AT (allmänt intryck, hull, muskulatur)				
Cor: (rutinauskultation i liggande)				
Pulm: (rutinauskultation i sittande)				
Buk: (rutinpalpation)				
Neurologiskt: (… …, nackstyv, smärta /vtl. beröring i tår)				
MoS: (inspektion … munhåla och svalg)				
Ögon: (inspektion, pupillrörelse, ögonrörelse)				
Resultat rutinlabprover (CRP, B-Hb, LPK, TPK, Kreatinin)				

Kan delta i studie: Ja / Nej

Leg. läkare……..…….. Datum……

Sida 3

Length/weight

Standard medical check

Minimal laboratory

Session summary

- ✓ Select you patients carefully for external validity mainly
- ✓ Select your primary outcome measure carefully for external validity and power for clinical relevance and validity
- ✓ Controls for critically ill patients are difficult to define

References and literature

Rothman KJ. Epidemiology: an introduction. Oxford University Press; 2012.

Szklo M, Nieto FJ. Epidemiology. Jones & Bartlett Publishers; 2012.

Nelson KE, Williams CM. Infectious disease epidemiology. Jones & Bartlett Publishers; 2013.Guidance for Industry;

E6 good clinical practice: consolidated guidance, ICH April 2006.; and amended version E6(R2). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf

World Medical Association. Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

U.S Food and Drug Administration; drugs development & approval process (drugs), how drugs are developed and approved types of applications: investigational new drug (IND) application. Available from http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm

References and literature

European Medicines Association; Clinical trials. Available from http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000489.jsp&mid=WC0b01ac058060676f

EUDraCT. Available from https://eudract.ema.europa.eu/ European Medicine Association; Clinical trial regulations. Available from http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000629.jsp&mid=WC0b01ac05808768df/

Guide for Investigator Initiated Trials; Editor(s): Fortwengel, G. (Hannover); Publication year: 2011

HMA: Common European submission Portal. Available from https://cespportal.hma.eu/Account/Login http://ec.europa.eu/health/human-use/clinical-trials/information/index_en.htm#ct2.

International ethical guidelines for health-related research involving humans; https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf

References and literature

Clinical Data Interchange Standards Consortium, CDISC. 2011. Clinical Data Acquisition Standards Harmonization. (CDASH).

A Comprehensive and Practical Guide to Clinical Trials; 1st Edition; Editors: Delva Shamley Brenda Wright eBook ISBN: 9780128047309; Published Date: 11th June 2017

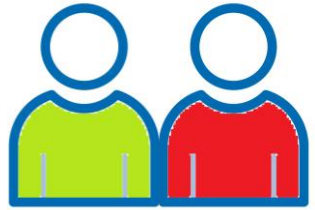
Department of Health and Human Services; Office of Human Research Protection. Available from http://www.hhs.gov/ohrp/about-ohrp/index.html#

ClinicalTrials.gov. Available from https://clinicaltrials.gov/ct2/manage-recs/fdaaa

http://www.consort-statement.org/consort-statement/flow-diagram

Declaration of Taipei on Health Databases and Biobanks: https://www.wma.net/policies-post/wma-declaration-of-taipei-on-ethical-considerations-regarding-health-databases-and-biobanks/

Inclusion and exclusion criteria



Common errors:

- using the same variable to define both inclusion and exclusion criteria (i.e.:, include only smokers; exclude non-smokers);
- selecting variables as inclusion criteria that are not connected to answering the research question;
- not describing key elements in the inclusion criteria that are needed to interpret the external validity of the study results.

Defining the trial participants

Prof. Mette Berger

FRESENIUS KABI
caring for life

JUMPstart Training Program

Defining the participants in clinical trials

Prof. Mette M Berger, M.D., Ph.D

Basic Module: Running a clinical trial; Day 1, Part I: A bird's eye view – getting the big picture of study design

Investigation subjects and patients

- « Healthy » Volunteers
  - Working in the institution
  - « Laic »
- Ambulant Patients
  - Obese
  - Diabetics
  - Transplanted …
- **Hospitalized patients**
  - Ward - stress
  - ICU – vulnerable patients – ethics …

Motivation ?
- altruism
- extra money
- time off
- constraint

Over-selected populations
→ differences RCT vs observation trials

	Screened	Enrolled	%
EPaNIC 2011	8703	4640	53.3
REDOXS 2013	5633	1223	21.9
SPN 2013	2555	305	11.9
CALORIES 2015	11108	2400	21.6
PERMIT 2016	6400	894	14.0
EAT-ICU 2017	586	203	34.6
NUTRIREA-2 2018	10855	2410	2.2
SPN2 2019	862	23	2.7

Problems associated with study population

1. **SIZE OF COHORT:**
   - Insufficient power for
     - mortality
     - primary endpoint
   - Early study interruption (INTACT, OMEGA
   - Slow enrollment (TICACOS2)
2. **SEVERITY OF DISEASE:**
   - Too "young" (PERMIT)
   - Potential negative response not considered
   - Admission criteria (EDEN, OMEGA)
   - Bad luck (REDOXS)
3. **UNSELECTED DIAGNOSTIC CATEGORIES**
   - All patients, including "short stayers"

Near-Target Caloric Intake in Critically Ill Medical-Surgical Patients Is Associated With Adverse Outcomes

Arabi et al, JPEN, 2010;34:280

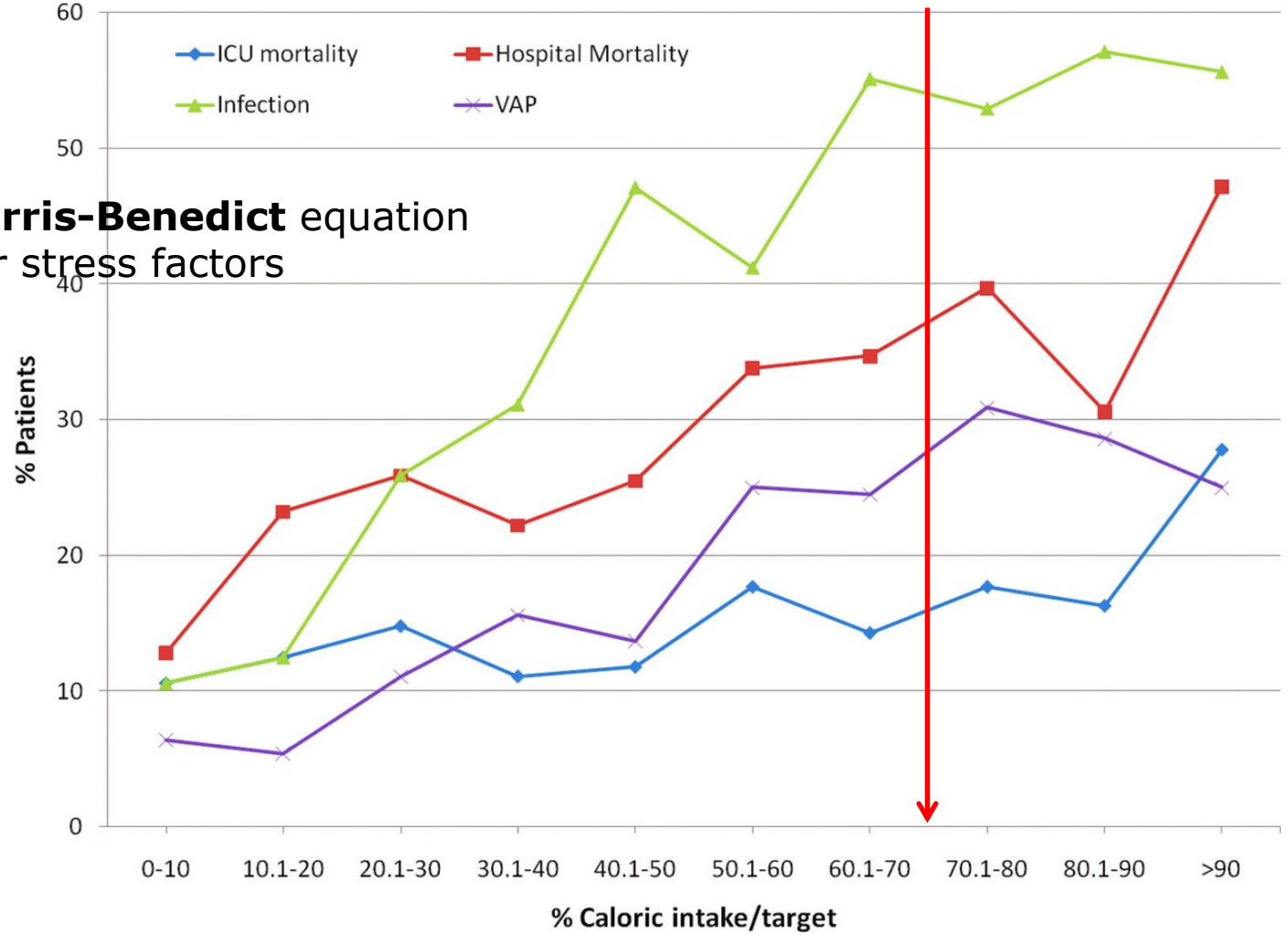
Variable	Total Group	Caloric Intake/Target			P Value
		Tertile I (<33.4%)	Tertile II (33.4%–64.6%)	Tertile III (>64.6%)	
Number of patients	523	170	181	172	
Age, mean ± SD, y	52.4 ± 21.7	54.5 ± 20.1	48.7 ± 21.6	54.3 ± 22.8	.02
Sex (female), n (%)	132 (25.2)	48 (28.2)	44 (24.3)	40 (23.3)	.54
BMI, mean ± SD, kg/m²	27.3 ± 7.5	28.2 ± 7.8	26.6 ± 6.9	27.3 ± 7.8	.14
APACHE II, mean ± SD	22.8 ± 8.1	21.6 ± 8.3	23.0 ± 8.5	23.8 ± 7.4	.04
Admission category, n (%)					
Nonoperative	435 (83.2)	120 (70.6)	156 (86.2)	159 (92.4)	<.0001
Operative	88 (16.8)	50 (29.4)	25 (13.8)	13 (7.6)	<.0001
Mechanically ventilated, n (%)	445 (85.1)	122 (71.8)	163 (90.1)	160 (93.0)	<.0001
Vasopressor, n (%)	341 (65.2)	104 (61.2)	126 (69.6)	111 (64.5)	.25
Diabetes history, n (%)	208 (39.8)	80 (47.1)	62 (34.3)	66 (38.4)	.04

Variable	Total Group	Caloric Intake/Requirement			P Value
		Tertile I (<33.4%)	Tertile II (33.4%–64.6%)	Tertile III (>64.6%)	
Number of patients	523	170	181	172	
ICU mortality, n (%)	80 (15.3)	21 (12.4)	24 (13.3)	35 (20.4)	.08
Hospital mortality, n (%)	155 (29.6)	35 (20.6)	51 (28.2)	69 (40.1)	.0003
ICU-acquired infections, n (%)	203 (38.8)	31 (18.2)	77 (42.5)	95 (55.2)	<.0001
Ventilator-associated pneumonia, n (%)	99 (18.9)	13 (7.7)	38 (21.0)	48 (27.9)	<.0001
Mechanical ventilation duration, mean ± SD, d	9.0 ± 9.6	4.7 ± 7.0	9.4 ± 9.3	12.8 ± 10.4	<.0001
ICU LOS, mean ± SD, d	10.2 ± 10.0	6.1 ± 6.9	10.5 ± 9.6	13.9 ± 11.4	<.0001
Hospital LOS, mean ± SD, d	55.8 ± 80.6	41.3 ± 63.7	53.2 ± 61.8	72.7 ± 106.4	.001

Near-Target Caloric Intake in Critically Ill Medical-Surgical Patients Is Associated With Adverse Outcomes

Arabi et al, JPEN, 2010;34:280

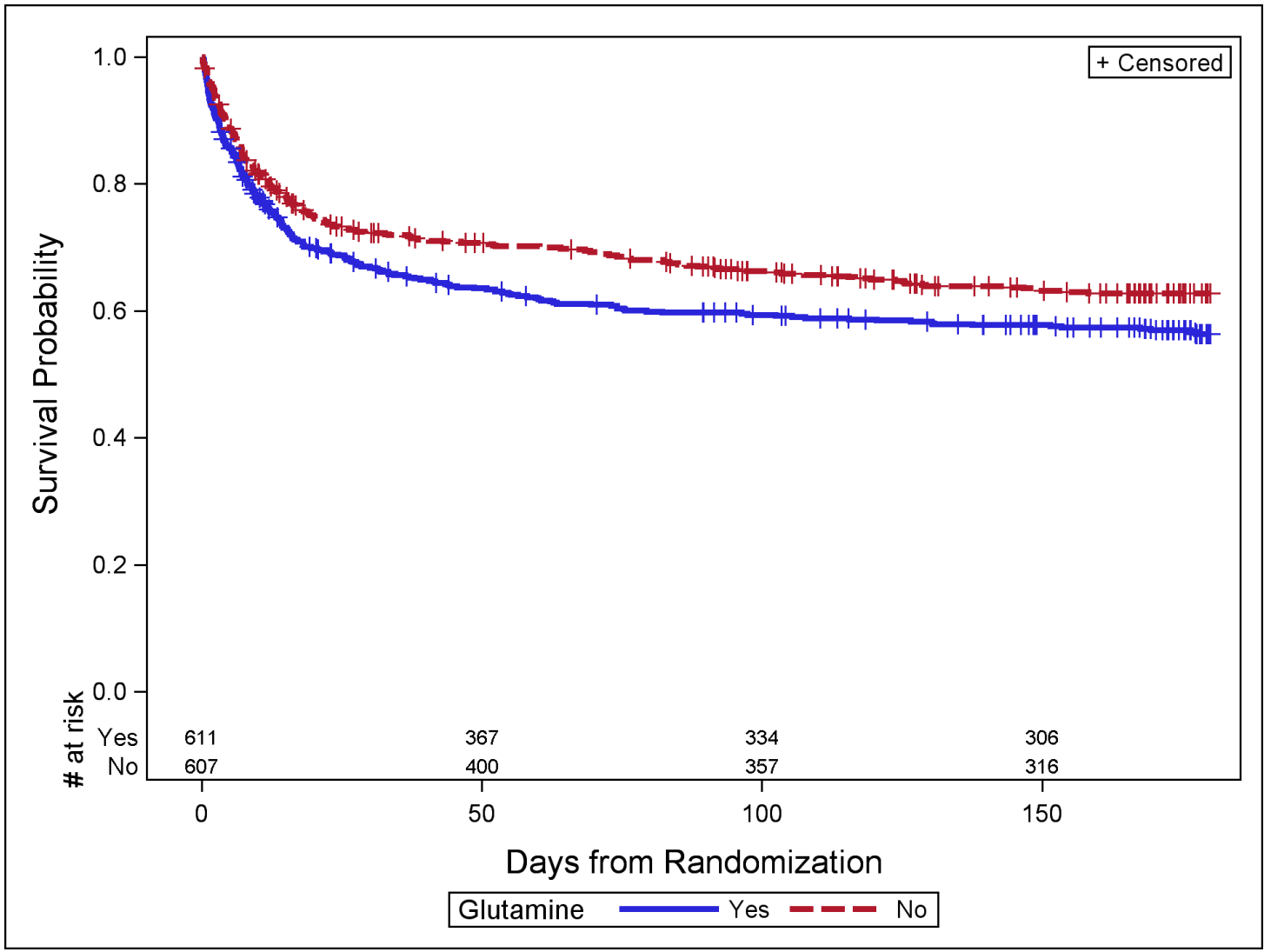
Target: Harris-Benedict equation adjusted for stress factors



Association among ICU mortality, hospital mortality, ICU-acquired infections, and VAP rate and caloric intake/requirement

REDOXS: A randomized trial of high dose Glutamine and Antioxidants in critically ill patients with MOF

Heyland et al, NEJM 2013



Kaplan-Meier 6 Month Survival curves

n=1218

Glutamine vs no-GLN 0.78 g/kg/d

Critical Care Nutrition

Specificities of REDOXS

- Extremely sick: ≥ 2 failures, including 35 % ARF
- Daily Dose 0.78 g/kg:_two times > recommendations
- Previous GLN studies were carried out in stabilised patients requiring PN with nutrition doses
- Very early administration of full GLN dose WITHOUT nutrition: mean US nutrition = 40% of target
- Predictors of mortality were over-represented in GLN groups: > 2 failures, renal failure, <30% nutrition on delivery, steroids, vasopressors

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Glutamine and Antioxidants in Critically Ill Patients

Daren Heyland, M.D., John Muscedere, M.D., Paul E. Wischmeyer, M.D., Deborah Cook, M.D., Gwynne Jones, M.D., Martin Albert, M.D., Gunnar Elke, M.D., Mette M. Berger, M.D., Ph.D., and Andrew G. Day, M.Sc., for the Canadian Critical Care Trials Group

Gln n = 611
0 Gln n = 607

3 or more organ failures

424	187
459	148

chi2
P = 0.015

28-day mortality

413	198
442	165

chi2
P = 0.046

Characteristic	Placebo (N=300)	Glutamine (N=301)	Antioxidants (N=307)	Antioxidants plus Glutamine (N=310)
Inclusion criteria — no. (%)				
PaO_2:FiO_2 ratio ≤300	282 (94.0)	285 (94.7)	287 (93.5)	285 (91.9)
Clinical evidence of hypoperfusion	277 (92.3)	278 (92.4)	286 (93.2)	293 (94.5)
Renal dysfunction	104 (34.7)	117 (38.9)	99 (32.2)	122 (39.4)
Platelet count ≤50×10^9/liter	16 (5.3)	21 (7.0)	12 (3.9)	18 (5.8)
Duration of ICU stay before randomization — hr				
Median	17.9	17.7	18.4	18.0
Interquartile range	13.4–21.5	12.7–21.1	12.3–21.5	13.3–21.6
No. of failed organs — no. (%)‖				
1	1 (0.3)	2 (0.7)	1 (0.3)	0
2	221 (73.7)	206 (68.4)	236 (76.9)	216 (69.7)
3	76 (25.3)	85 (28.2)	69 (22.5)	90 (29.0)
4	2 (0.7)	8 (2.7)	1 (0.3)	4 (1.3)

By courtesy Jan Wernerman

TICACOS international: A multi-center, RCT study comparing tight Calorie control vs Liberal calorie administration study

Singer et al, Clin Nutr E-pub 2020

Aim: to perform a multicenter RCT non blinded study in critically patients to assess the added value for measuring daily resting energy expenditure as a guide for nutritional support.
Methods: target 580 newly-admitted, adult ventilated ICU patients that were planned to stay >48 h in the ICUs.
The nutritional support was aimed to meet 80–100% of energy requirement measured by indirect calorimetry. The calorie needs were determined by IC in the Study group and by an equation (20-25 kcal/kg ideal body weight/day) in the Control Group

Results: Due to **slow inclusion rate**, the study was stopped after 6 years and after inclusion of 417 patients only.
From these ITT patients, only 339 (81%) followed the protocol.

The rate of infection (40 vs 31), including pneumonia rate, need for surgery, dialysis requirement, length of ventilation, ICU length of stay, and hospital length of stay were not different between groups.
Mortality (30 in the control vs 21 in the study group) was not significantly different between groups.

Intensive Nutrition in Acute Lung Injury (INTACT)

Braunschweig et al, JPEN 2015;39:13

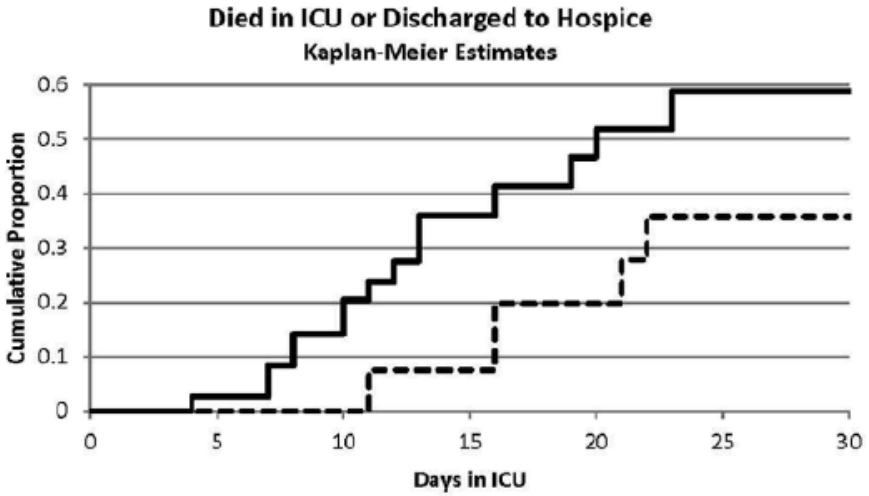
Table 3. Clinical Outcomes in IMNT vs SNSC Participants (N = 78).

Variable	IMNT (n = 40)	SNSC (n = 38)	*P* Value
Hospital LOS, d	27.2 (18.2)	22.8 (14.3)	.33
ICU LOS, d	15.5 (12.8)	16.1 (11.5)	.83
Number of days between hospital admission and enrollment	8.8 (8.7)	6.4 (6.6)	.17
Days on ventilator (median, IQR)	6 (4–10)	7 (3–14)	.85
Number of infections, n (%)	5 (12)	8 (21)	.29
Any hyperglycemic event, n (%)[a]	30 (73)	26 (68)	.64
Number of days with hyperglycemia	2.2 (3.0)	2.4 (4.0)	.85
Any hypoglycemic event, n (%)[a]	12 (29.3)	11 (28.9)	.98
Number of days with hypoglycemia	0.3 (0.6)	0.9 (0.7)	.08
Insulin received per day, U	23.6 (47.6)	14 (23.6)	.25
Insulin received per day on days insulin was received in participants who were given insulin, U	77.7 (70.4)	35.9 (27.9)	.03
Died	16 (40.0)	6 (15.8)	.017

E. Target ACCP: 30 kcal/kg admission BW or obesity-adjusted IBW

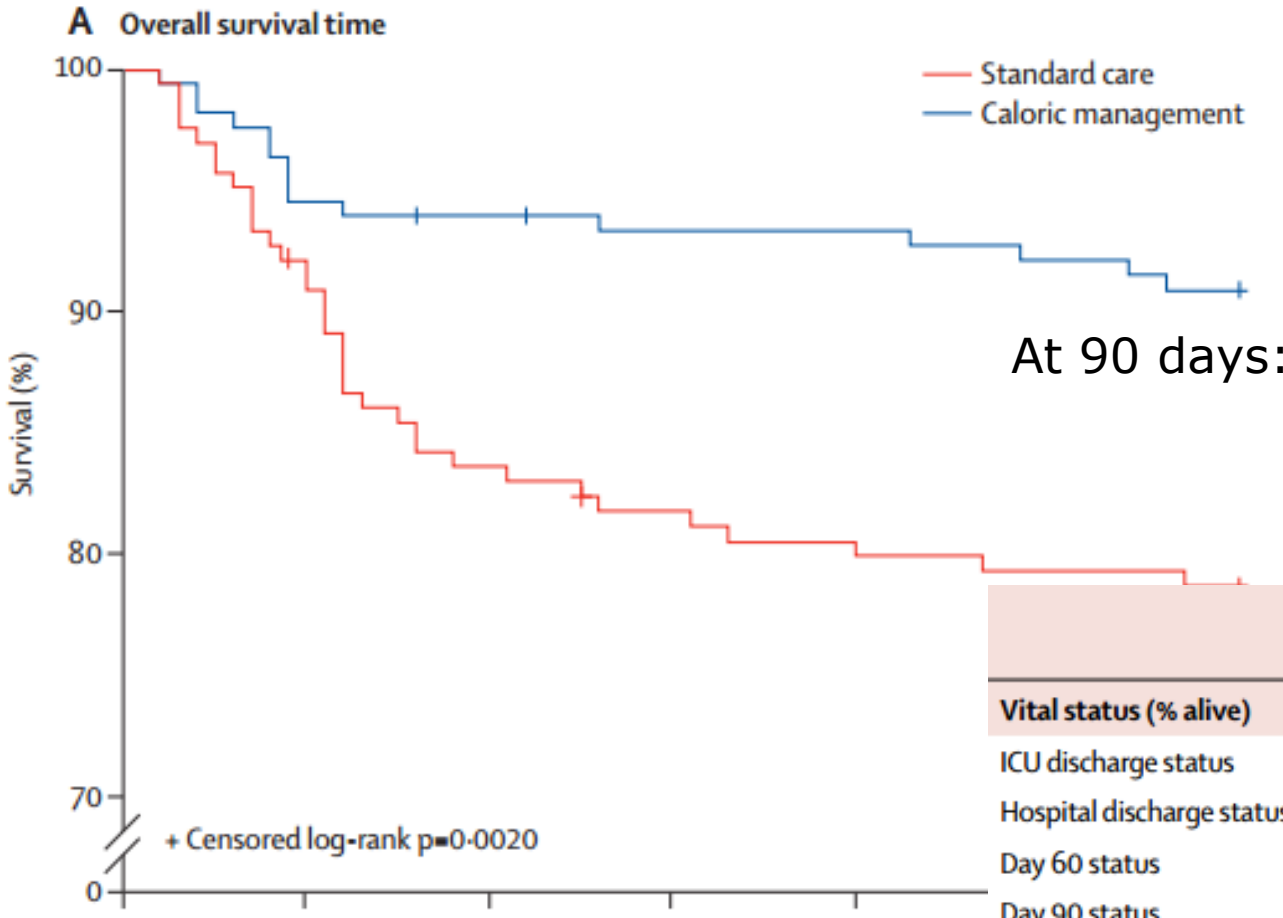
Trial Stopped ← mortality

Unadjusted analysis: participants in the IMNT group experienced a 2.65 times higher hazard of death vs those randomized to standard care.
Adjusted for age (HR, 1.04; 95% CI, 1.02–1.07; *P = .001) and baseline SOFA score* (HR, 1.32; 95% CI, 1.14–1.54; *P = .0003), the hazard of death* in the IMNT group was 5.67 times (*P = .001) > in the* SNSC group.



Restricted vs continued standard caloric intake during the management of refeeding syndrome in critically ill adults

Doig et al, Lancet Resp Med, 2015; 3:943



At 90 days: p=0.041

Inclusion criteria
Development of hypo P < 0.65 mmol/l upon initiation of artificial nutrition

Both groups received same amount of phosphate

	Standard care (n=165 patients)	Caloric management (n=166 patients)	Risk difference (95% CI)	p value
Vital status (% alive)				
ICU discharge status	150/165 (91%)	157/166 (95%)	3·7% (−5·3 to 12·7)	0·20
Hospital discharge status	135/165 (82%)	151/166 (91%)	9·2% (0·7 to 17·7)	0·017
Day 60 status	128/163 (79%)*	149/164 (91%)*	12·3% (3·9 to 20·7)	0·002
Day 90 status	128/163 (79%)*	143/164 (87%)*	8·7% (0·04 to 17·0)	0·041
Length of stay (days)				
ICU	10·0 (9·2 to 10·9)	11·4 (10·5 to 12·4)	1·4 (−0·42 to 3·5)	0·14
Hospital	21·7 (20·0 to 23·5)	27·9 (25·7 to 30·3)	6·2 (2·0 to 11·2)	0·003

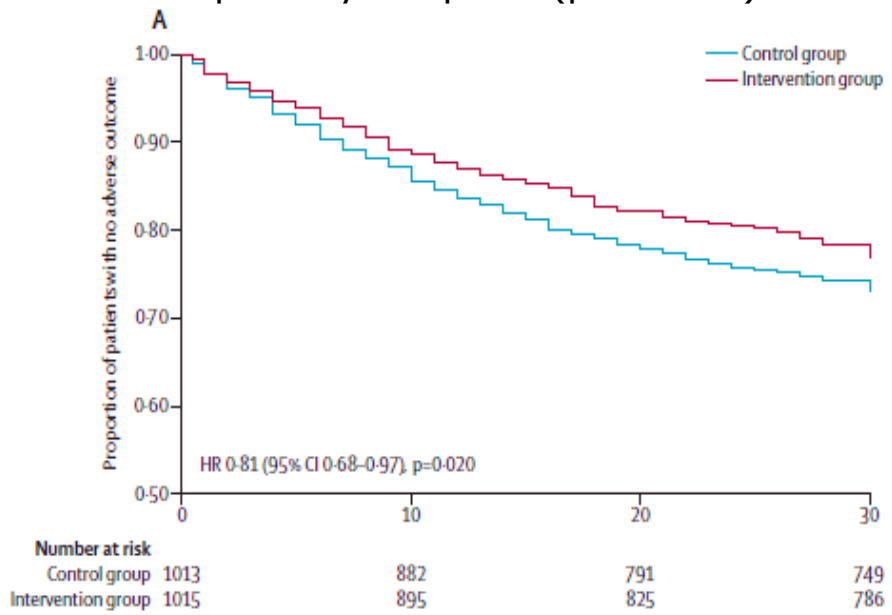
Individualised nutritional support in medical inpatients at nutritional risk: a RCT

Schuetz et al, Lancet 2019, 393: 2312–21

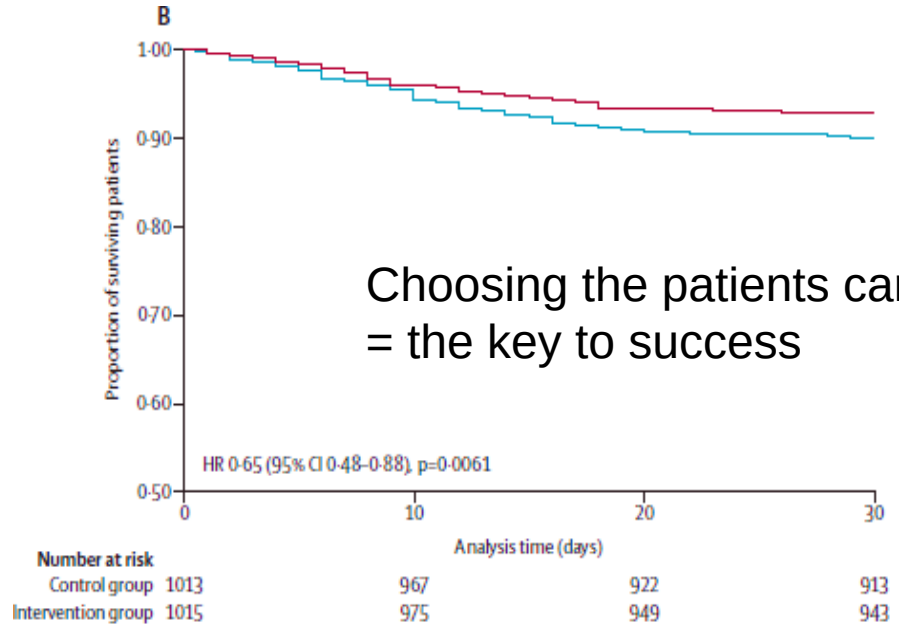
Inclusion criteria: medical patients at nutritional risk NRS 2002 score ≥3 points, and with an expected length of hospital stay >4 days from eight Swiss hospitals.

Intervention: individualised nutritional goals defined by dietitians and nutritional support was initiated no later than 48 h after admission. Control – no counseling

(A) Time to the first event of the composite primary endpoint (p =0·035).



(B) Time to death (log-rank p value=0·031).



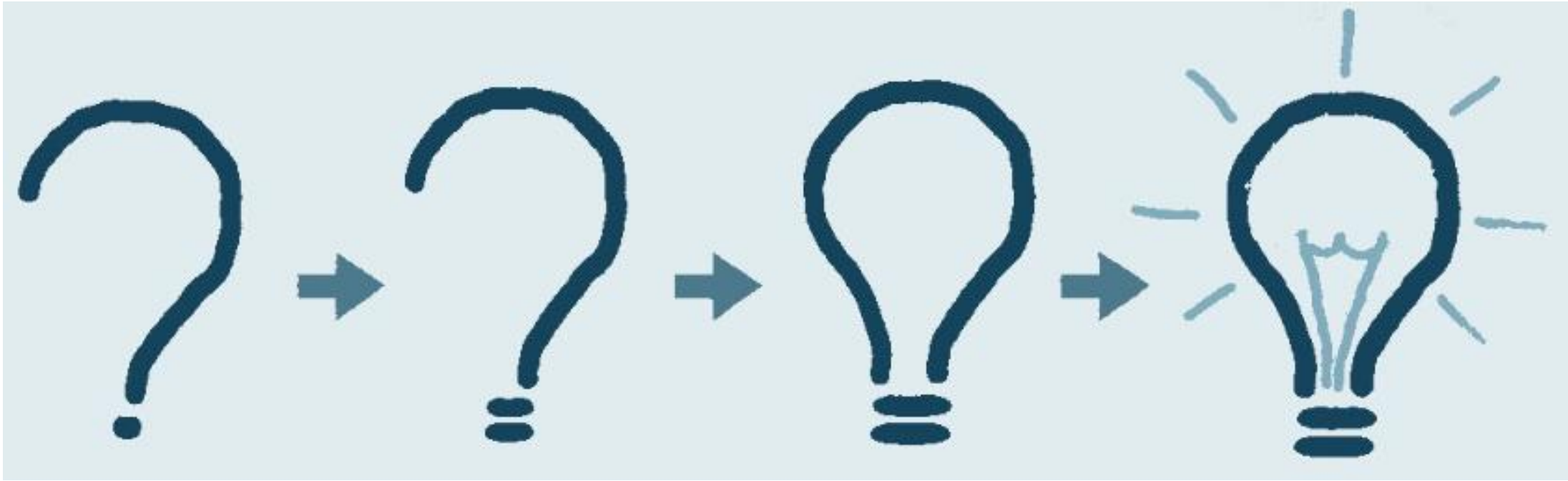
Choosing the patients carefully = the key to success

Patients selection

Problems differ according to the design:

- Cohort studies → real life
- RCTs → selected patients: external validity limited
    - Importance of study inclusion criteria

Both types : consent issues (proxy in ICU)



Part II: Down to the nitty gritty - Running a clinical study in detail I

From evidence gap to archiving: Life cycle of a CT

Prof. Ho-Seong Han

FRESENIUS KABI
caring for life

JUMPstart Training Program

From evidence gap to archiving:
Life cycle of a clinical trial

Prof. Ho-Seong Han, M.D., Ph.D

Basic Module: Running a clinical trial; Day 1, Part II: Down to the nitty gritty – running a clinical study in detail I

FRESENIUS KABI
caring for life

Agenda

This segment of the training program will cover:

- An overview of the clinical trial process

The clinical trial process: Defining the study objective

What helps you decide on the **central points of your research**?

The usual suspects:

- Unexplored areas of treatment effects
- Ambiguous data in the literature
- Personal observations that lead you to a particular hypothesis that you wish to test
- Gaps in scientific literature

Formulating the study hypothesis

How to proceed:

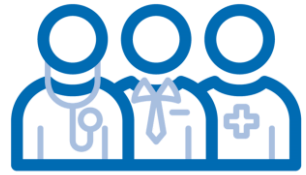
1. Identify gaps in the scientific landscape
2. Arrange data gaps according to category (side effects, drug interactions, population bias, etc.)
3. Formulate your **study hypothesis**
4. Verify that there are no findings in literature that will answer your hypothetical questions

Planning the protocol

Follow PICO (population, intervention, control, outcome) to define the basic tenets of your research:

a. *Population:* **who** do I need to study in order to produce data that fits my hypothesis?
b. *Intervention:* what does my **intervention** need to be to test my hypothesis?
c. *Control:* against **which control group/substance** do I test my hypothesis?
d. *Outcome:* what **outcome variable** to I wish to test to further knowledge in this particular field of research?

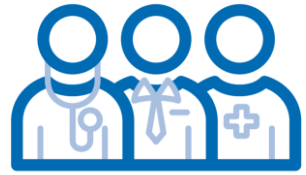
Involving the team I



Start involving cross-functional team members to plan the protocol considering all relevant aspects for a successful study:

1. Are all relevant participants (statistician, pharmacy, labs, study coordinator, etc.) informed and have they provided their input regarding the protocol and schedule of visits?

Involving the team II



2. Is the site appropriately equipped to handle the investigation?
3. Does the institution have all necessary medical and technical provisions to support the protocol?
4. Is there enough staff to allow for a safe and effective investigation?

Administrative aspects I

Submission of appropriate paperwork:

1. Application to the IRB/EC and your local institution
2. Application or notification to the responsible regulatory authority
3. Registration of your study in an appropriate clinical trial register

Administrative aspects II

4. Formal finalization of trial related documents:
   a. Protocol
   b. Informed consent form
   c. Declaration of financial and conflicts of interest
   d. Trial budget
   e. Advertisements, etc. for recruitment purposes
   f. Training documents up to date (GCP, life support, etc.)
   g. Any other relevant documents before the trial is approved and can start

The clinical phase

All approvals granted ⇨

The **first patient** or participant may be screened for inclusion.

PI supervision during the study:

- Close contact to several pivotal members of the study team to address any and all issues from the study
- Continuous observation of all clinical and documentation by study team
- safety reporting and data quality measurements executed as laid out in the protocol, the local regulatory requirements and principles of GCP.

➢ To ensure ultimate PI responsibility for the patient's safety and the integrity of the entire study.

Study closeout activities

Upon finalization of your study**, notify all initially involved agencies and boards** of the trial's conclusion and supply general data points of the study:

- ✓ Total number of screened and included patients
- ✓ Total number of drop-outs
- ✓ Total number of treated patients
- ✓ Total length of the study
- ✓ Any other metric required by the IRB/institution or regulatory authority

Data cleaning and analysis

Perform and document all data cleaning and verification activities

⇨ biometrician for analysis.

Analyze data according to the methods outlined in the protocol

Finalize the interpretation and conclusion of the study

Manuscript

Start publication process: Write introduction and methods first, results and conclusions after analyses are finalized (use the publication plan outlined in your protocol to allocate responsibilities for authors)

Send draft version to all authors for review, commentary and editing.

After all co-authors approve and verify that the manuscript is their own, original work, select an appropriate journal for publication.

Publication

Beware of timelines, impact factors and journal preferences of topics.

Ensure to include all contributors in the acknowledgements and follow the instructions to authors meticulously prior to submission.

Once your manuscript is accepted for publication (usually with varying degrees of necessary revisions), submit trial results to the registry.

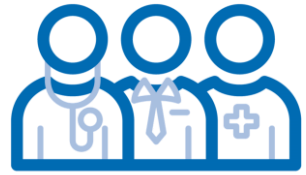
Archiving

Follow your institution’s requirements and local regulatory requirements for **archiving**.

Archive study data, patient information and all trial outcomes (paper and electronic data) in an appropriate storage facility:

Safely, protected from water, fire or theft for the minimally required timeframe

Celebrate!



Once you have completed all necessary tasks for archiving and your manuscript has been published you should embark on the next trial idea to fill the knowledge gaps in the scientific literature while taking some time to **celebrate** the successful completion of your study and its subsequent publication.

A small token of "thank you" (a get-together with food and beverages) to the contributing team of the study will ensure continued success on your next project.

Session summary

- ✓ A bird’s eye view on the process from the clinical trial idea to the publication and archiving of results

References and literature

Guidance for Industry; E6 good clinical practice: consolidated guidance, ICH April 2006.; and amended version E6(R2). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf

World Medical Association. Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

European Medicines Association; Clinical trials. Available from http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000489.jsp&mid=WC0b01ac058060676f

Department of Health and Human Services; Office of Human Research Protection. Available from http://www.hhs.gov/ohrp/about-ohrp/index.html#

Statistics in planning and evaluating CTs

Prof. Tim Friede

FRESENIUS KABI
caring for life

JUMPstart Training Program

How to get the results you trust:
Statistics in planning and evaluating clinical trials

Prof. Tim Friede

Basic Module: Running a clinical trial; Day 1, Part II: Down to the nitty gritty - Running a clinical study in detail I

Outline

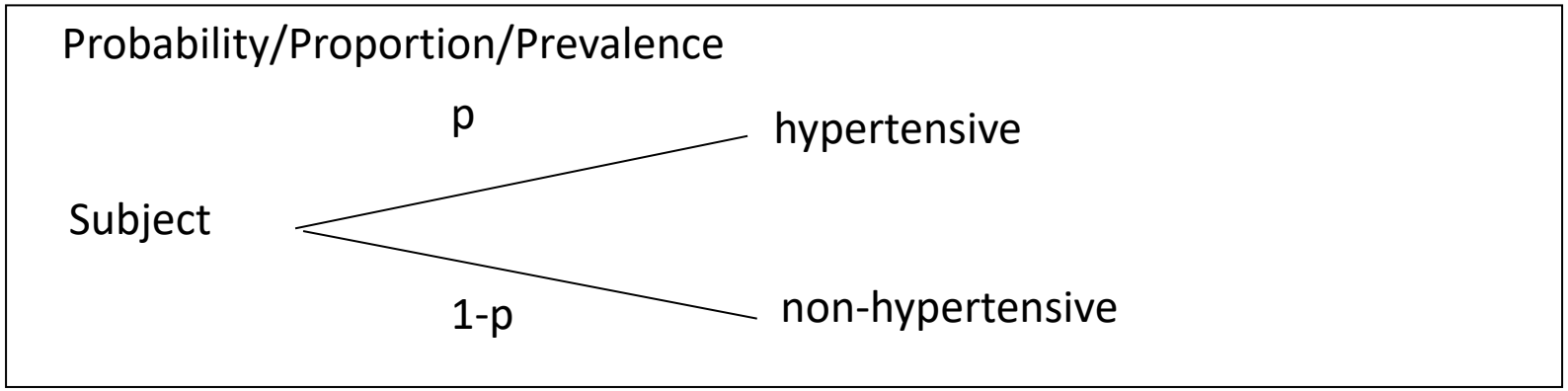
- **Some statistical concepts**
  - e.g. confidence intervals, hypothesis tests
- **Some concepts in clinical trials**
  - Randomization and treatment blinding
  - Sample size calculation and recalculation
  - Adaptive designs

Populations and Samples

- **Aim:** draw conclusions for a **population**
  - e.g. prevalence of hypertension in ethnic groups in a certain area
- **Sample**
  - assessment of entire population often not feasible
  - representative **sample** (ideally random sample)

Statistical Models: An Example

- **Binary probability model**



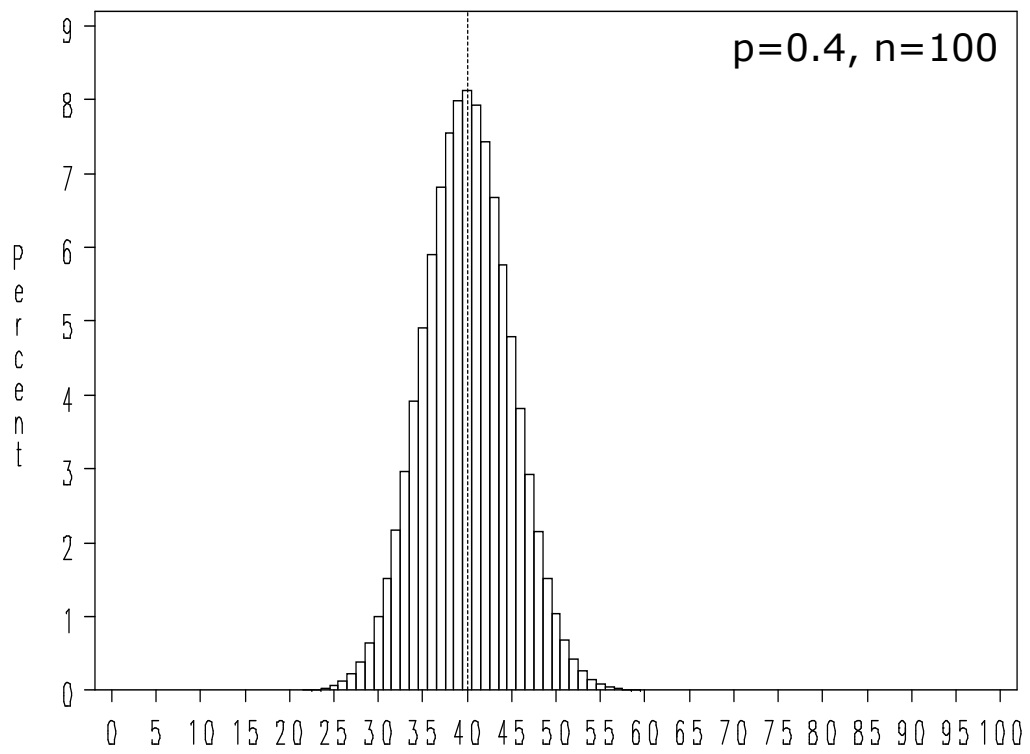
- **Binary endpoints**
  - Cross-sectional studies
  - Longitudinal studies: Death/survival after a certain period of follow-up time

“Essentially, all models are wrong, but some are useful.”*

- Always ask: **“What’s the purpose?** What do I want to achieve?”
- Based on this assess how useful a model is.
- **Example:** Prediction model in A&E setting
  - A simple model with few, easy to assess predictors might be more useful than a complex model with high precision in prediction

* Quote by George Box; source http://en.wikiquote.org/wiki/George_E._P._Box

Sampling Variation



- Binary probability model
- Prevalence of hypertension in African/Caribbean group is roughly 40%*
- Suppose study with n=100 subjects to estimate prevalence
- Number of subjects with hypertension follows **Binomial distribution** with parameters n and p

* *Cappuccio FP et al. Heart 1997;78:555-63*

Estimation

- **The observed value** of a quantity of interest (e.g. prevalence, incidence rate) is the best estimate of the quantity's true value.
- Estimates are subject to **sampling variation**
- Precision of an estimate is described by its **Standard Error** (SE)

Estimating a Proportion

- **Quantity of interest:** true proportion p (e.g. prevalence of hypertension)
- **Sample** of n subjects (e.g. n=100)
- k hypertensive subjects (e.g. k=43)
- **Estimate** of proportion: $\hat{p} = k / n$ (43/100=0.43=43%)
- **Standard error** of a sample proportion:

$$\sqrt{p(1-p)/n} \quad \left(\sqrt{.43 \times .57 / 100} = 0.0495\right)$$

Confidence Interval of a Proportion

- **95% CI of proportion (prevalence) p**

$$\left(\hat{p} - 1.96\sqrt{\hat{p}(1-\hat{p})/n},\ \hat{p} + 1.96\sqrt{\hat{p}(1-\hat{p})/n}\right)$$

  with $\hat{p} = k/n$

- **Example:** sample of n=100, k=43 hypertensive
  - Estimated proportion (prevalence)

    $\hat{p} = 43/100 = .43$

  - Standard error $\sqrt{.43(1-.43)/100} = .0495$
  - 95% CI $\left(.43 - 1.96 \times .0495,\ .43 + 1.96 \times .0495\right)$

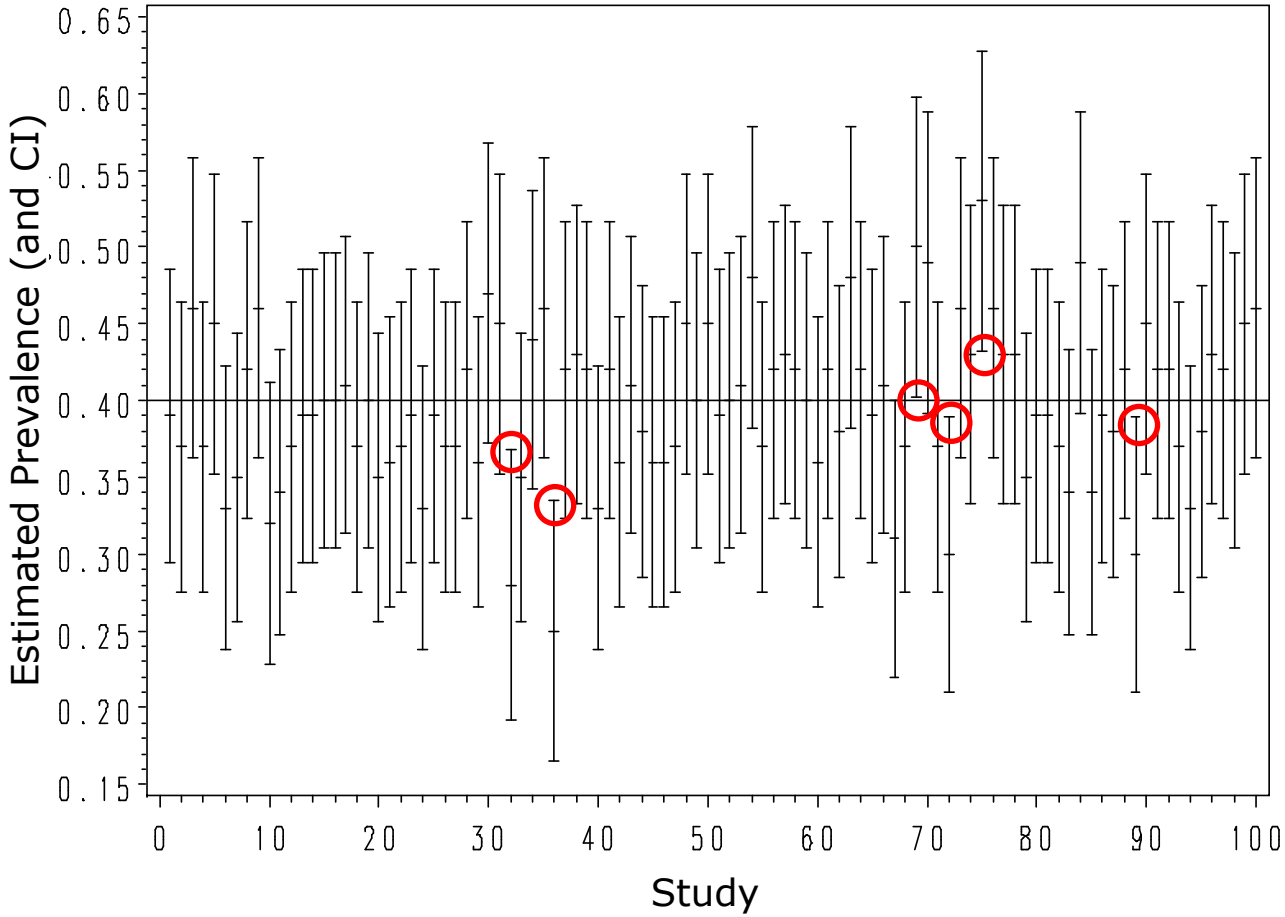
    $= (.33, .53)$

97.5% quantile of the standard normal distribution; often rounded to 2.

Interpretation of Confidence Intervals

- **Usual interpretation:** "The range which includes the true value with probability 95%"
- **Strictly speaking**, the probability statement applies to the construction principle (we expect 95 out of 100 CI to overlap the true value) and not to an individual CI calculated from a specific data set. A specific CI does or does not overlap the true value – we simply do not know.

95% Confidence Intervals of Prevalence from 100 Sampled Studies of Size 100 with True Prevalence 40%



94 out of 100 CI cover the true value in this simulation.

Null Hypothesis

- A lot of analyses include a **comparison**
  - either between different groups
  - or a sample with a known quantity
- The numerical value corresponding to the comparison is called the **effect.**
  - Difference of means; risk ratios; …
- The hypothesis of no effect is called the **'null hypothesis'.**
  - Difference of means is 0.
  - Risk ratio is 1.

Confidence Intervals and Null Hypotheses

- If the 95% CI **includes** the 'null hypothesis', then the data are consistent with the null hypothesis of no effect at a level of 95%.
- **Example:**
  - As before: n=100, k=43 hypertensive
  - 95% CI: (33%, 53%)
  - CI includes 40%, therefore …
  - The confidence interval is consistent with the null hypothesis that the true prevalence is 40%.

Hypothesis Tests

- Alternative approach to using a CI to check whether data are consistent with a null hypothesis
- Calculate the probability that we could have obtained the observed data or more extreme data if the null hypothesis were true.
- This probability is known as the **p-value.**

Difficulties in the Interpretation of P-values

- **Statistical significance is not clinical relevance.**
  - Statistically significant effects might be so small that they are considered clinically irrelevant.
  - Estimate and CI are important in the interpretation of study results.
- **How to interpret p-values just above or below cut-off of 5%?**

Standard Error and Confidence Interval for the difference of two proportions

- **Observed proportions**

$$\hat{p}_1 = k_1 / n_1 \quad \text{and} \quad \hat{p}_2 = k_2 / n_2$$

- **Standard error**

$$SE(\hat{p}_1 - \hat{p}_2) = \sqrt{\hat{p}_1(1-\hat{p}_1)/n_1 + \hat{p}_2(1-\hat{p}_2)/n_2}$$

- **95% Confidence interval**

$$\hat{p}_1 - \hat{p}_2 \pm 2 \times SE(\hat{p}_1 - \hat{p}_2)$$

Key points so far

- The ‘best’ estimate of the underlying ***true value*** is the ***observed value***
- Estimates are subject to ***sampling variation.***
- Sampling variation in estimates can be described by ***standard errors***
- The range of likely values can be characterized by ***confidence intervals.***
- Confidence intervals and ***p-values*** can be used to test hypotheses

Outline

- **Some statistical concepts**
  - e.g. confidence intervals, hypothesis tests

- **Some concepts in clinical trials**
  - Randomization and treatment blinding
  - Sample size calculation and recalculation
  - Adaptive designs

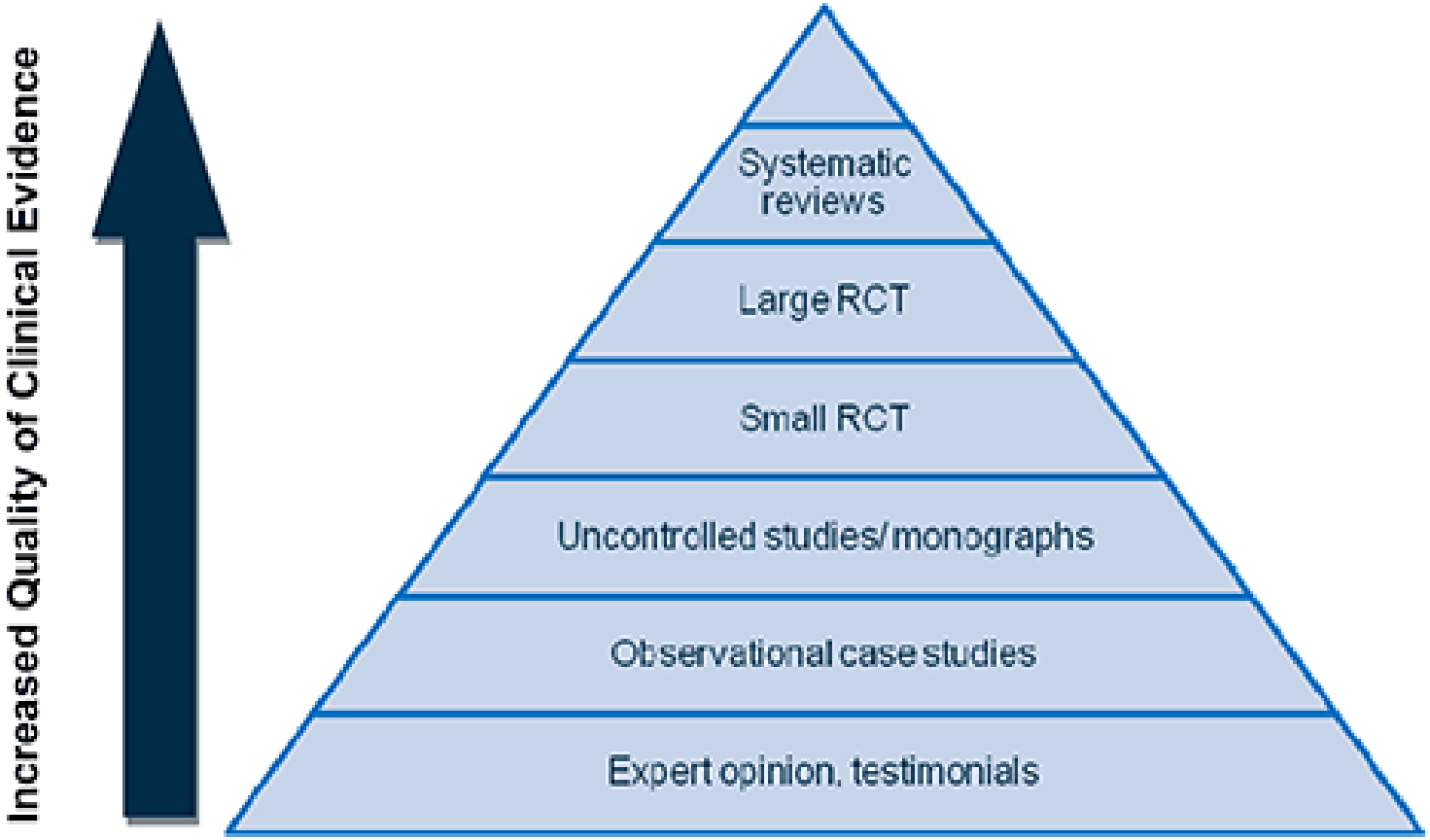
PICO(S)

- Study design: e.g. randomized controlled trial

Patient, Population, or Problem	How would I describe a group of patients similar to mine?
Intervention, Prognostic Factor, or Exposure	Which main intervention, prognostic factor, or exposure am I considering?
Comparison or Intervention (if appropriate)	What is the main alternative to compare with the intervention?
Outcome you would like to measure or achieve	What can I hope to accomplish, measure, improve or affect?

http://hsl.mcmaster.libguides.com/content.php?pid=337527&sid=2763810

Hierarchy of Evidence



From https://www.tga.gov.au/book/scientific-indications-what-evidence-do-you-need-support-your-scientific-indication

Randomized Controlled Trial (RCT)

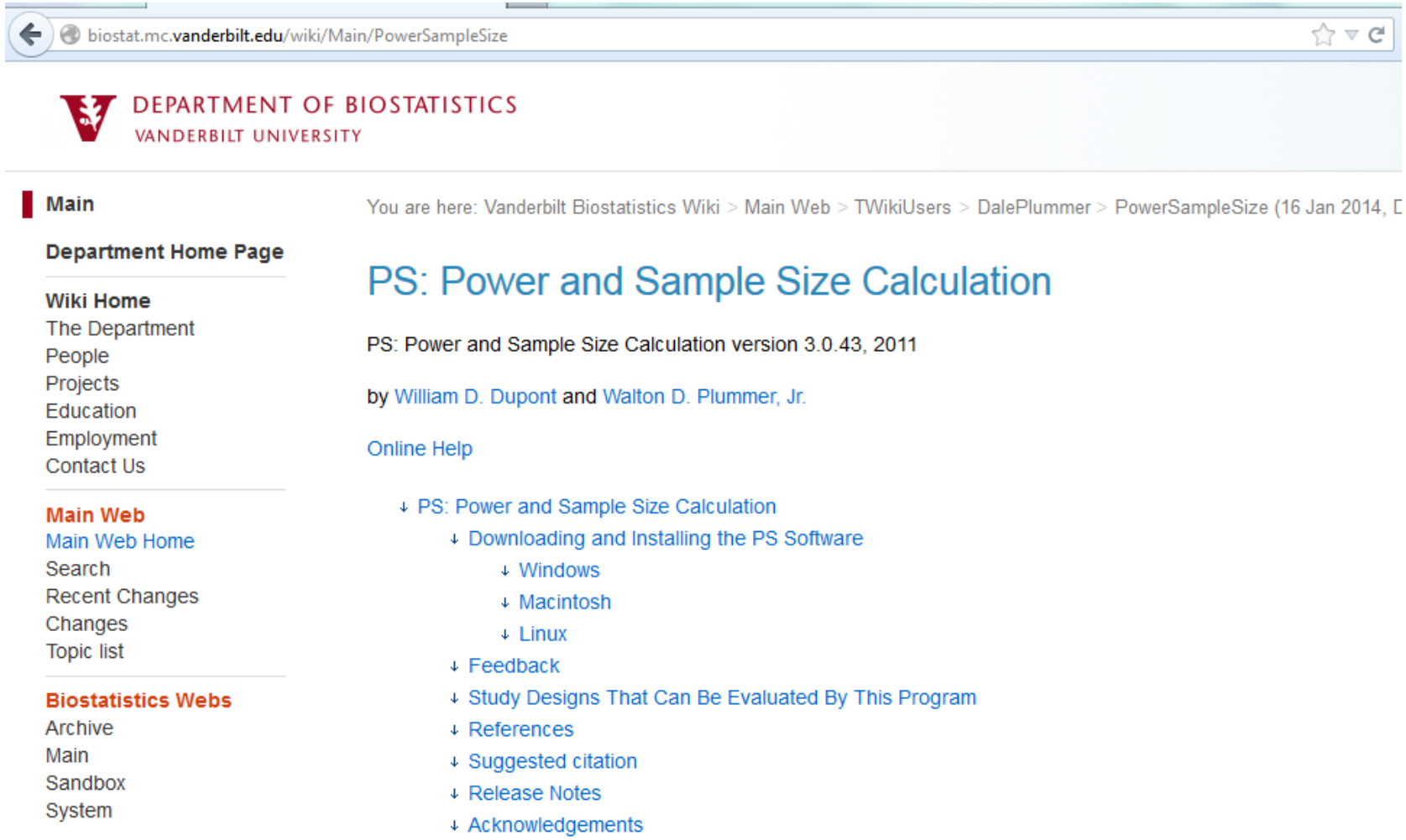
- **Randomised controlled trial:** The gold standard design to evaluate interventions
- **Contemporary controls** (not historical ones)
- **Randomisation**
  - Purpose: Avoid bias due to differences in demographic and clinical characteristics
  - Principle: known chance to receive each treatment, but not predictable!
- **Treatment blinding**
  - Purpose: avoid bias due to differences in treatment or outcome assessment

Sample Size Calculation: Continuous Data

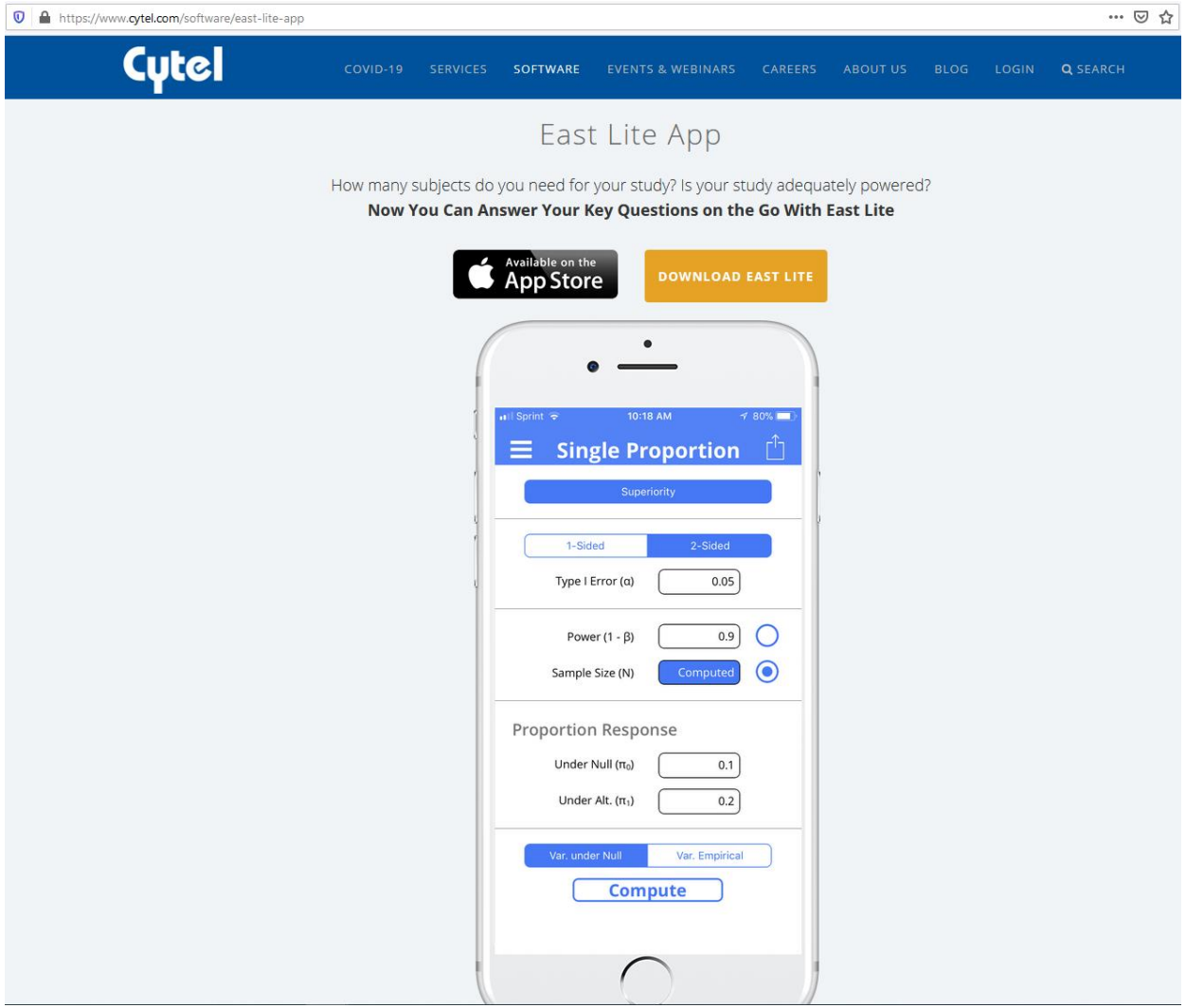
- Significance level α (one-sided)
- Power 1-β
- Clinically relevant difference Δ*
- Standard deviation σ
- Total sample size (with k:1 randomization):

$$\mathrm{N} = \frac{(k+1)^2}{k} \frac{(\Phi^{-1}(\alpha) + \Phi^{-1}(\beta))^2}{\Delta^{*2}} \sigma^2$$

Software for Sample Size Calculation



Apps for Sample Size Calculation



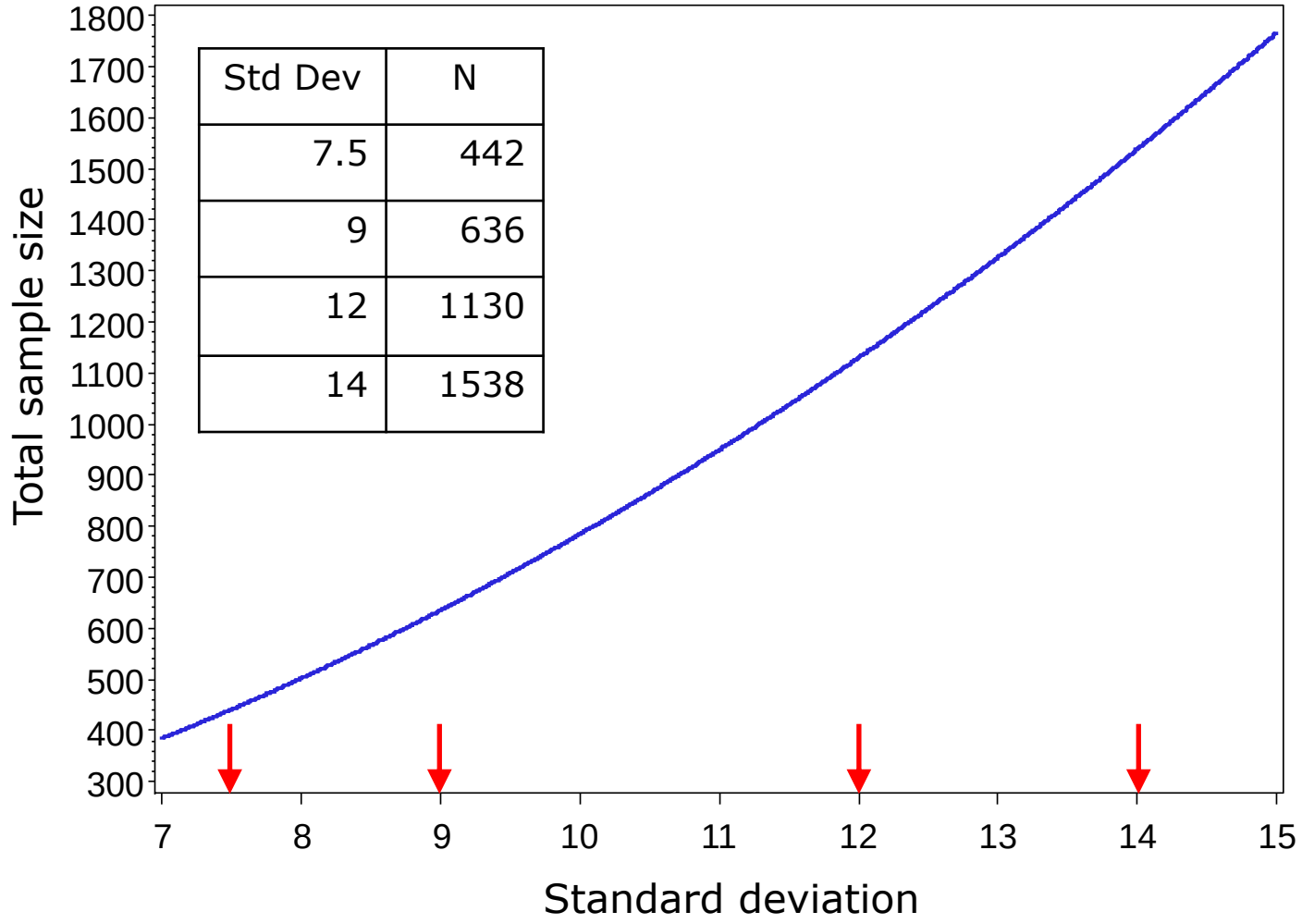
Example: MacDonald et al. (2008)

- **Objective:** Assessment of the effect of Lumiracoxib on blood pressure
- **Design:** multi-center, double-blind, randomised, controlled trial
- **Population:** Osteoarthritis (OA) patients at least 50 years of age with hypertension controlled by antihypertensive medication
- **Treatments:** Lumiracoxib or Ibuprofen
- **Primary endpoint:** change from baseline at week 4 in average 24 h systolic BP

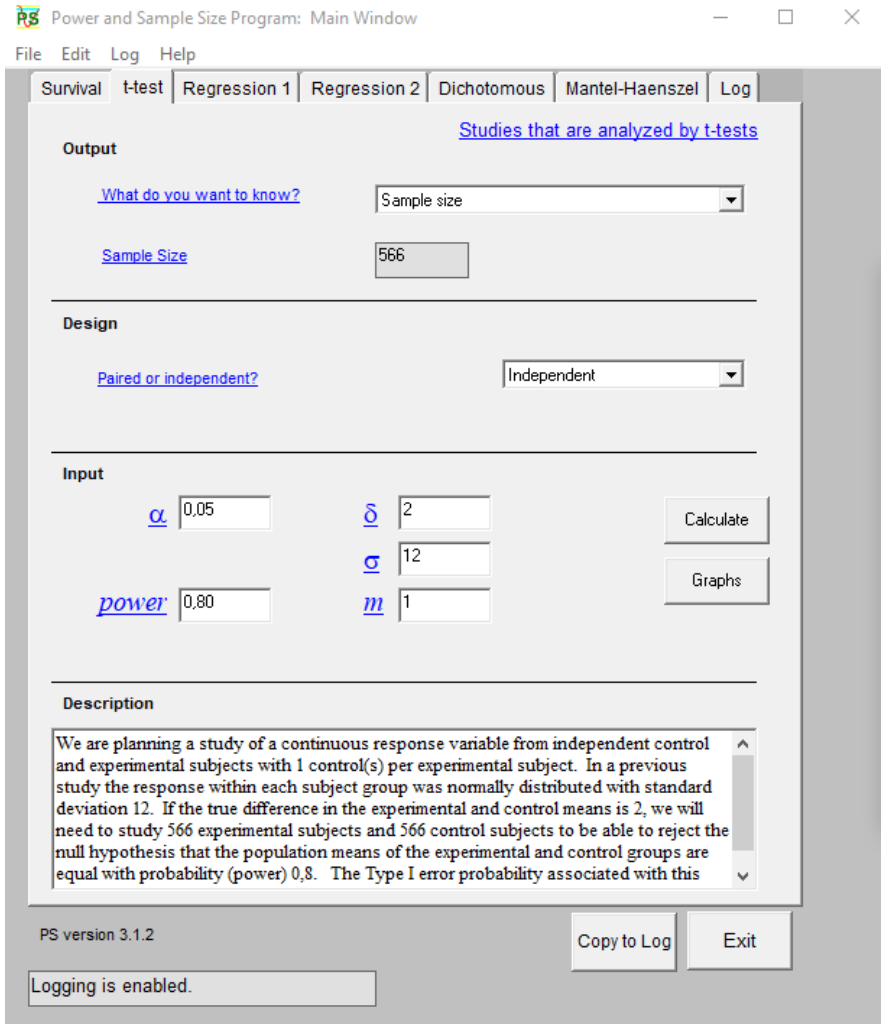
Sample size calculation

- Significance level α=0.025 (one-sided)
- Power 1-β=0.80
- Clinically relevant difference Δ*=2 mmHg
- **Standard deviation σ= ??? mmHg**
  - White et al (2002): 9 mmHg observed (but slightly different population)
  - Sowers et al (2005): sized trial based on 7.5 mmHg, but observed 12 mmHg (but 6 week follow-up)
  - Other studies in non-OA population with same endpoint: up to 14 mmHg

Uncertainty in the Planning Phase



Sample Size calculation



Internal Pilot Study (IPS) Design (Wittes & Brittain,1990)

Three step procedure:

- **Initial sample size calculation** $\rightarrow N_0$
  - based on estimates of the standard deviation from previous studies
- **Sample size review**
  - when n1=p N0 (e.g. p=1/2) patients completed the study
  - reestimation of sample size based on estimate of standard deviation from the n1 patients
- **Final analysis**
  - based on all n_1+n_2 patients

International Guidelines

- **ICH Guideline E9 (1998),** Section 4.4 Sample Size Adjustment

> "The steps taken to preserve blindness and consequences, if any, for the type I error […] should be explained."

- **Requirements**
  - Maintain blinding (trial integrity)
  - and control type I error rate

Blinded Variance Estimation

- **Variance decomposition**

total variance =
variance within groups (usually big)
+ variance between groups (much smaller)

- **One-sample variance estimator**

$$S_{OS}^2 = \frac{1}{n_1 - 1} \sum_{i,j} (X_{ij} - \overline{X})^2$$

Blinded Sample Size Reestimation

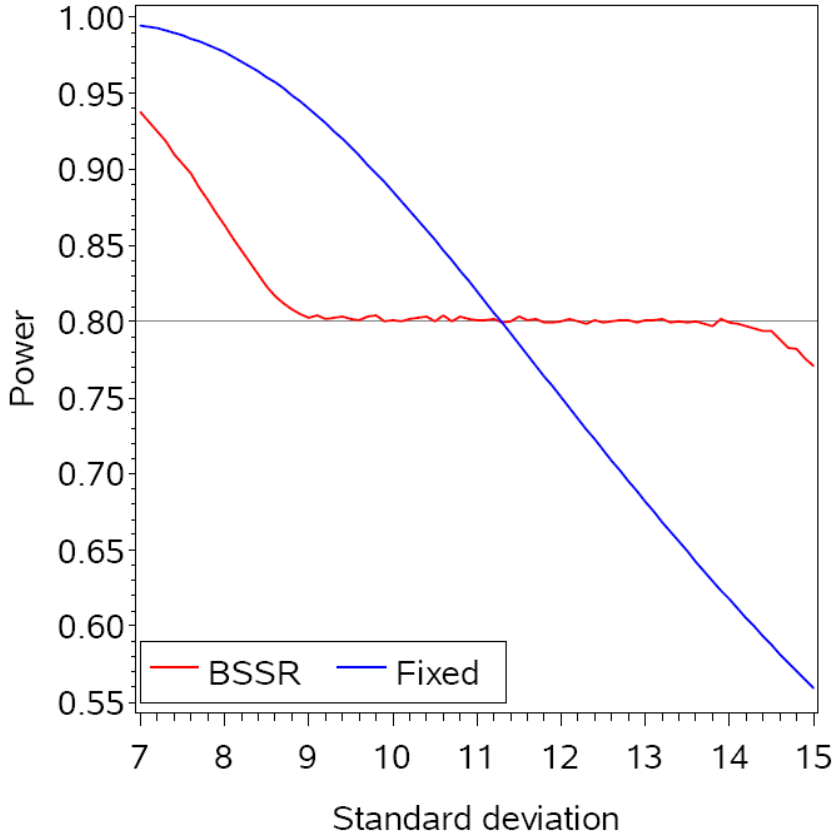
- No (practically relevant) inflation of the type I error rate (see e.g. Kieser & Friede, 2003)
- No unblinding necessary
- Fulfils requirements of regulatory authorities
- Does it make studies more robust against misspecifications in the planning phase? …

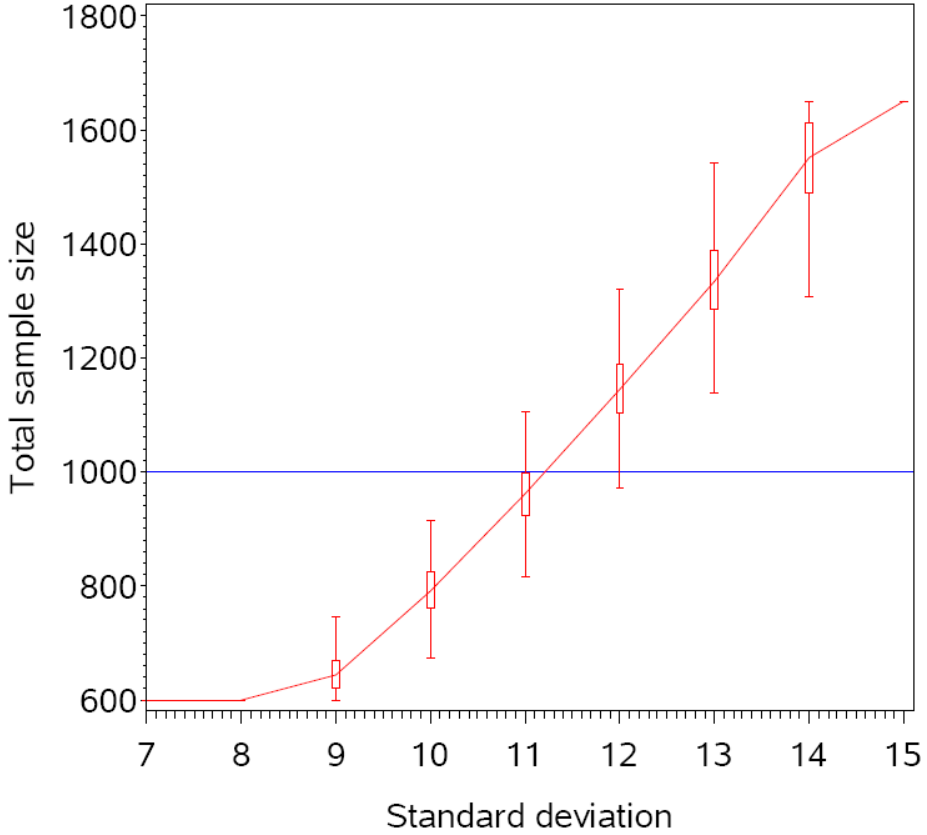
Let's return to the example …

- **Blinded sample size reestimation with n_1=600** patients who completed the study
- **Sample size adaptation rule**
  - maximum sample size 1,650 patients
  - if reestimated sample size is larger than 1,650:
    - recruit 1,650 patients as long as the power is 70% given the observed standard deviation and maximum sample size
    - otherwise stop recruitment
- **Power of 80% targeted,** independent of size of standard deviation
- **Did it work? …**

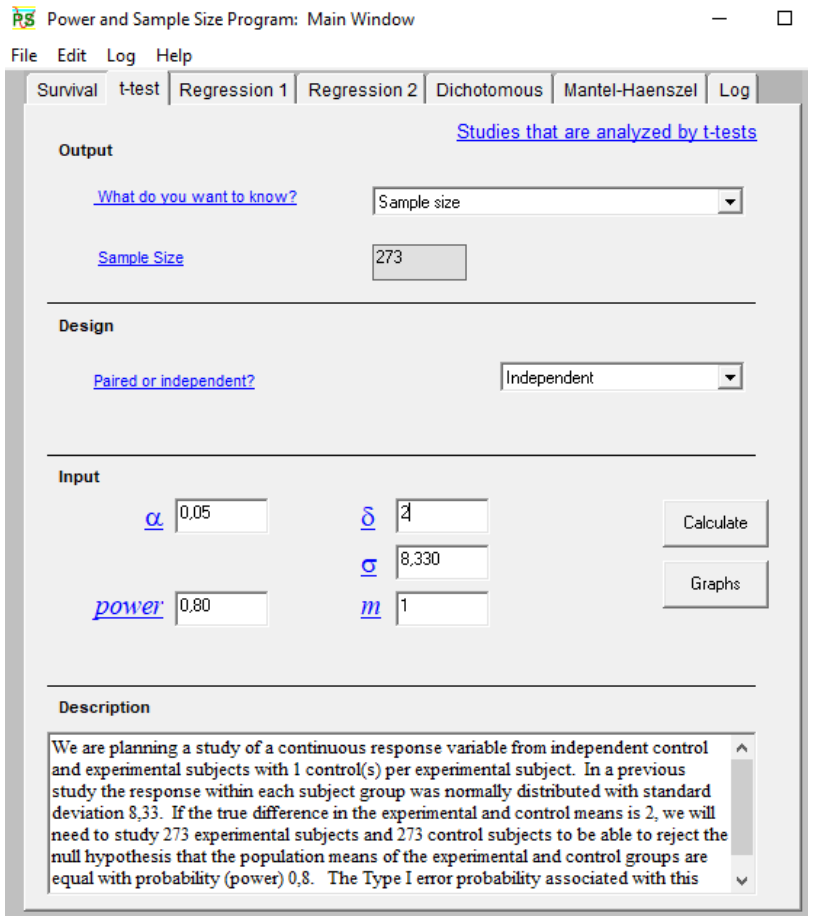
Simulated Power and Distribution of the Sample Size

Fixed sample size design with N=1,000 for comparison in blue.





Carrying out a Blinded Review: An Example



MacDonald et al (2008)

- Sample size review with n_1=600 patients
- Blinded estimation of SD resulted in 8.33 mmHg
- Recalculated sample size: 546 patients
- Already 787 patients recruited
- Decision: Stop recruitment into the study

Example: MacDonald et al (2008) Results

- Table 1 from MacDonald et al (2008)

Table 1 **Summary of the ABPM assessments at week 4 (ITT population)**

Parameter	LSM (SE) change from baseline: Lumiracoxib 100 mg o.d. ($n=363$)	LSM (SE) change from baseline: Ibuprofen 600 mg t.i.d. ($n=359$)	Estimated difference (95% CI)	*P* value
Primary endpoint				
24-h MSABP[a]	−2.7 (0.43)	2.2 (0.44)	−5.0 (−6.1 to −3.8)	<0.001
Secondary endpoints				
24-h MDABP[a]	−1.5 (0.27)	0.5 (0.28)	−2.0 (−2.7 to −1.3)	<0.001
Daytime MSABP[a]	−3.0 (0.47)	2.7 (0.48)	−5.7 (−6.9 to −4.5)	<0.001
Night-time MSABP[a]	−2.1 (0.50)	1.3 (0.50)	−3.4 (−4.7 to −2.1)	<0.001
Daytime MDABP[a]	−1.7 (0.31)	0.7 (0.31)	−2.4 (−3.2 to −1.6)	<0.001
Night-time MDABP[a]	−1.0 (0.32)	0.2 (0.33)	−1.2 (−2.0 to −0.4)	0.004

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CI, confidence interval; ITT, intention-to-treat; LSM, least squares mean; MDABP, mean diastolic ambulatory blood pressure; MSABP, mean systolic ambulatory blood pressure; o.d., once daily; SE, standard error; t.i.d., three times daily; daytime was considered to be from 0600 to 2200 h and night-time was from 2200 to 0600 h. [a] Change from baseline at week 4.

Sample Size Calculation: Binary Data

- Significance level α (one-sided)
- Power 1-β
- Clinically relevant risk difference Δ*
- Overall event probability π
- Total sample size (with k:1 randomization):

$$\mathrm{N} = \frac{(k+1)^2}{k} \frac{(\Phi^{-1}(\alpha) + \Phi^{-1}(\beta))^2}{\Delta^{*2}} \pi\,(1-\pi)$$

Rules of Thumb

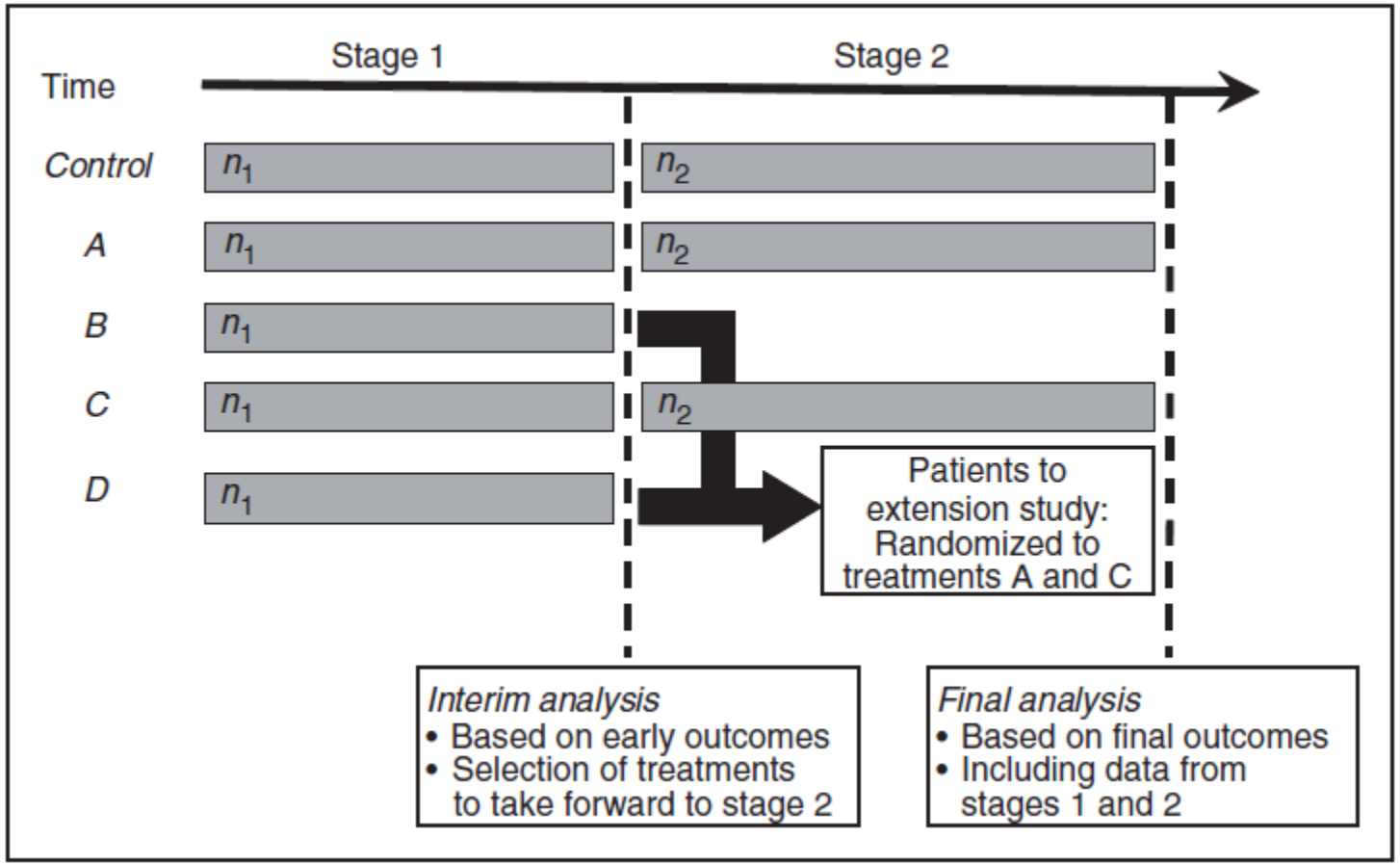
- For instance, **by how much does the sample size increase if the randomization is not 1:1 but say 2:1**? Randomizing more patients to the experimental treatment can be attractive to patients and investigators thereby helping recruitment, but it comes at the cost of an increase in total sample size. As follows directly from the formulae given above this increase is a **modest 12.5% independent of the choice of endpoint.**
- Also one might ask how much the sample size increases **powering a study for 90% rather than for 80%**. Again the answer results directly from the formulae provided above. Testing at the usual two-sided level of 5%, the **sample size increases by about a third**.
- **Reference:** Friede T (2018) Clinical trial design: statistical issues. In: Camm AJ, Lüscher TF, Maurer G, Serruys PW (eds) . ESC CardioMed (3rd edition).

Definition(s) of Adaptive Designs

- **Pharmaceutical Research and Manufacturers of America (PhRMA) Working Group on Adaptive Designs** (Gallo et al 2005)
  - "[. . .] a clinical study design that uses accumulating data to decide how to modify aspects of the study as it continues, without undermining the validity and integrity of the trial."

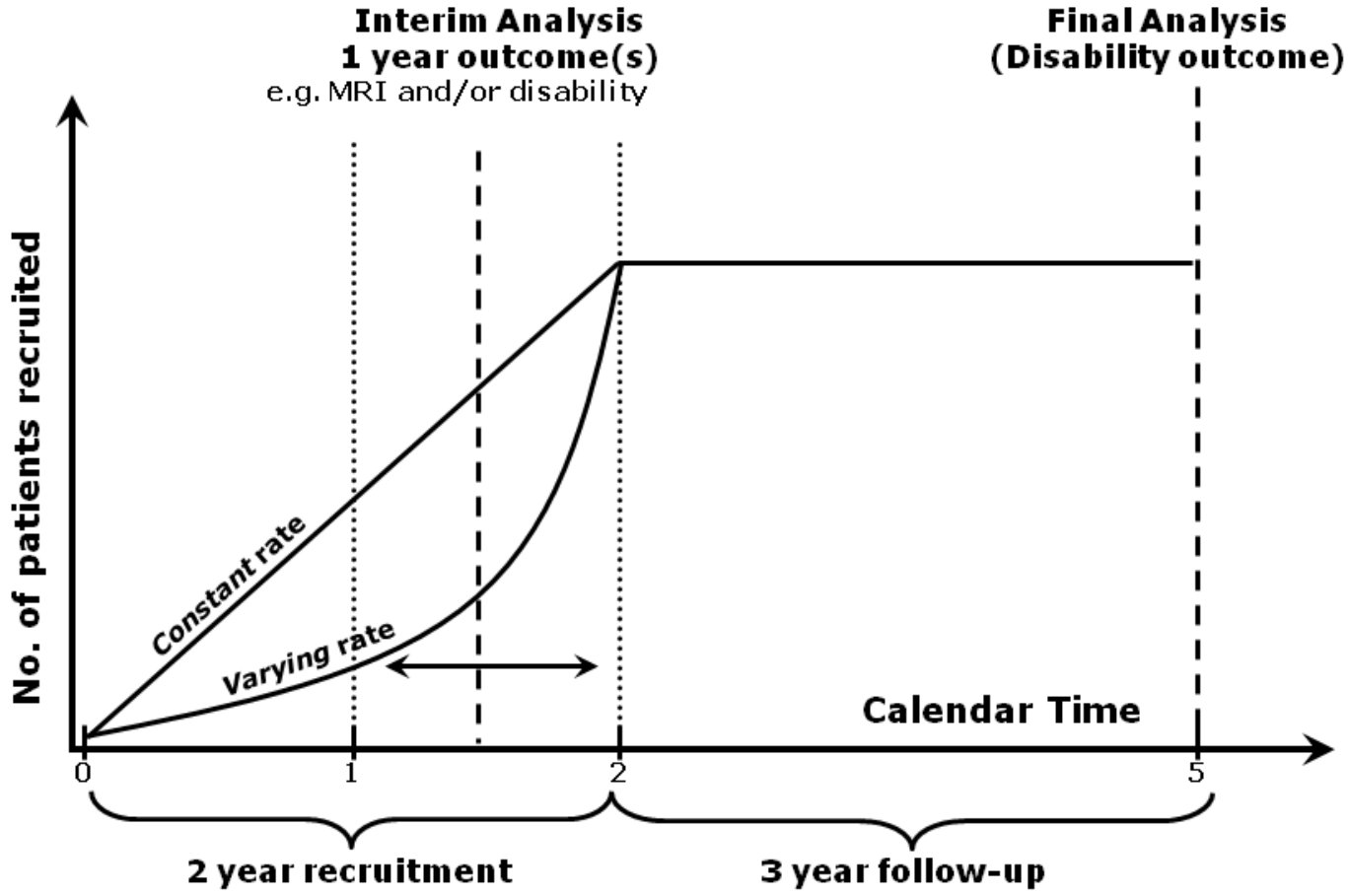
- **EMEA Reflection Paper on Adaptive Designs (CHMP 2007)**
  - "A study design is called 'adaptive' if statistical methodology allows the modification of a design element (e.g. sample-size, randomisation ratio, number of treatment arms) at an interim analysis with full control of the type I error."

Adaptive seamless phase II/III design in secondary progressive MS



Chataway et al (2011) MSJ

Adaptive seamless phase II/III design in secondary progressive MS

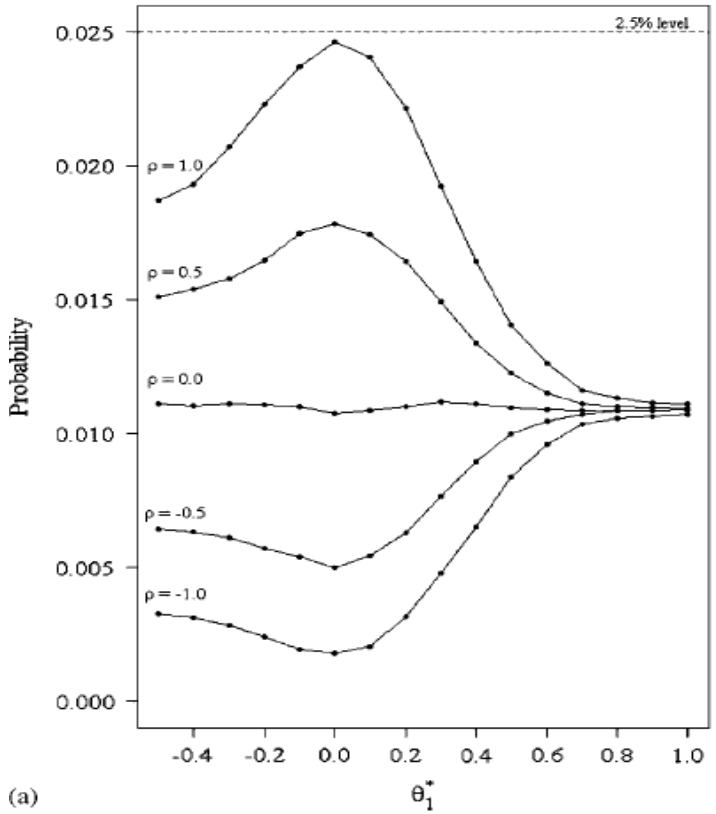


Chataway et al (2011) MSJ

Adaptive seamless phase II/III design in secondary progressive MS

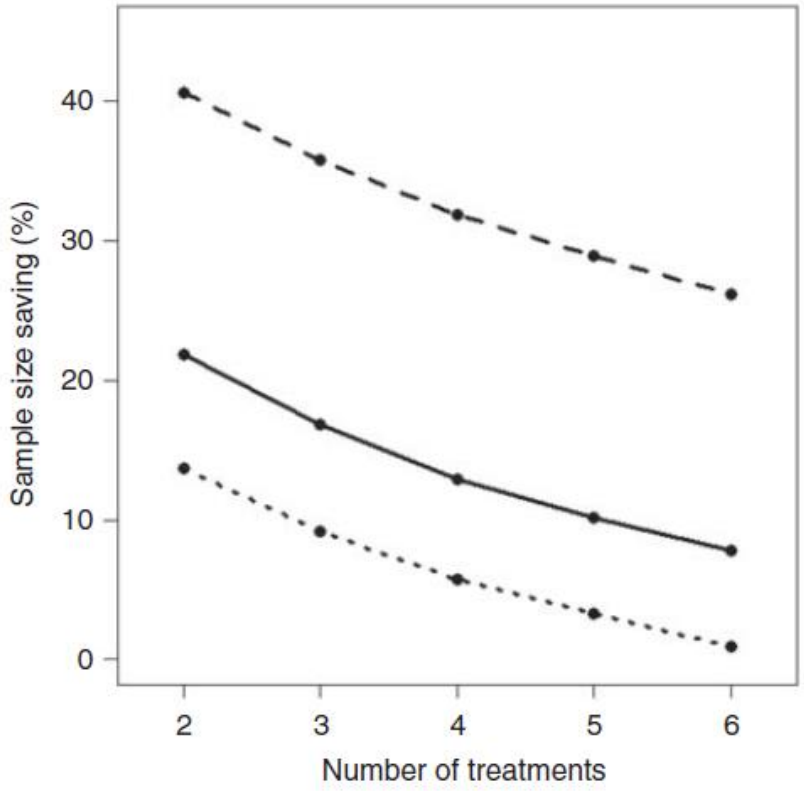
Multiple Sclerosis Society

Type I error rate control



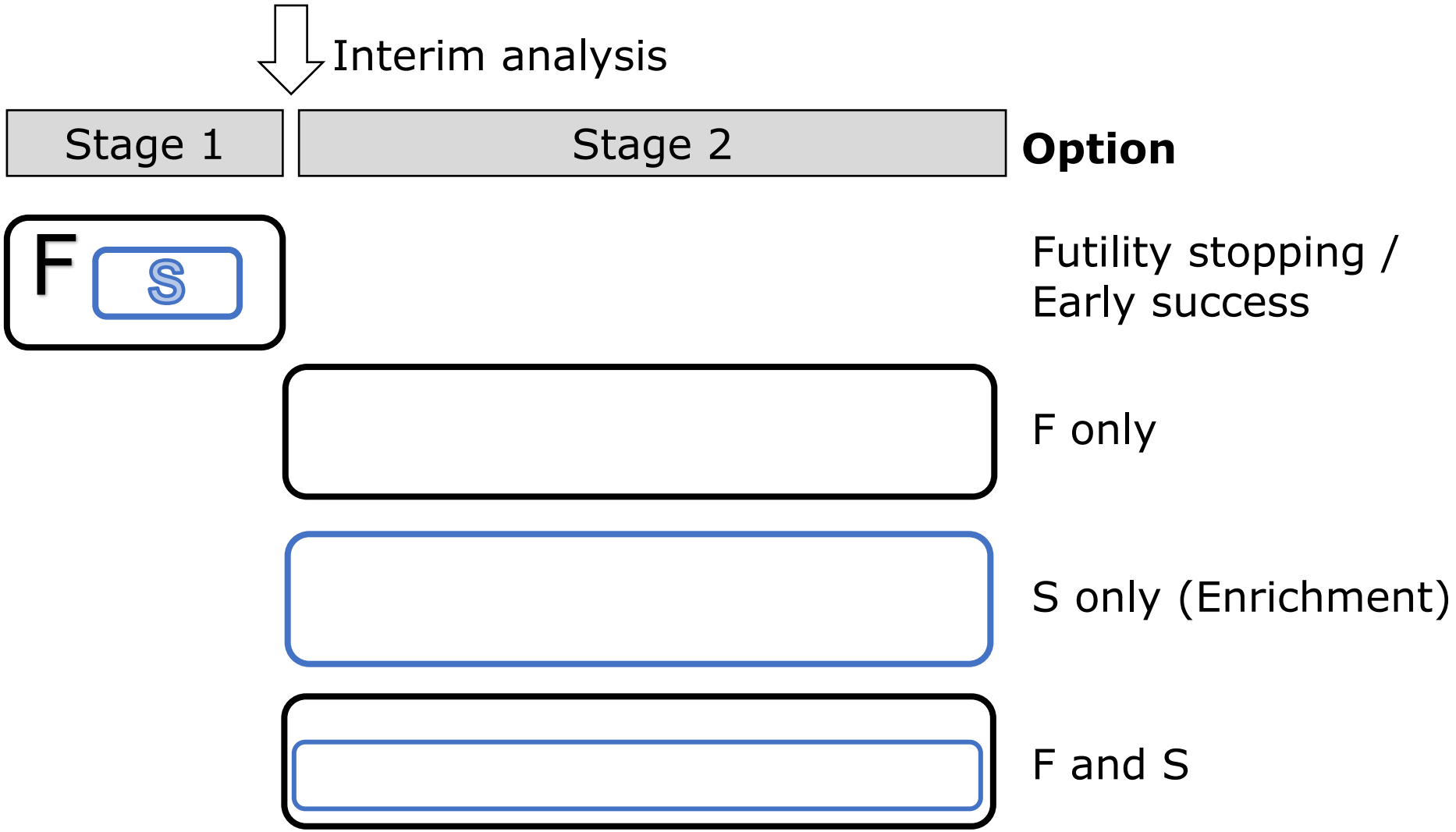
Friede et al (2011) SiM

Sample size savings



Chataway et al (2011) MSJ

Adaptive enrichment design



Adaptive designs: Pros and cons

- In comparison to traditional designs, **adaptive designs** are often more …
- **Robust:** e.g. **(blinded) sample size reestimation** makes trials more robust against misspecification of planning assumptions
- **Efficient:** e.g. by combining learning and confirming in a single trial (treatment or subgroup selection)
- **Difficult to plan:** requiring often extensive simulations (sometimes referred to as clinical scenario evaluation)
- **Logistically more involved:** e.g. drug supply, iDMC

The Swiss army knife analogy

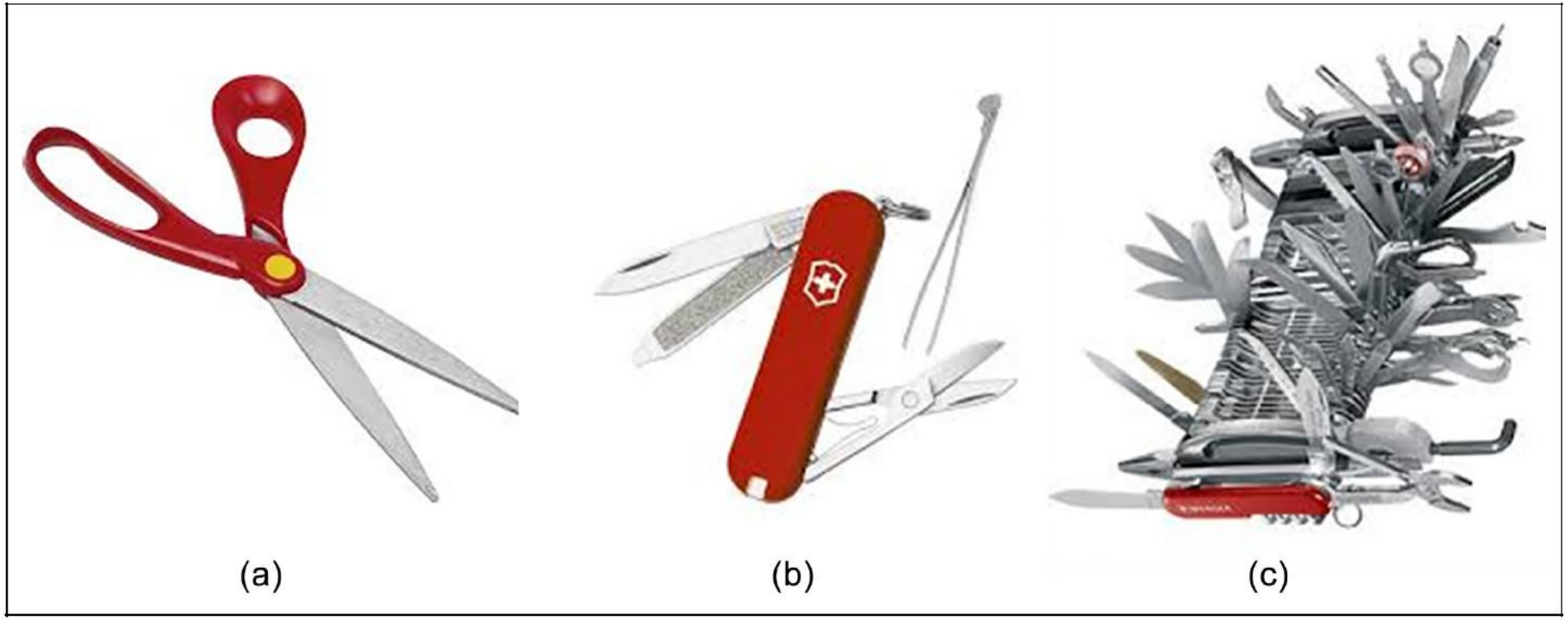


Figure 3. Analogy to adaptive designs: (a) scissor, (b) regular Swiss Army knife, and (c) giant Swiss Army knife.

Taken from Bretz, Gallo and Maurer (2017) Clinical Trials