

Eye-openers in designing F&B Clinical Trials? Insights beyond the obvious!

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Agenda

- Health Claims strategy - capitalizing on existing research vs. generation of new data
- How to interpret EFSA's guidance - getting into the mindset of EFSA
- Navigating the pitfalls of validated techniques and established methods
- How to gain from statistics beyond power calculation
- Changing the mindset from cost reduction into return on investment

Capitalizing on existing research

Relevant/sufficient(?) data may still be retrieved from the published scientific literature

New evidence emerged during the ‘time gap’ between submission deadline (2008) and now (2013).

- Dried plums & normal bowel movement (further assessment)

Article 13.1 procedure (44.000 claims) did not fully explore the options to capitalize on existing research

- Vitamin D & risk of falling
- Cocoa flavanols & endothelium-dependent vasodilation (EDV)

Capitalizing on existing research

May also apply to e.g.:

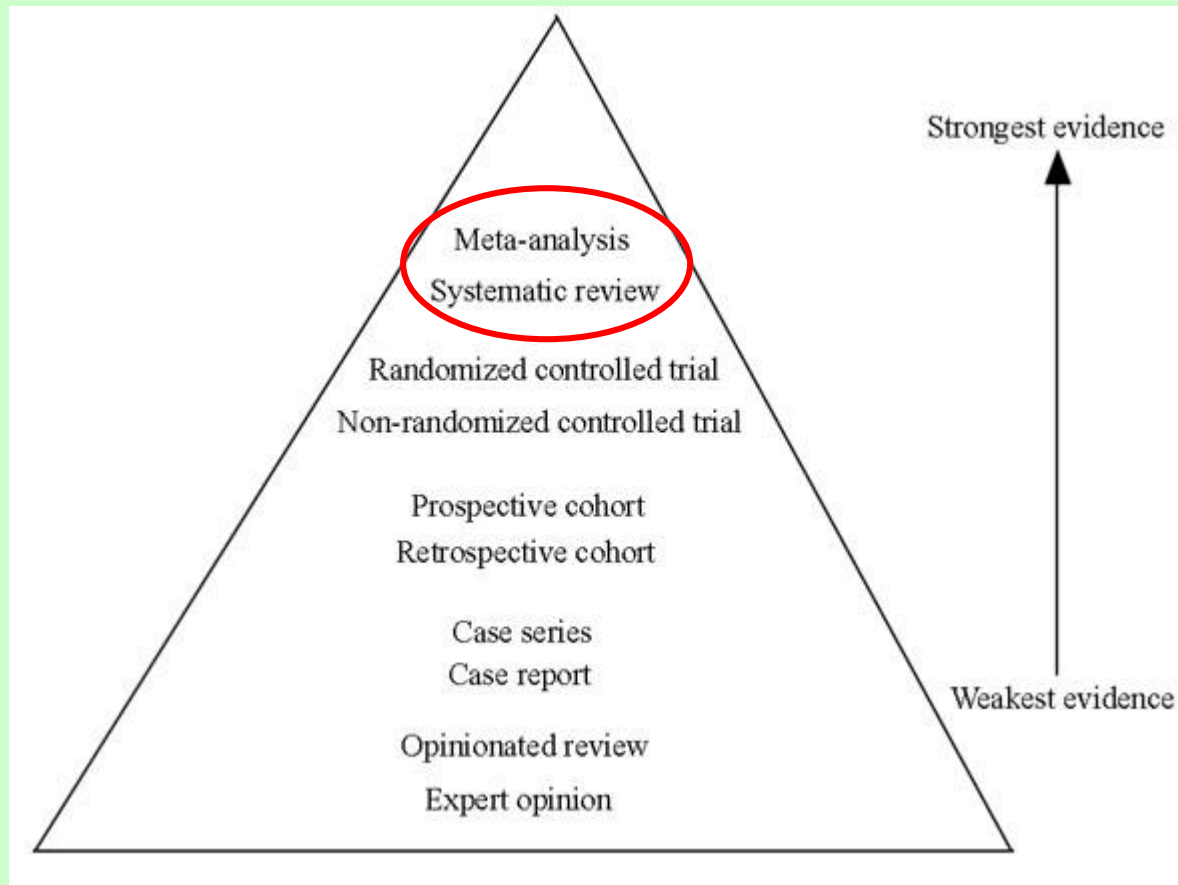
- Cocoa flavanols & blood pressure (insufficient evidence)
- Grape seed extract & blood pressure (not submitted)
- Green tea extract & EDV (not submitted)
- etc.

Capitalizing on existing research

Article 13.5 route allows:

- Application stringent study selection criteria
- Development of concept health relationship - claimed effect (primary endpoint - biomarker)
- Rationales for choices made with regard to dose, duration, effect size, target population etc.
- lower/no dependence on published meta-analyses
- submission of 'tailored' meta-analysis (proprietary)

Getting into the mindset of EFSA



Getting into the mindset of EFSA

Wrong-footed by Meta-analysis!?

- Soy protein & lowering of LDL-cholesterol
- Meta-analysis by Anderson & Bush (2011)
- 20 parallel-design studies and 23 crossover peer-reviewed studies

Conclusion:

Regular consumption of 1 to 2 servings of soy protein
daily (15 to 30 g)
has a significant favorable impact
on serum lipoprotein risk factors for CHD.

Getting into the mindset of EFSA

- Cause and effect relationship
- You can't blindly rely on peer-review - publication mindset
- You may even have to redo peer-review, even for newly performed (proprietary) studies.

- EFSA Guidance is by no means a cook-book approach to successful claim substantiation
- Be inquisitive/interrogative and use your Common Sense!
- Respect expertise but don't take it for granted
- In case of the slightest sense of doubt - don't submit!!

Getting into the mindset of EFSA

A positive EFSA evaluation doesn't come easy
but is by no means an impregnable fortress!

Established Methods?

e.g. UV-photoprotection

Sun Protection Factor (SPF): Colipa Guidelines 1996

- Numerical value for protective capacity sunscreens
- Minimal UV-dose → erythema (skin redness) -/+ sunscreen
- Protective effect through UV-absorbance or UV-blocking
- $SPF = \text{UV-dose without sunscreen} / \text{UV-dose with sunscreen}$

Established Methods?

e.g. UV-photoprotection

- Photo-protective ingredients (?) - reduction in UV-induced erythema
 - carotenes
 - polyphenols
- MoA most likely (in part) anti-inflammatory
- Additional proof - reduction in erythema not caused by tissue inhibition from mounting inflammatory response
- SPF method (although established) not useful for determination of photo-protective effect ingredients

Validated techniques? - e.g. Rome III Q - IBS

Rome III criteria - Validated Questionnaire

- Considered useful for research purposes
- Claim: ingredient increases number bowel movements
- Subjects may be included on basis of Rome III criteria even if they have rel. high number bowel movements per week
- Calculated # study subjects (Power) too low to detect difference in primary endpoint!

Statistical Power - Correct conclusions

Which type of errors are inherently present in any study and how can we set good boundaries for these?

What is True in the Population ?

		Treatments Have No Effect	Treatments Have An Effect
Conclusion Reached in a Study	No Effect	Correct Conclusion ($p = 1 - \alpha$)	Type II error ($p = \beta$)
	Treatment Effect	Type I error ($p = \alpha$)	Correct Conclusion ($p = 1 - \beta$)

↑
Power

Murphy & Myers. Statistical power analysis. 2004.

Power analysis

Dependent on:

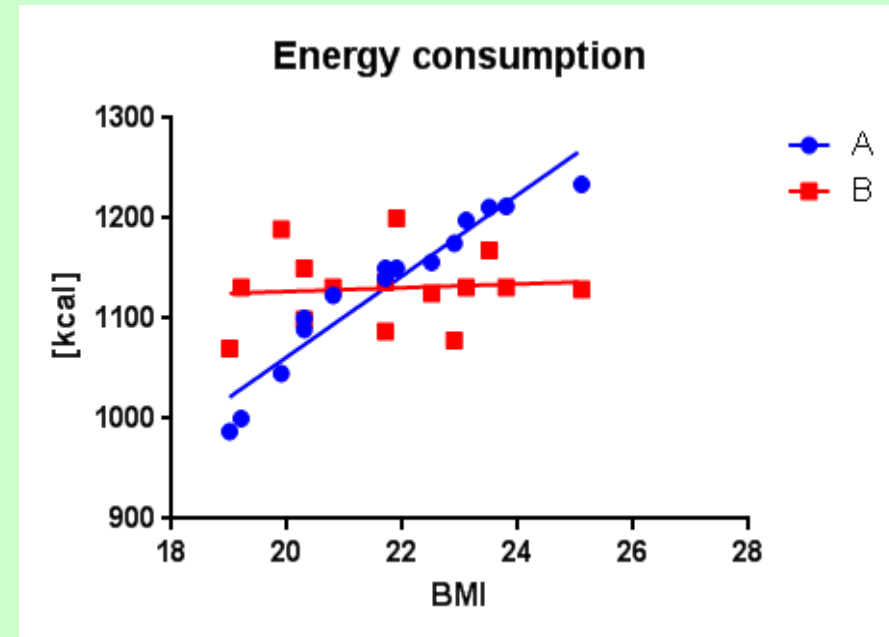
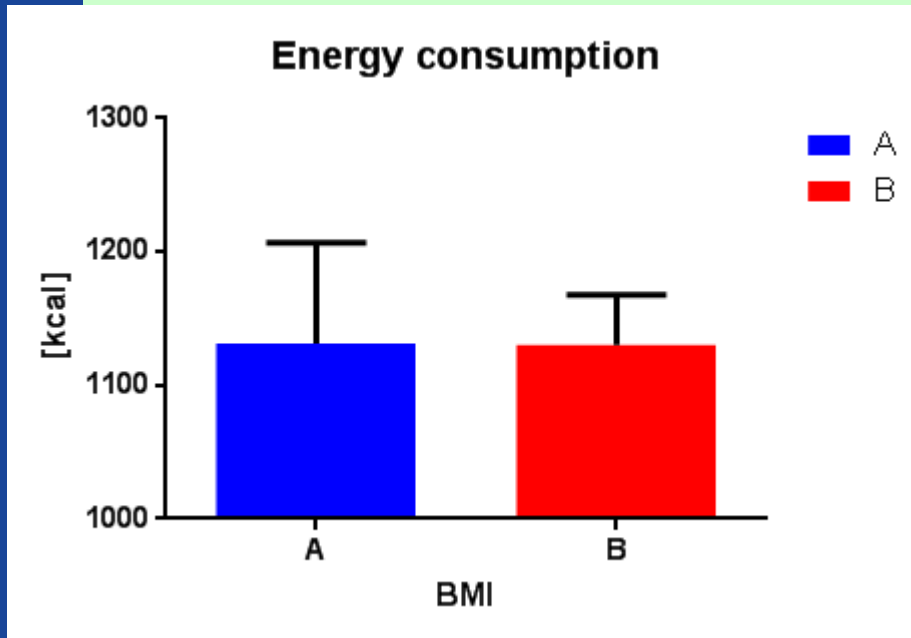
- Sample size
- Anticipated effect size vs. plc/control
- Variation around the mean effect size (SD)
- Cut-off values set for α and β

Various ways to optimize power: examples

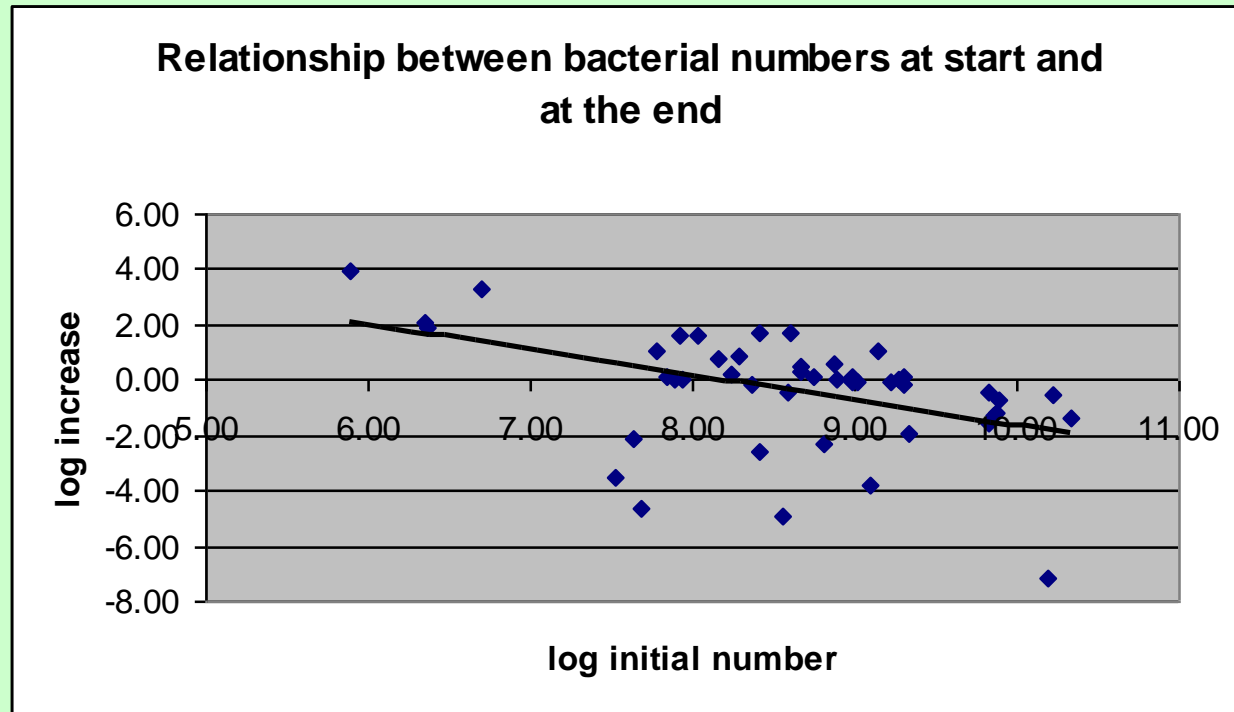
- Appropriate randomization at the start
- Increase in independent determinations
 - *adding a time-interval*
- Identification of outliers
- Optimization in the balance between inter- and intravariation
- Cofactor analysis
 - *energy intake at a specific interval versus energy intake within a BMI range at a specific interval*

Cofactor analysis:

energy consumption at a fixed interval:
addition of cofactor might reveal a totally different picture



Lack of appropriate randomisation at the start may determine the outcome.



outgrowth dependent on initial numbers of bacteria

-low number at start results in outgrowth at the end

-high number at start may even result in reduction at the end.

Appropriate statistics

Soy isoflavones & reduction of vasomotor symptoms associated with menopause

The Panel notes that most RCTs were at high risk of bias due to **major methodological weaknesses in the statistical analyses** performed e.g.:

- analysis of data with a high risk of **not being normally distributed** by parametric tests without verification of the assumption of the statistical test applied
- inadequate handling or no consideration of missing data
- repeated measures and/or multiple comparisons not taken into account
- data were inadequately reported
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Cost reduction may imply waste of money

- No power calculation performed - **potential type II error**
- Techniques not validated for research question
- 'Established methods' not appropriate for research question
- Few (two) time intervals
- Basic or even inappropriate statistics
-

Return on Investment

Value for money through:

- EFSA mindset - cause-and-effect!
- Correct sample size determination (power calculation)
- Scrutiny of techniques and methods in advance
- Statistical considerations and choices in advance
- Extra time interval
- Appropriate statistical analysis of the data
- ...



Thank you!

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