Hierarchical composite endpoints - time to untie the 'not's?

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Disclaimer

- The views expressed in this presentation are the personal views of the presenter(s). They shall not be understood or cited as opinions of the Paul-Ehrlich-Institut or any other European agency.

… but most of the presentation is based on
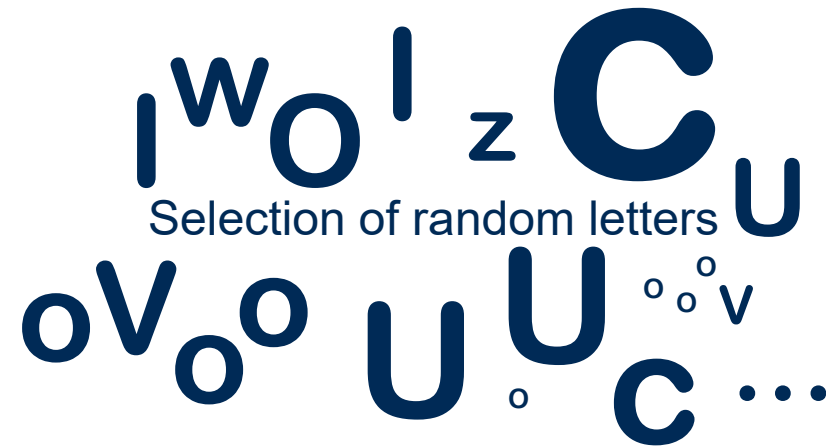clever things that other people wrote*

* WHENEVER YOU SEE A MYSTERY ASTERISK THAT DOESN'T HAVE A MATCHING FOOTNOTE, IT POINTS HERE.

https://xkcd.com/2708

Drug regulation – what really matters

benefits

risks
uncertainties

"The broad aim of the process of clinical development of a new drug is to find out whether there is a dose range and schedule at which the drug can be shown to be simultaneously safe and effective, to the extent that the risk-benefit relationship is acceptable. The particular subjects who may benefit from the drug, and the specific indications for its use, also need to be defined."
(ICH Topic E 9 Statistical Principles for Clinical Trials, CPMP/ICH/363/96)
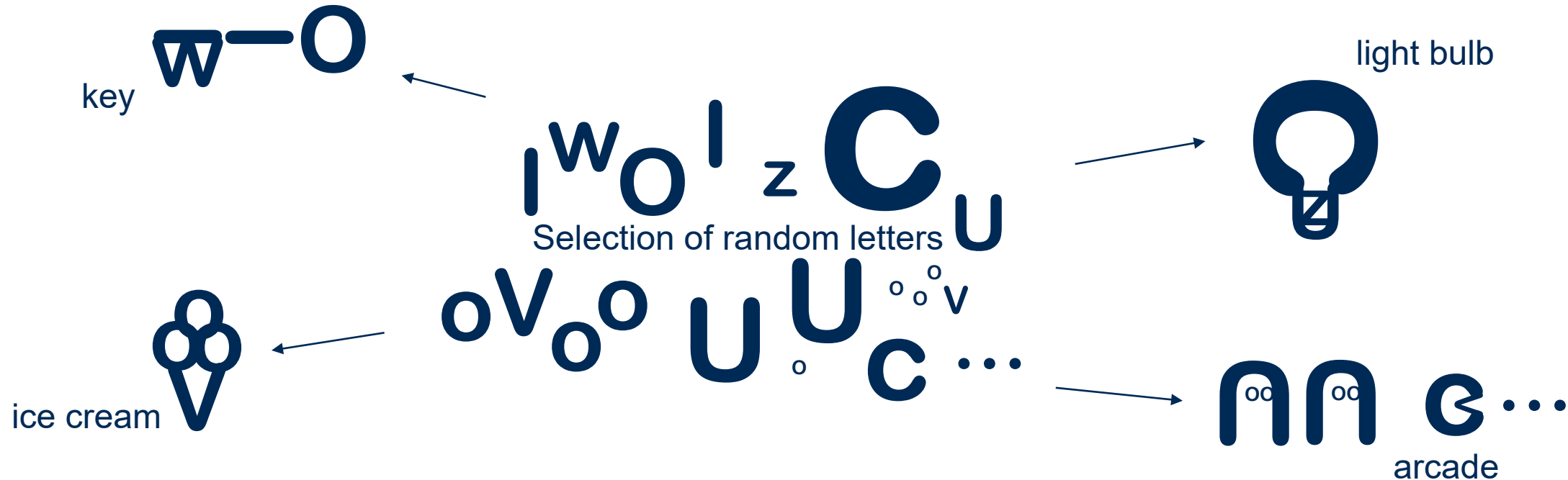
Combinations can make sense

Selection of random letters

"If a single primary variable cannot be selected from multiple measurements associated with the primary objective, another useful strategy is to integrate or combine the multiple measurements into a single or 'composite' variable, using a pre-defined algorithm."
(ICH Topic E 9 Statistical Principles for Clinical Trials, CPMP/ICH/363/96)

Combinations can make sense

key

light bulb

Selection of random letters

ice cream

arcade

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# Selected requirements for composite endpoints in regulatory guidance

- "A composite endpoint must make sense from a clinical perspective"

- "The clinically more important components should at least not be affected negatively"

- "Any effect of the treatment on one of the components that is intended to be reflected in the product information should be clearly supported by the data"

(Guideline on multiplicity issues in clinical trials, EMA/CHMP/44762/2017)

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THE OMNITAUR

https://xkcd.com/2653
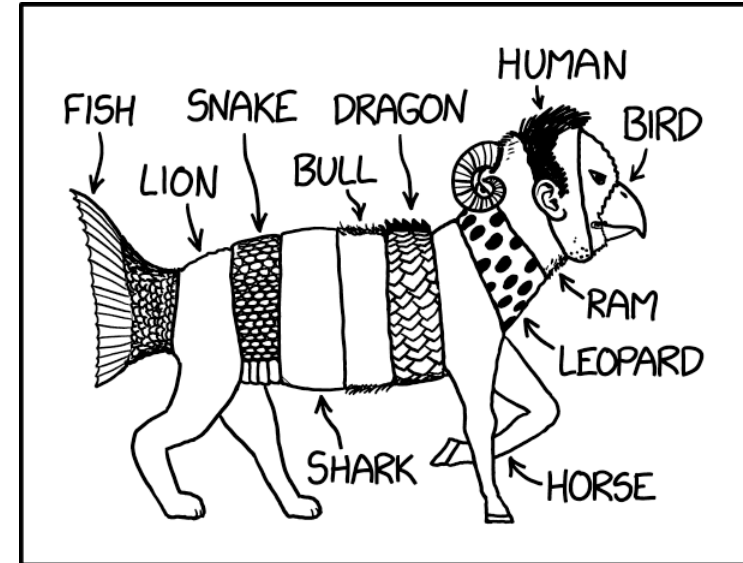
Choice and interpretation of composite endpoints

Choice of components in regulatory guidance

- "it is usually appropriate that any additional component reflecting a worse clinical event is also included."
  (EMA/CHMP/44762/2017)

- Estimand framework introduces composite strategies for intercurrent events "informative about the patient's outcome"
  (EMA/CHMP/ICH/436221/2017)

Interpretation of composite endpoints

- can be challenging …

- …but treating the composite like the "original" outcome is usually not terribly wrong (e.g. time to progression "or worse")

Hierarchical Composite Endpoints (HCEs) challenge our thinking

- Can HCEs address the weakest / the strongest component?

- Can a holistic interpretation fit in this framework?

HCE IN SCIENTIFIC ADVICE

RELEVANCE, CONCERNS AND LEARNINGS

A hint on the empirical relevance

AI search* through Final Advice Letters (FAL) of Scientific Advice

- 2524 FALs with the term „composite"
  - 11 include the word „hierarchical composite"
  - 29 include the word „win ratio"

  < 2%, in fact approx. 1 in 84 (incl. duplicates)

- 2268 FALs with the term „composite" included in the <u>primary endpoint definitions</u>
  - 5 include the word „hierarchical"
  - 0 include words like "win ratio"

  about 0.2%, approx. 1 in 454

Feedback given on HCEs

- Rarely accepted as primary

- Useful as sensitivity analyses - for certain types of analyses

- OK for secondary analyses, with caveats

*: search included similar terms to the ones listed here,
e.g. „win ratio" includes „win-ratio", „Win Ratio", „winratio", …

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Concerns raised on HCE in Scientific Advice

- Interpretation on clinical scale

- Interpretation of win statistics not trivial

- Statistical significance does not imply clinical relevance
  / p-value vs. clinical interpretation

- „Tiebreaker" less relevant than higher order components

- How to account for strata?

- Interpretation of (consistency across) subgroups

- Consistency of effects on components / absence of detrimental effects

- …

?

Summarising quote?

"Although there are no objections that the win ratio is provided, it will probably play only a minor role for interpretation of the results and their relevance. The analyses of the single components of the composite primary endpoint […] are considered more relevant in this respect."*

Win Ratio was suggested by regulators in one specific setting

- Proposed primary endpoint: composite of a recurrent event (of high clinical importance) and death

- Problems with available methods
    - Bias in case of effect on death
    - Type-I-error inflation
    - Interpretable estimators?
    - …

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- This was BEFORE the *Qualification opinion of clinically interpretable treatment effect measures based on recurrent event endpoints that allow for efficient statistical analyses* (EMA/CHMP/SAWP/120610/2020)

- This does not qualify Win Ratio as an acceptable summary measure

- But discussions may have contributed to better understanding of challenges with recurrent events
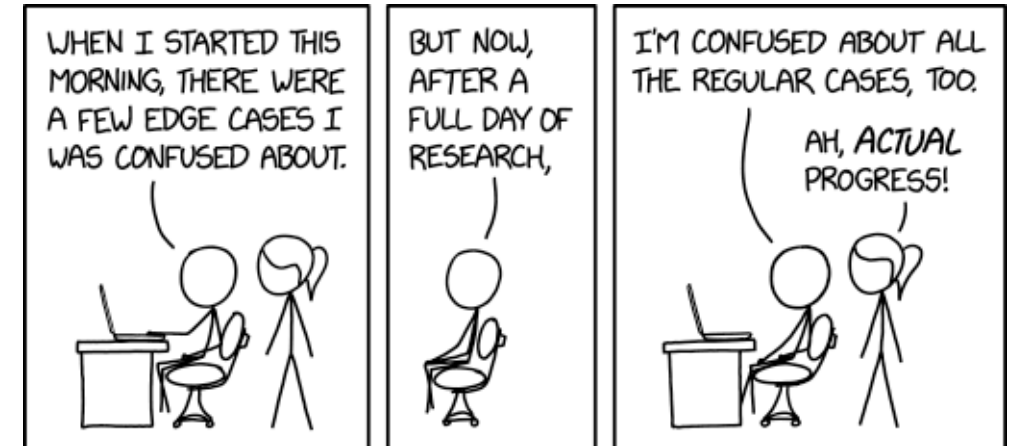
PERSONAL SUMMARY

My personal summary

- General considerations for composite endpoints should apply also to HCEs

- Interpretation of estimates is a key issue

- Some variables are difficult to combine anyway
  - Will not get easier with HCEs
  - But HCE discussions may contribute to understanding
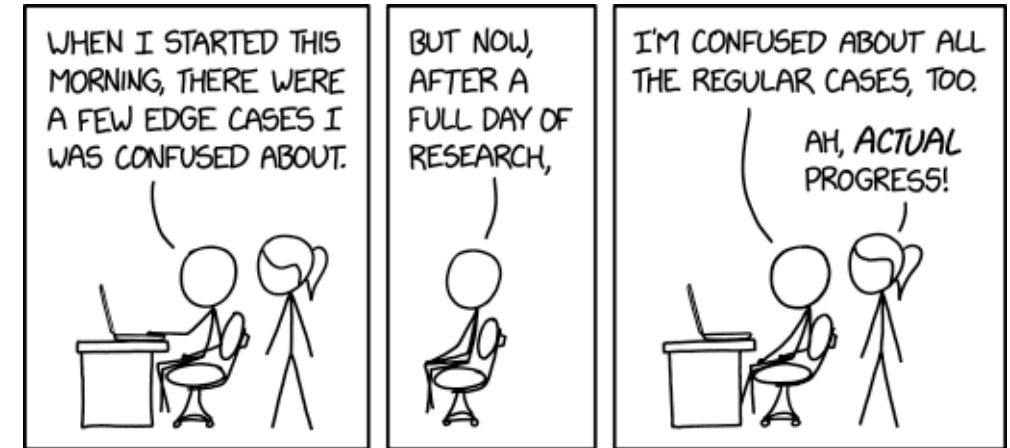
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https://xkcd.com/2797

- Increased complexity can tip the balance in the wrong direction

- Don't stop looking for situations where the benefits of HCEs outweigh their downsides

benefits

risks
uncertainties

Paul Ehrlich at work

Ehrlich in seinem Arbeitszimmer

HCE – time to untie the not's? | Lukas Aguirre Davila | Data Science and Methods

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THANK YOU VERY MUCH

FOR YOUR ATTENTION