Specifické designy klinických studií

Na cestě k personalizované medicíně

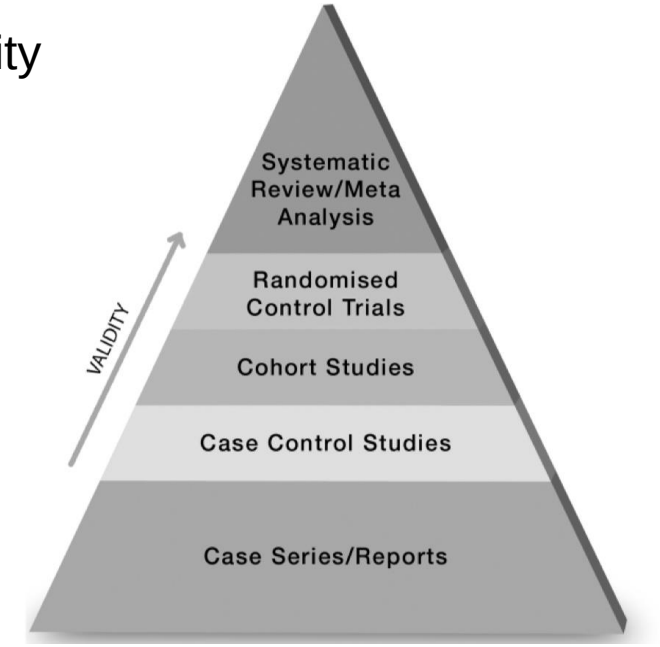
Michal Kýr

Brno 2022

Medicína založená na důkazech

Potřeba inovativního přístupu

- Populační medicína x personalizovaný přístup x comparative effectiveness research
- **Specifika (dětské) onkologie a personalizované medicíny**
- RCT jako “zlatý standard” pro regulační authority
- N-of-1 přístup
- Kombinovaný přístup analýz i důkazů
- Příklady



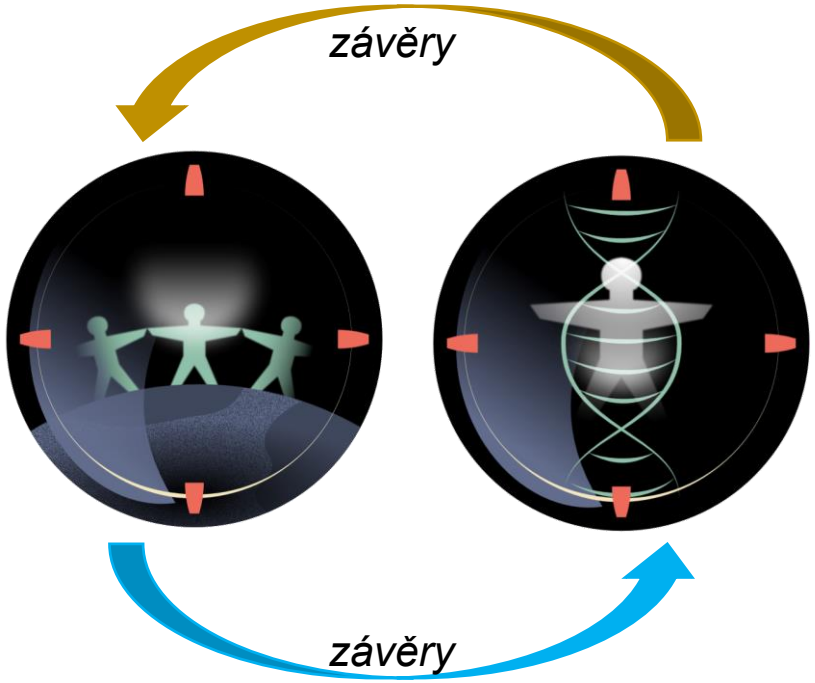
Medicína založená na důkazech – současnost

Populační studie
(RCT)
Jeden lék pro všechny

„marginal models“

Personalizovaný přístup
(N-of-1 trials)
Každý má ”svůj” optimální lék

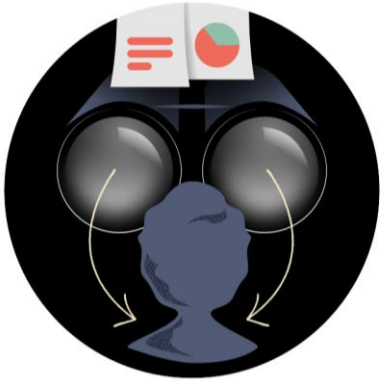
„conditional models“



Variabilita
=
Nežádoucí
šum

Variabilita
=
Cenná
charakteristická
informace

Observační studie
Comaprative effectiveness research



Reálná data

Reálná data

Specifika dětské onkologie

Personalizované medicíny

- Vzácná onemocnění -> **malé soubory**
- **Heterogenita**
- Limitovaný časoprostor pro léčbu
- Randomizace (etický problém), translace důkazů ze studií dospělých
- Nedostupnost tumormarkeru, statisticky méně silné parametry účinnosti (EFS, OS)
- Časově proměnné parametry na individualizované léčbě
- Potřeba akcelerace translace důkazů

Limitace populačních studií/RCT

Heterogenita a průměrný léčebný efekt

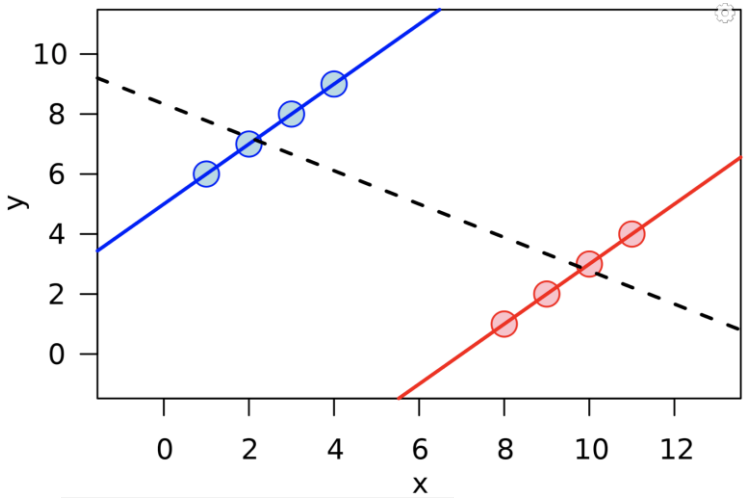
RCT populační důkaz o účinnosti – regulační autority léčí populaci

(Simpsonův paradox)

≠

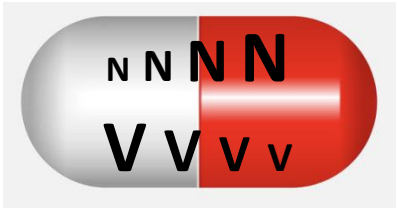
Pohled lékaře – je lék účinný u mého pacienta?

	1. semestr		2. semestr		součet	
Student A	2/8	**25%**	2/2	**100%**	4/10	40%
Student B	1/5	20%	4/5	80%	5/10	**50%**



Limitace populačních studií/RCT

Variabilita a velikost souboru



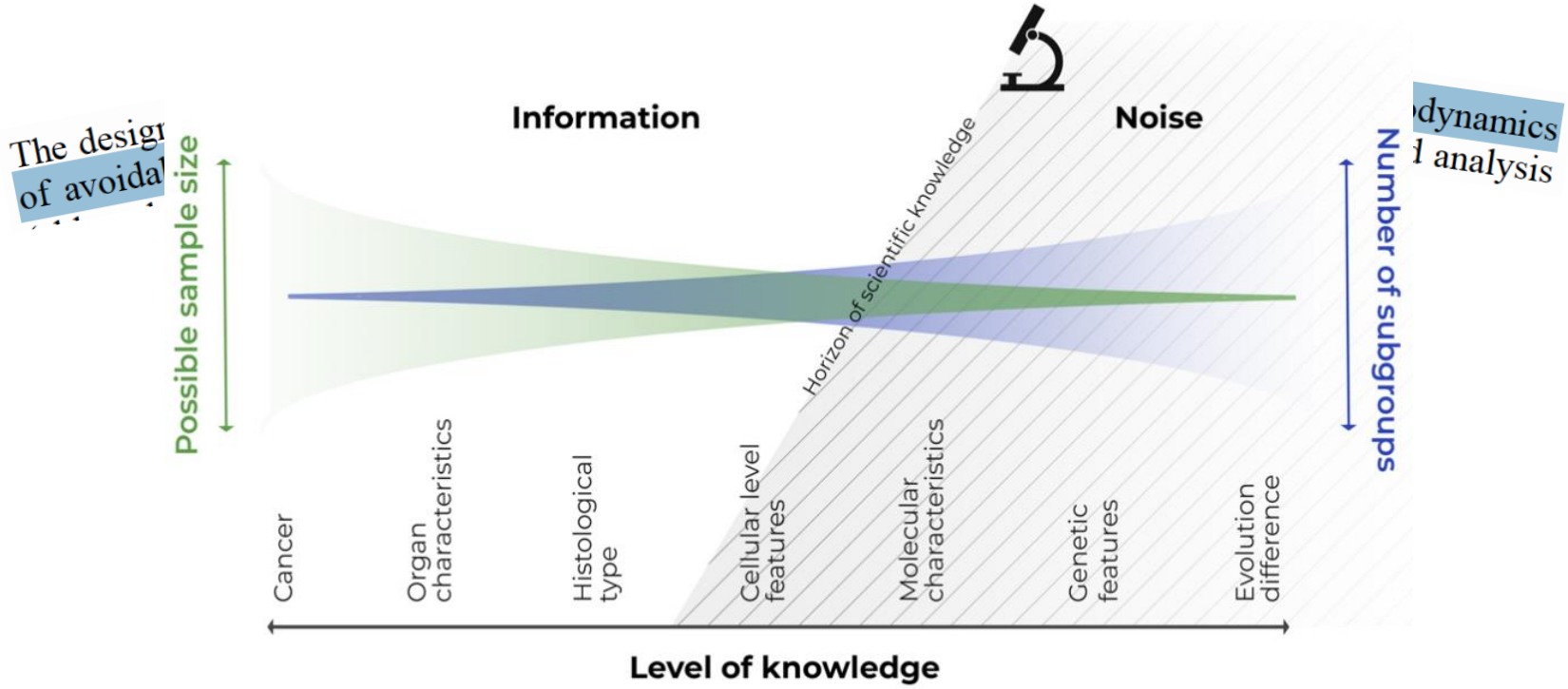
Variabilita

šum

informace

Variability (whether in terms of disease
or pharmacokinetics)
bio-noise is minimised. Bio-noise is the sum
conduct of a trial. It usually

The desig
of avoida
dynamics
l analysis



Limitace populačních studií/RCT

Randomizace

Balancuje soubor s ohledem na neznámé kovarianty

Control Clin Trials. 1988 Dec;9(4):312-26. doi: 10.1016/0197-2456(88)90046-3.

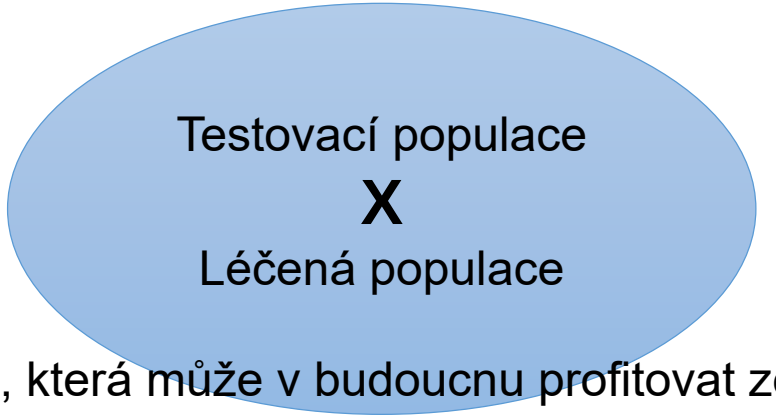
Properties of simple randomization in clinical trials

J M Lachin [1]

where the total sample size n is known exactly a priori. The likelihood of treatment imbalances is readily computed and is shown to be negligible for large trials (n greater than 200), regardless of

Limitace populačních studií/RCT

Horizont pacientů



Cílová populace, která může v budoucnu profitovat ze závěrů studie

Náhodné podávání léků
Žádná studie =
Znalost 0%

=
Paradox benefitu

Znalost 100%
Celá populace
randomizována

Optimum = $\sqrt{horizont\ pac.}$

Determination of the optimal sample size for a clinical trial accounting for the population size

Nigel Stallard, Frank Miller, Simon Day, Siew Wan Hee, Jason Madan, Sarah Zohar, Martin Posch

First published: 17 May 2016
https://doi.org/10.1002/bimj.201500228

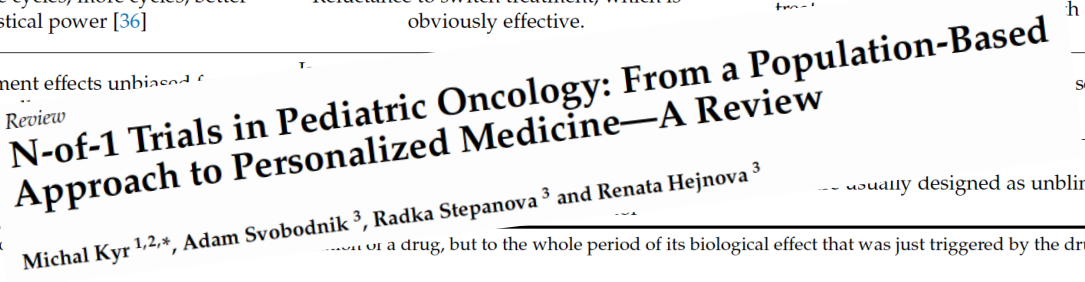
Personalizovaný přístup/N-of-1

Aspekty N-of-1

Table 2. Assumptions of N-of-1 trials (as research) and their limitations in pediatric oncology.

N-of-1 Trials' Assumptions	Rationale for the Assumption	Limitation in Pediatric Oncology	Possible Solution for Pediatric Oncology
The half-life of the medication being tested is short [36]	Rapid washout as cycles alternate	Half-life itself is not a limiting factor	Most drugs either in supportive care or cancer treatment can be tested
Carryover effect (the effect of the treatment stops soon after it is discontinued) [76]	Either slow-onset, carryover effects, or both, can compromise the validity of the trial [83]	Limiting factor. Mainly for targeted treatment with drugs of which the effect is not well known. Classical MTD-based chemotherapy cycles are usually designed to begin after the wearing off of the acute toxicity effect. Although treatment effect may be proportional to the toxicity, it is assumed to last longer, thus carrying over *.	Could be addressed via model design using reversed switches. Hardly utilized for cancer treatment efficacy. More suitable for the supportive part of treatment.
There is rapid onset/offset of the biological action of the medication [36]	Slow onset can compromise the validity of the trial [83]	Not limiting for classical MTD-based chemotherapy with assumed relatively rapid effect. Maybe a limiting factor for metronomic or targeted treatment where a slower	Targeted treatment is given to patients based on life expectancy to incorporate the assumed latency of treatment effect. Used for more indolent courses of disease, where a longer period for evaluation may be designed. It is a
The medication or condition is important enough to warrant an N-of-1 trial [36]	N-of-1 trials are intensive for the participant and resource-intensive for the participating unit	Assumption is fulfilled	
Chronicity and stability of the disease	To reduce the chance that differences between parts of each trial cycle are caused by the treatment vs. comparator and not changes in the underlying condition (not the effect of the medication) [36]	Crucial limiting factor. High-grade cancers in children limit treatment opportunities	Suitable for indolent cancers on metronomic or long-term targeted treatment
Fixed number of cycles needed [36]	In typical N-of-1 trials the minimum number of cycles is three cycles, more cycles, better statistical power [36]	Crucial limiting factor for high-grade cancers. Reluctance to switch treatment, which is obviously effective.	Using aggregated approaches. Suitable for diseases with indolent cours
Randomization	Obtain treatment effects unbiased		
Blinding	To reduce bias du		usually designed as unblinded

* In MTD-based chemotherapy, the treatment/toxicity effect should n of a drug, but to the whole period of its biological effect that was just triggered by the drug.



Review

N-of-1 Trials in Pediatric Oncology: From a Population-Based Approach to Personalized Medicine—A Review

Michal Kyr [1,2,*], Adam Svobodnik [3], Radka Stepanova [3] and Renata Hejnova [3]

Personalizovaný přístup/N-of-1

Možnosti využití v dětské personalizované onkologii

- Agregace skupin a opakovaná měření (série N-of-1, „meta-analýzy pacientů)
  - zejména MTD-based chemoterapii

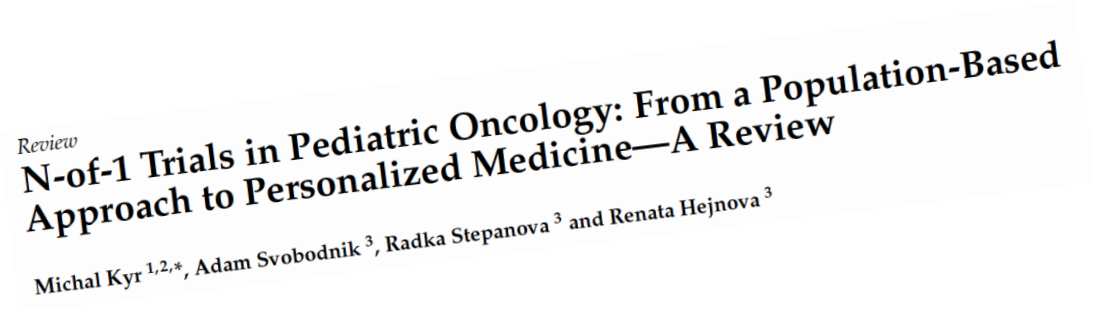
- Klasický N-of-1 design
  - Chonické „pomalé“ choroby, low-dose metronomická chemoterapie, potřeba vhodného parametru nebo tumormarkeru

- Nastavení operačních charakteristik statistických nástrojů $(\alpha, power)$

Principy určující velikost souboru

Table 1. General principles affecting sample size.

Principle to Be Addressed	Examples
Affecting overall trial efficacy	factorial, multi-arm, sequential designs, adaptive, enrichment designs
Changing operational characteristics	inflating type I/II errors, targeting larger effects
Handling interindividual variability	Cross-over, paired designs, time series, PFS ratios
Utilizing efficacy of endpoint measure	Surrogate continuous measures, EFS
Trial power and sample size enrichment	Integrative analysis, aggregation/combining, Bayesian approaches, meta-analyses, dynamic borrowing and power priors, historical controls



Review

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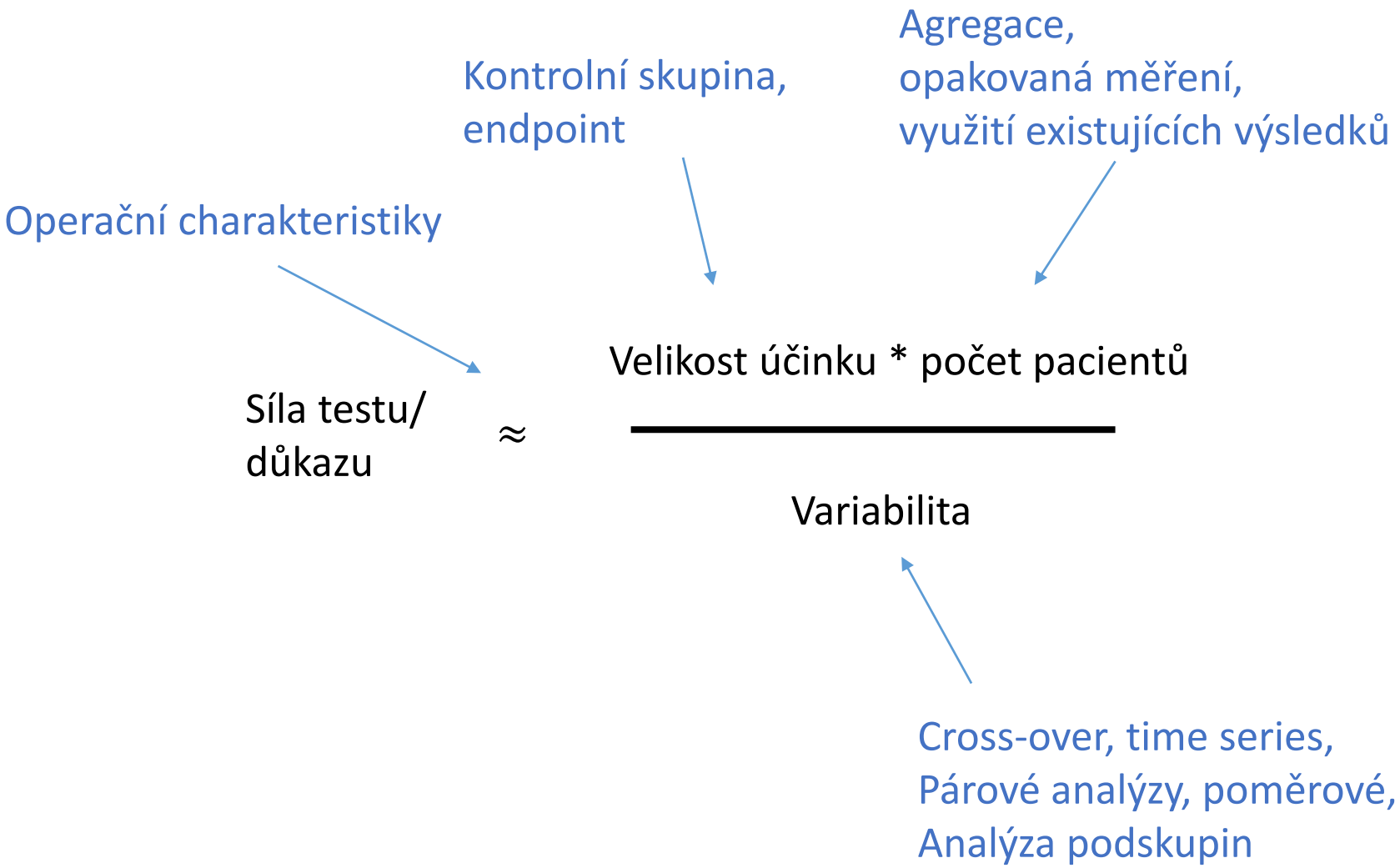
Principy určující velikost vzorku



Specifické nástroje pro malé vzorky

?

European Medi

There are no special methods for designing, carrying out or analysing clinical trials in small populations. There are, however approaches to increase the efficiency of clinical trials. The need for statistical efficiency should be weighed against the need for clinically relevant/interpretable results; the latter being the most important.

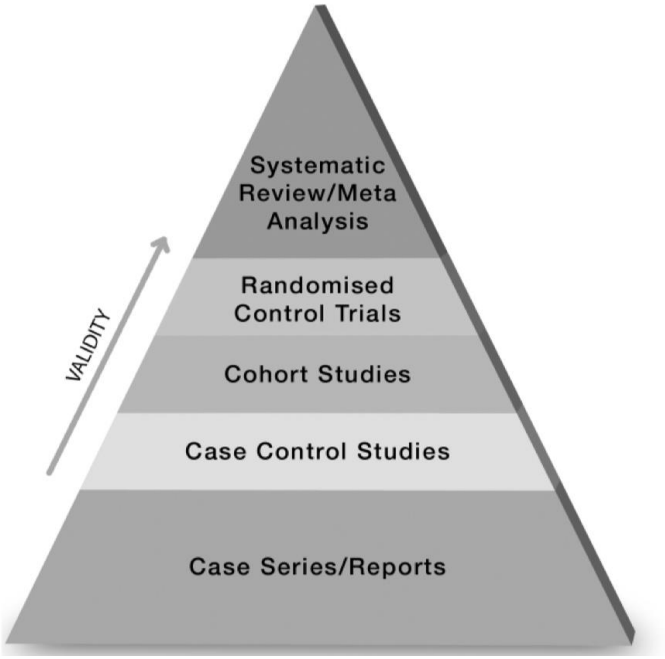
- In situations where obtaining controlled evidence on the efficacy and safety of a new treatment is not possible, the regulatory assessment may accept different approaches if they ensure that the patients' interests are protected.

OR HUMAN USE

GUIDELINE ON CLINICAL TRIALS IN SMALL POPULATIONS

EBM

Malé soubory



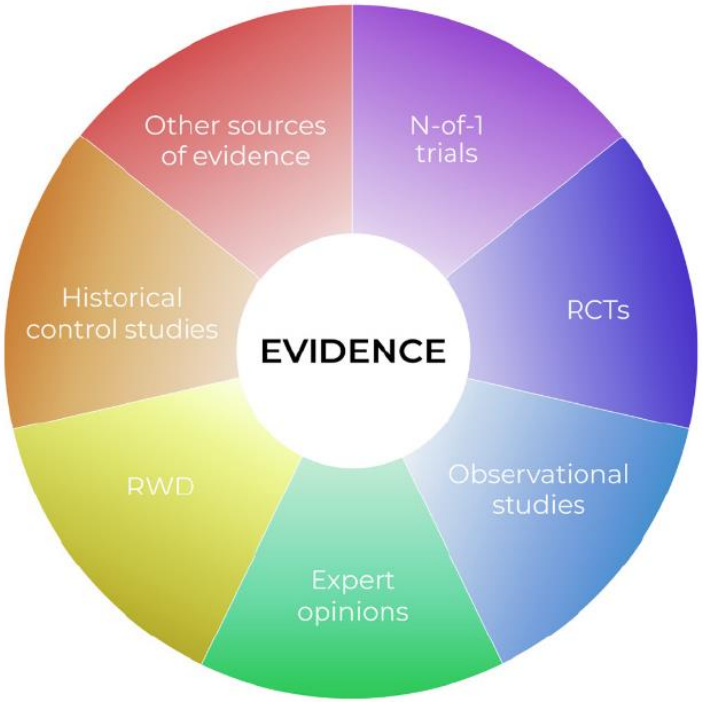


Figure 2. The complementary puzzle of evidence in rare diseases.

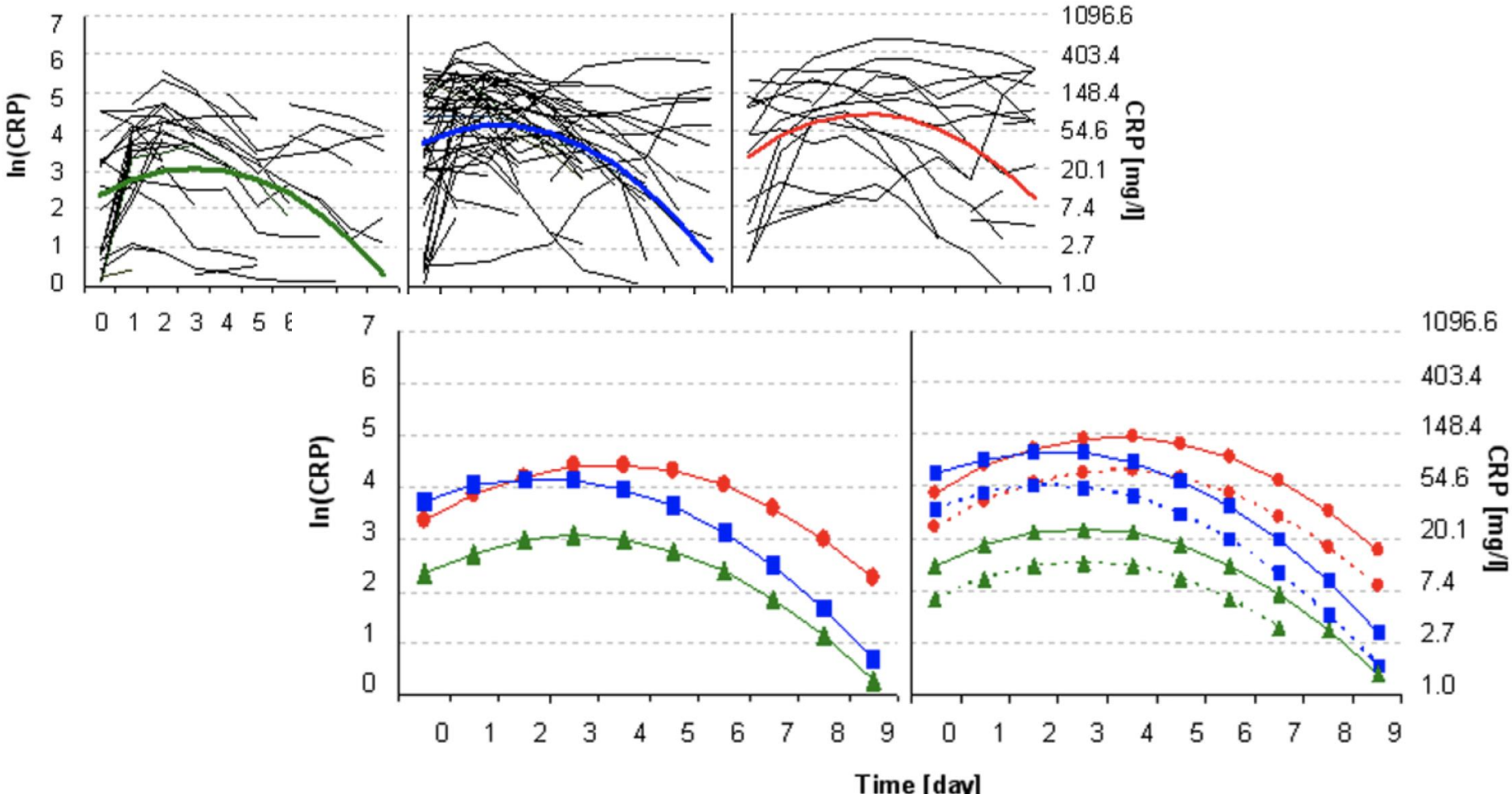
Příklady aplikací

Příklady aplikací

mixed-models, opakovaná měření

Modeling effect of the septic condition and trauma on C-reactive protein levels in children with sepsis: a retrospective study

Michal Kyr[1,2], Michal Fedora[3], Lubomir Elbl[4], Nishan Kugan[5] and Jaroslav Michalek[1]



Příklady aplikací

Využití heterogenity, mixed-models, semilongitudinální model

Apolipoprotein E ε4-Positive Multiple Sclerosis Patients Develop More Gray-Matter and Whole-Brain Atrophy: a 15-Year Disease History Model Based on a 4-Year Longitudinal Study

(multiple sclerosis / *APOE* / brain atrophy / gray matter / MRI / mixed-e

D. HORÁKOVÁ[1], M. KÝR[2,6], E. HAVRDOVÁ[1], O. DOLEŽ
L. POSPÍŠILOVÁ[5], N. BERGSLAND[3], M. G. DWYER[3], J.
Z. SEIDL[4], M. VANĚČKOVÁ[4], J. KRÁSENSKÝ[4], R. ZIVA

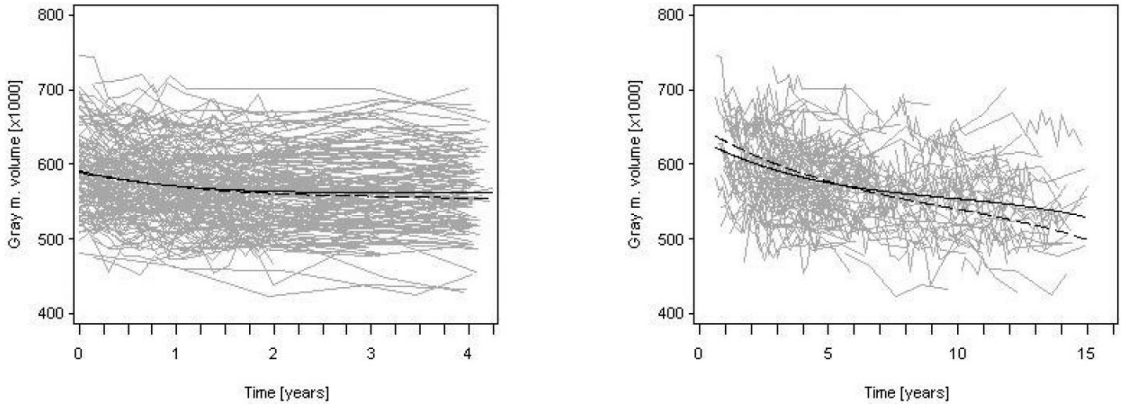
Level 1: $Y_{ij} = \beta_{0i} + \beta_{1i}T_{ij} + \beta_{2i}T_{ij}{*}T_{ij} + \beta_{3i}T_{ij}{*}T_{ij}{*}T_{ij} + e_{ij}$

Level 2: $\beta_{0i} = \beta_0 + \beta_4 apoE_i + b_{0i}$

$\beta_{1i} = \beta_1 + \beta_5 apoE_i + b_{1i}$

$\beta_{2i} = \beta_2 + b_{2i}$

$\beta_{3i} = \beta_3 + b_{3i}$



ray matter volume (GMV) evolution in the 4-year (left) and 15-year (right) models (dashed line – *APOE* ε4 solid line – *APOE* ε4 negative). Gray lines – case profiles. Black lines – mean profiles.

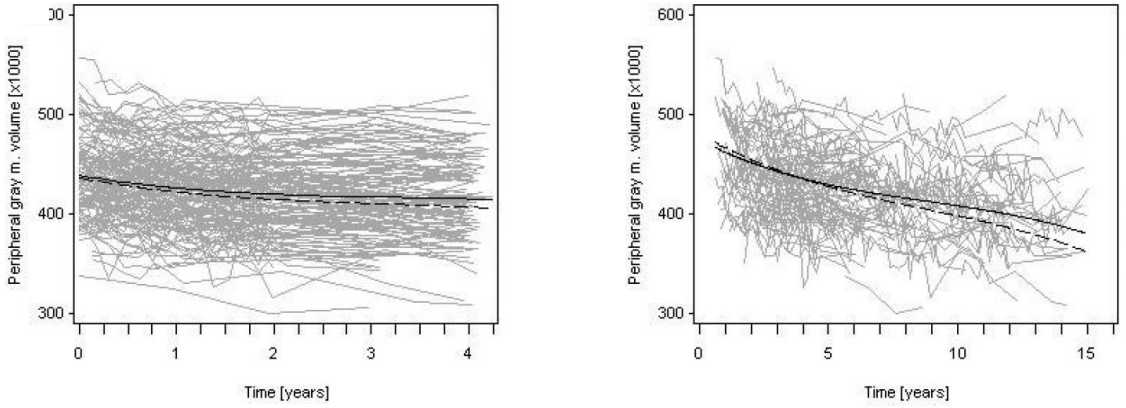


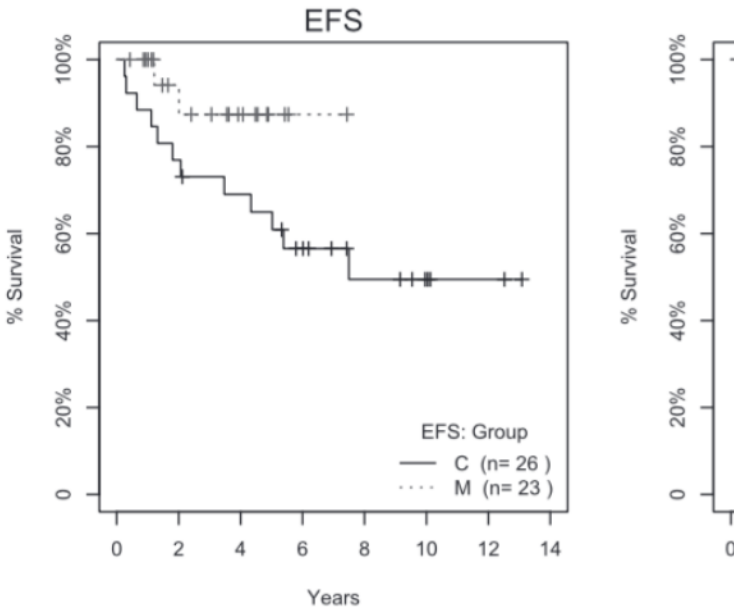
Fig. 3. Peripheral gray matter volume (PGMV) evolution in the 4-year (left) and 15-year (right) models (dashed line – *APOE* ε4 positive, solid line – *APOE* ε4 negative). Gray lines – case profiles. Black lines – mean profiles.

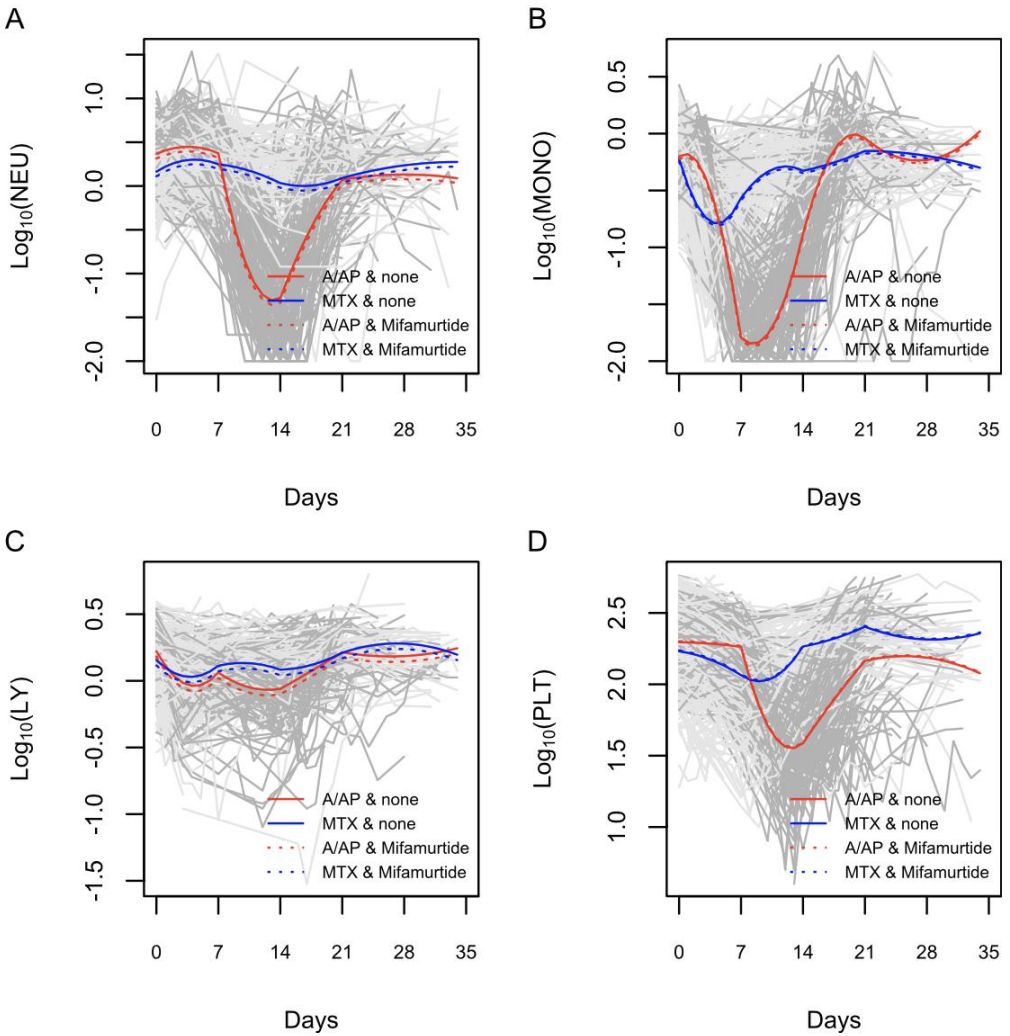
Příklady aplikací

mixed-models, opakovaná měření

Improved osteosarcoma survival with addition of mifamurtide to conventional chemotherapy – Observational prospective single institution analysis

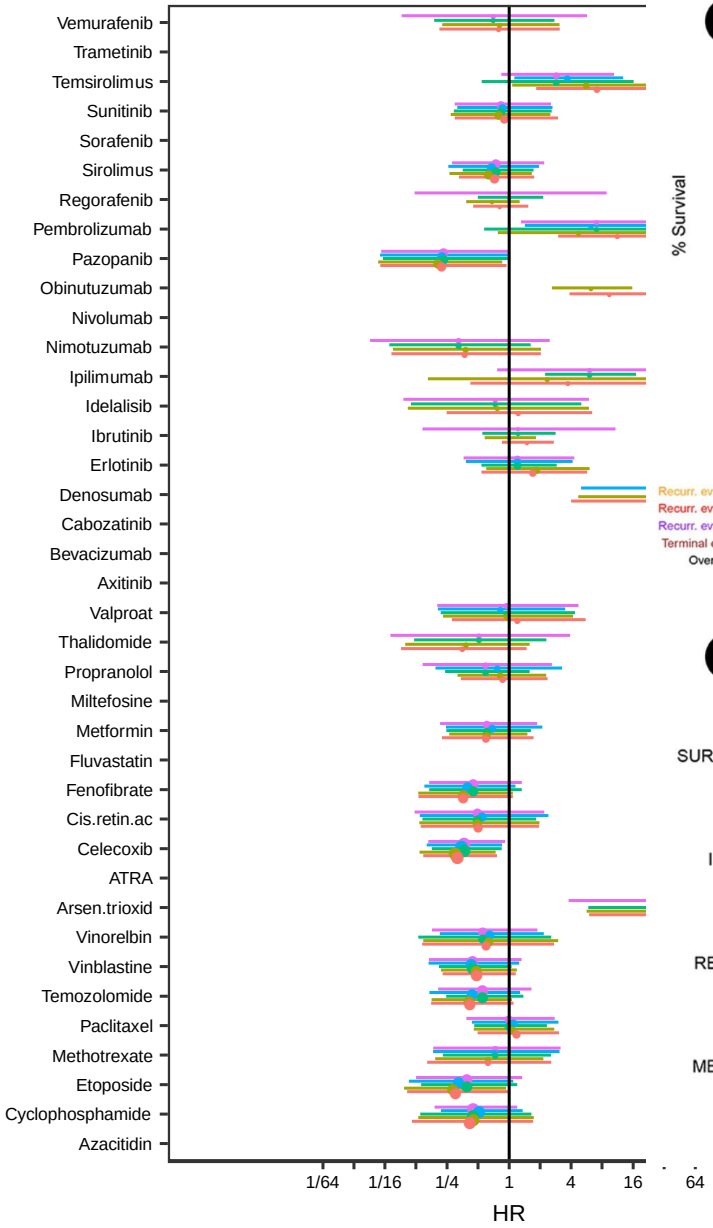
Peter Múdry [a,b,*,1], Michal Kýr [a,b,1], Ondřej Rohleder [a,b], Michal Mahda
Marta Ježová [e], Tomáš Tomáš [c], Jaroslav Štěrba [a,b]

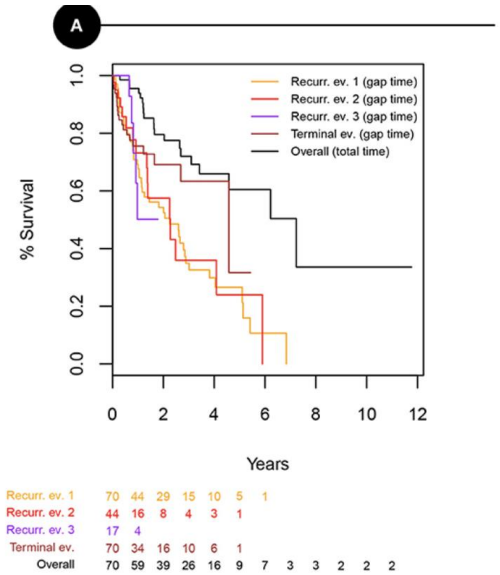


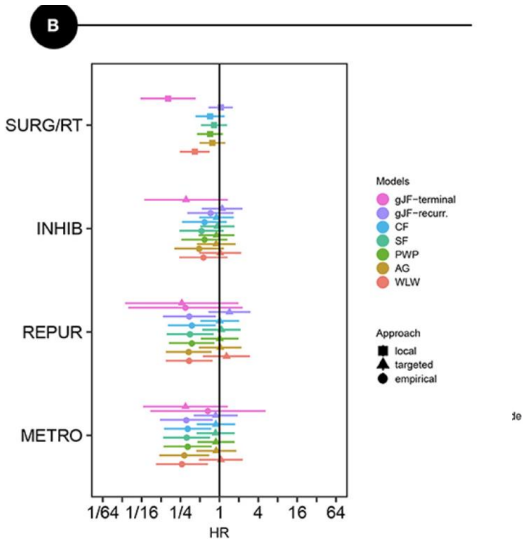


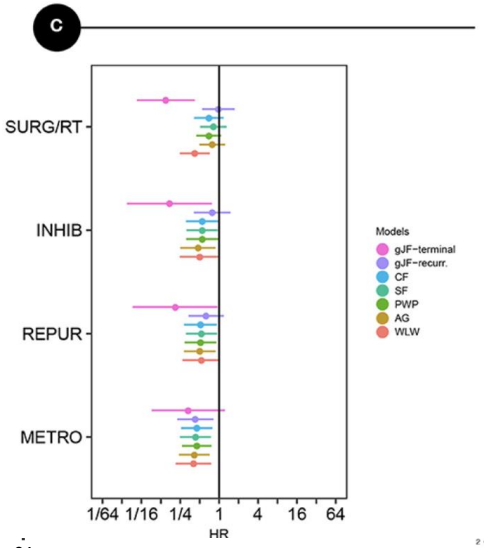
Příklady aplikací

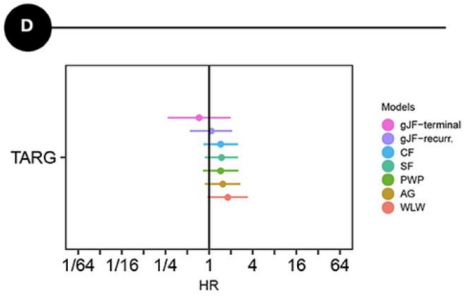
Série N-of-1, agregace, frailty modely

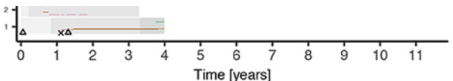






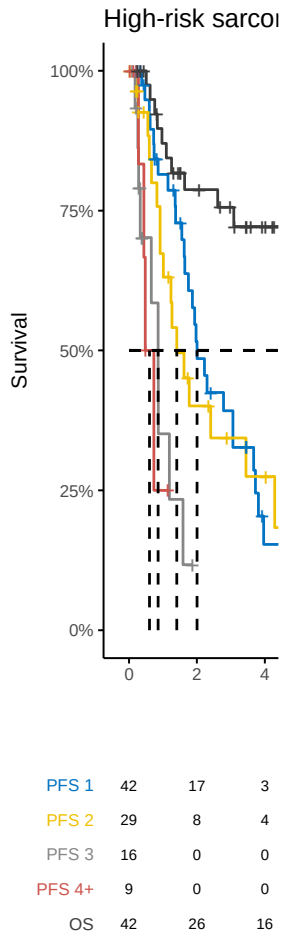


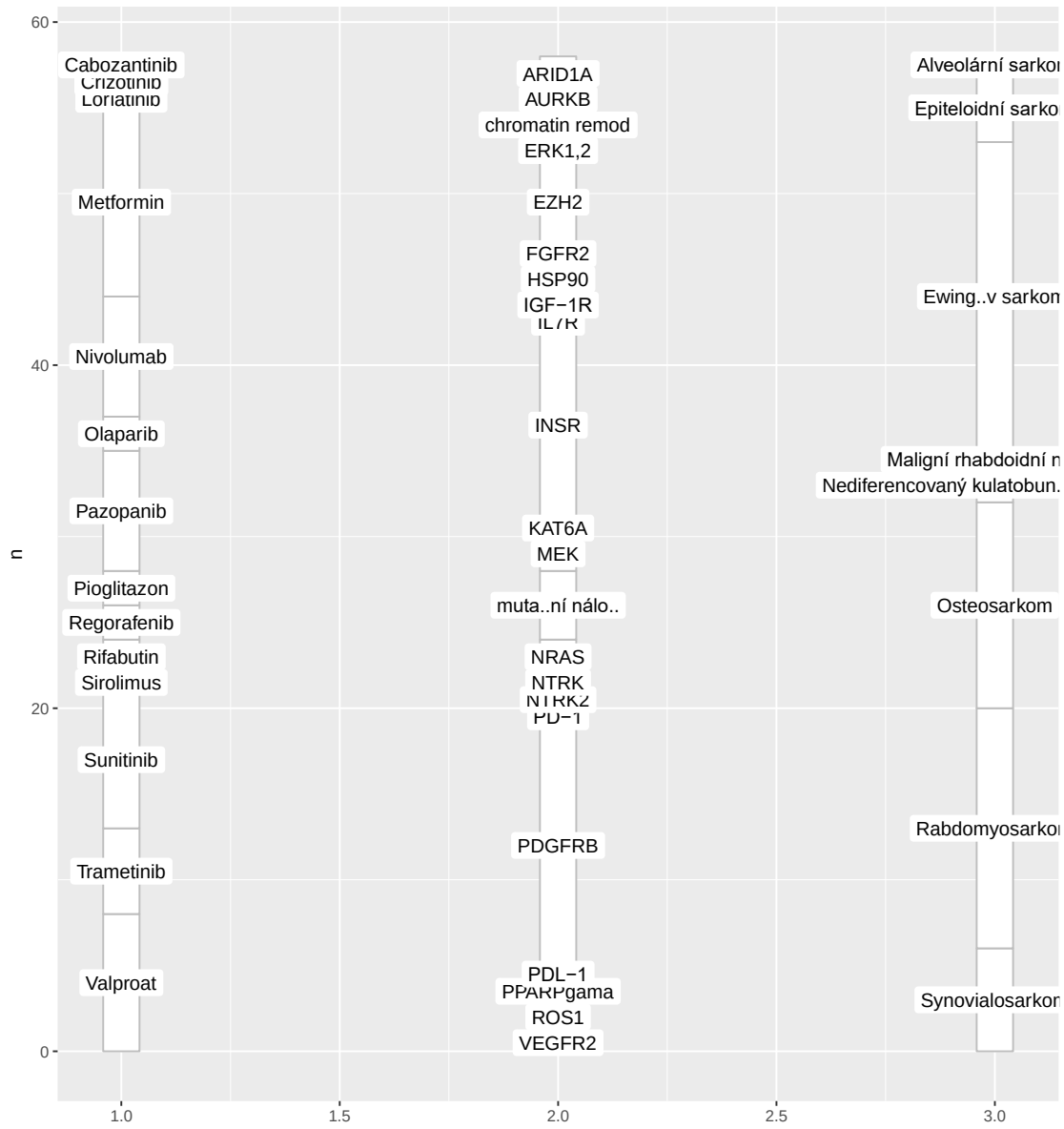




Příklady aplikací

Frailty Cox modely, agregace, heterogenita, EFS ratio, podskupiny





FS0 ratio	p
	0.003
	0.621
	<0.001
	<0.001
	0.571

p
0.662
0.490
<0.001
<0.001
0.859
0.307
0.572
0.003

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