MRC Biostatistics Unit

UNIVERSITY OF CAMBRIDGE

Bayesian Methods for Clinical Trials

Lecture 1: Clinical trials and the role of statistics

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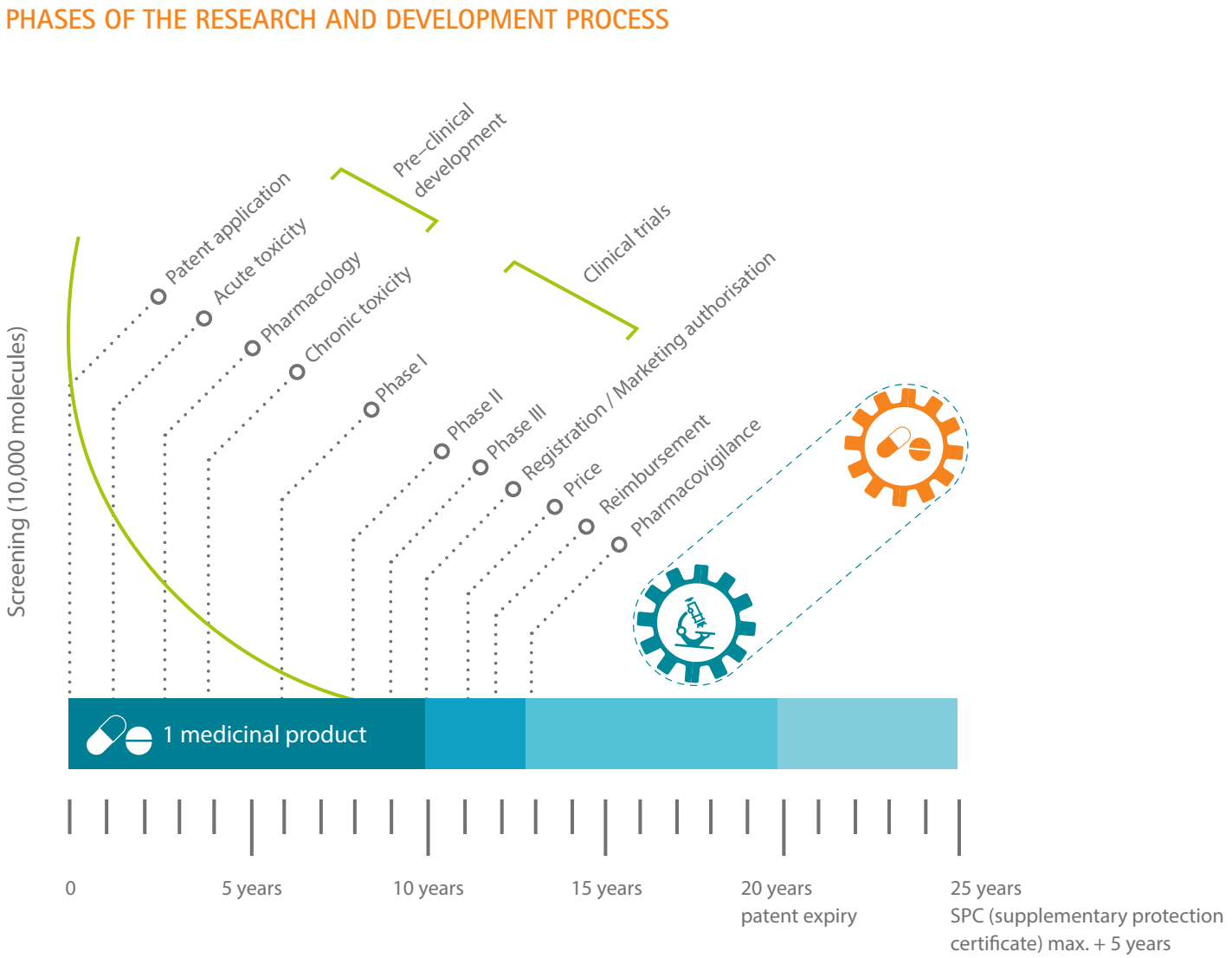
A dose of reality

Ben Goldacre, Guardian 1-09-08:

- **Before 1935** doctors were basically useless
- **1935-1995**: - antibiotics, dialysis, transplants, intensive-care units, heart surgery, every drug you've ever heard of
- **1995-now**: - the low-hanging fruit of medical research has all been harvested, and the industry is rapidly running out of new drugs

The development process



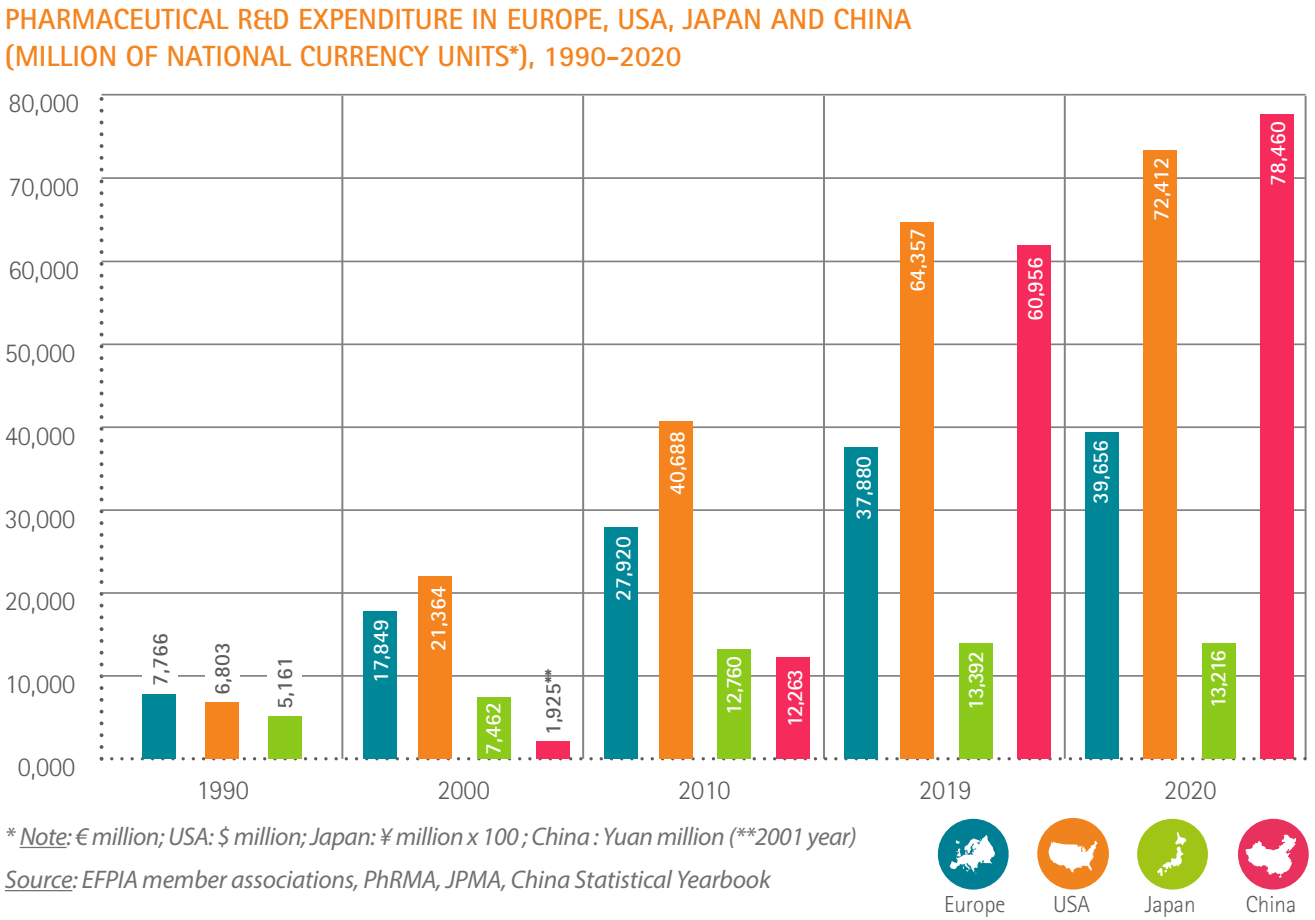
Source: European Federation of Pharmaceutical Industries and Associations (2022)

Drug development

Development of a novel medicinal product

- takes 10-15 years
- costs several hundred million euros on average
  - largest contributors are confirmatory (phase III) trials
  - often involve thousands of patients with follow-up period frequently lasting years

Cost on R&D in Pharmaceutical industry



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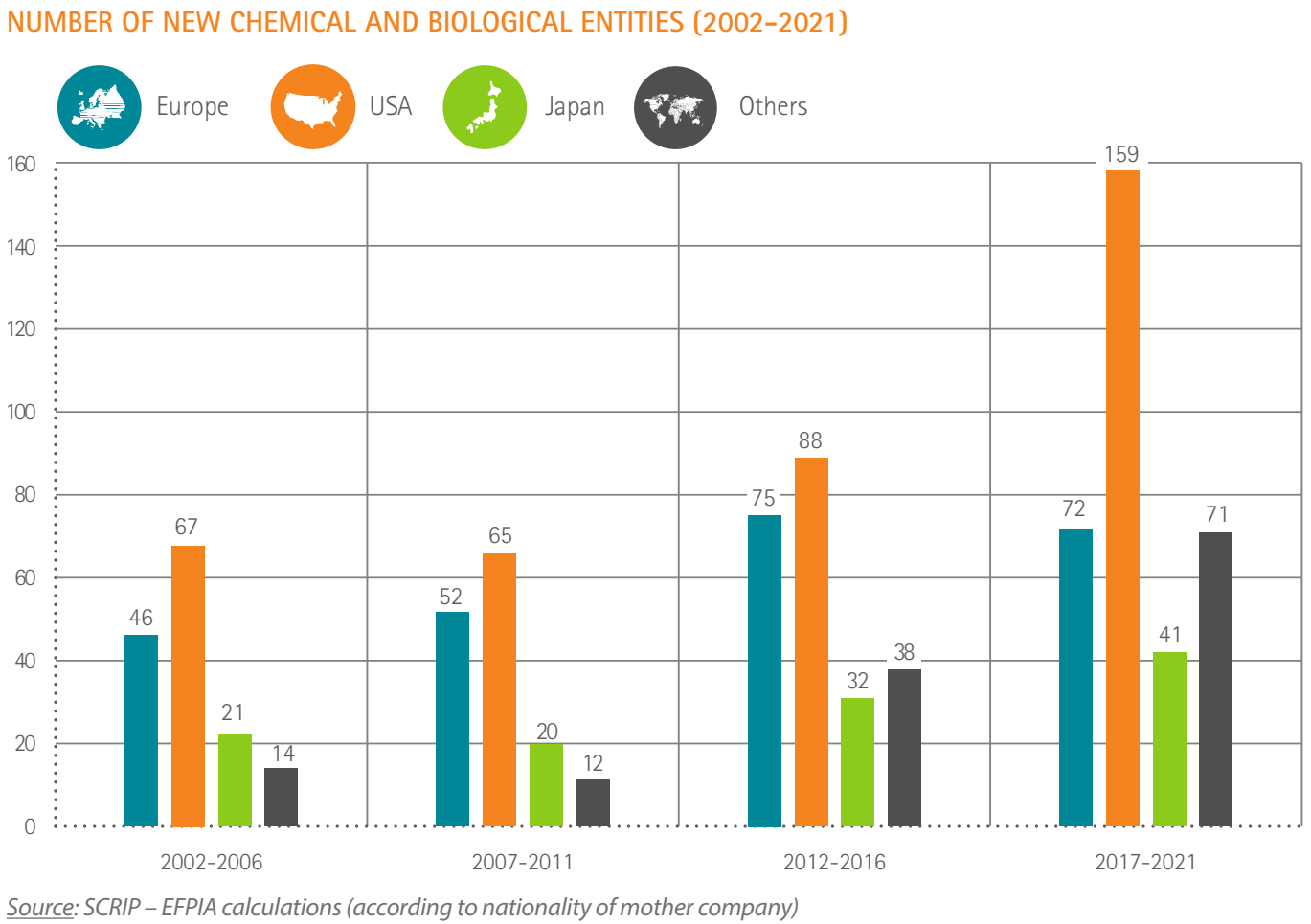
New molecular entities



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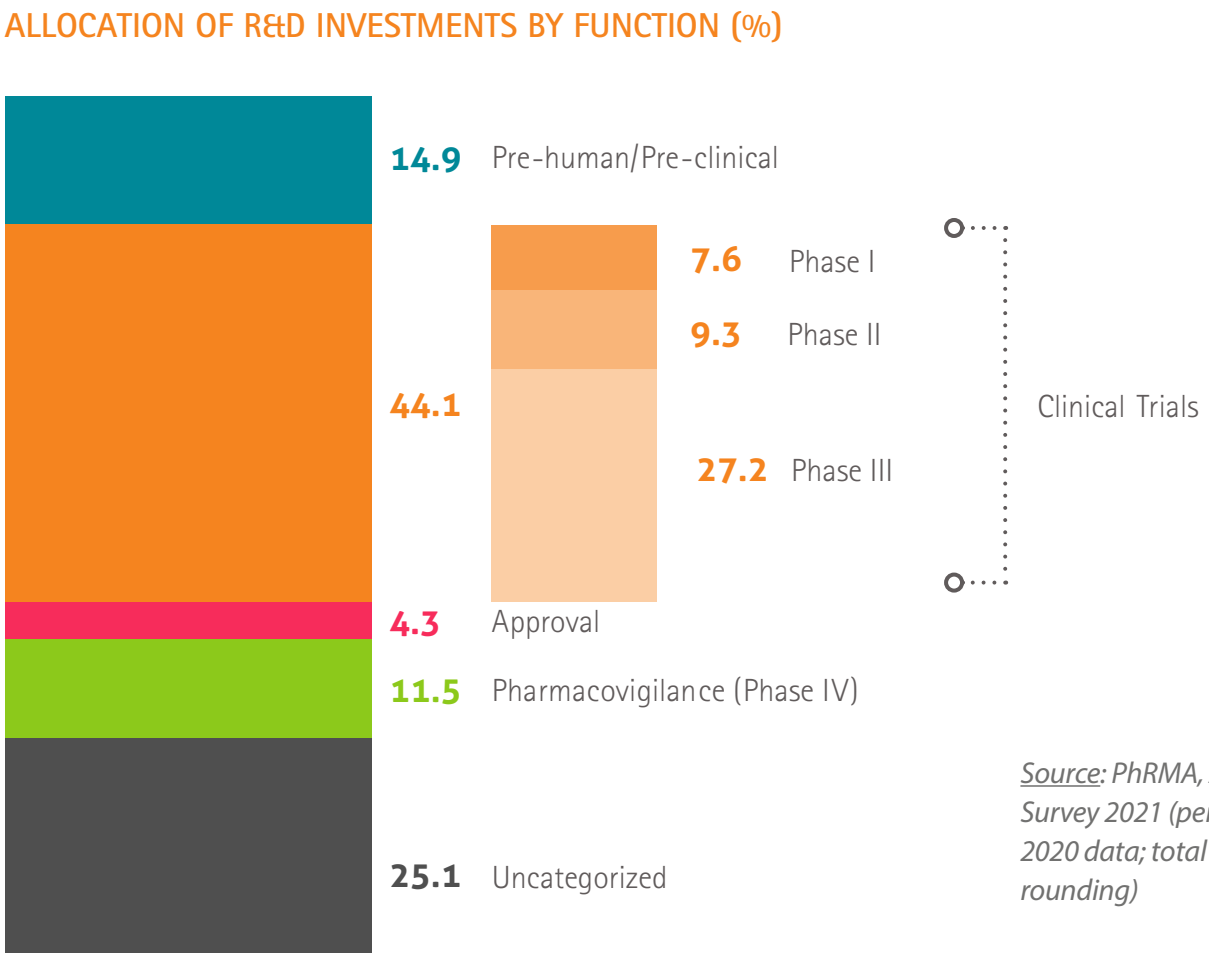
Cost on R & D in Pharmaceutical industry



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Success rates

According to a recent review (Wong, Siah & Lo, Biostatistics, 2019), between 2000 and 2015

- **41.0%** of confirmatory clinical trials overall and
- **64.5%** of confirmatory clinical trials in oncology

have been unsuccessful.

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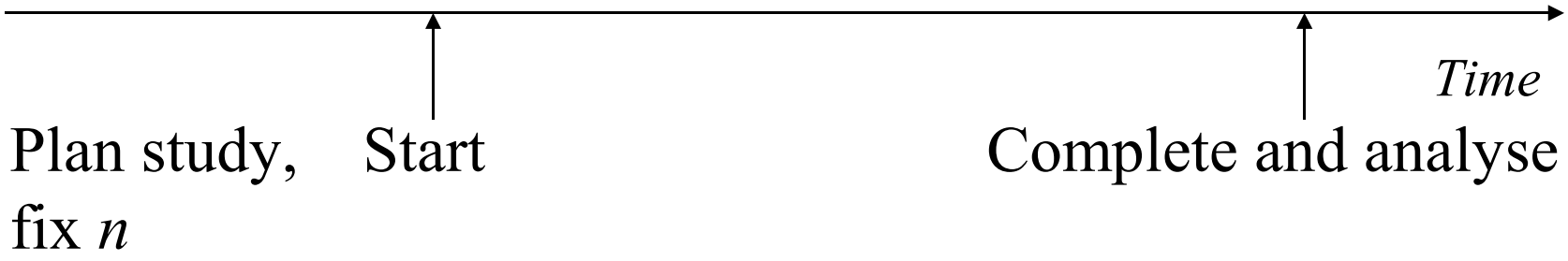
have been unsuccessful.

- **13.4%** of treatments entering Phase I receive approval
- In Oncology only **3.4%** of treatments entering Phase I receive approval

Consequences

- Avoid going straight into large and expensive phase III trials
- Take more care during phases I and II
- Explore the potential of ”new” statistical methods:
  - Sequential designs
  - Adaptive designs
  - Bayesian methods

Fixed Sample Designs



- no learning during conduct of trial
- clear separation between development phases

A general approach for fixed sample designs

- Parallel group comparison of efficacy
- E: Experimental, C: Control
- $n = n_E + n_C$
- Superiority trial (advantage for E sought)

H_0 : E no different from C vs H_1 : E superior to C

A general approach for fixed sample designs

θ: measure of advantage of E over C
$\theta > 0$: E superior
$\theta = 0$: No difference
$\theta < 0$: E inferior

θ_R: target measure of advantage of E over C (target effect)

α: $\mathbb{P}\{\text{Reject } H_0 | \theta = 0\}$
Type I error rate (one-sided)

$1 - \beta$: $\mathbb{P}\{\text{Reject } H_0 | \theta = \theta_R\}$
Power to detect the target effect

Score Test

- $x_1, x_2, \ldots$ each with density $f(x|\theta)$
- Log-likelihood of θ is

$$l(\theta|x_1, \ldots, x_n) = \sum_{i=1}^{n} \log f(x_i|\theta)$$

- Expanding a Taylor's expansion gives

$$\begin{aligned} l(\theta) &= l(0) + \theta l'(0) + \frac{1}{2}\theta^2 l''(0) + \ldots \\ &\approx const + \theta B - \frac{1}{2}\theta^2 V \quad \text{(for small } \theta\text{)} \end{aligned}$$

where $B = l'(0)$ and $V = -l''(0)$.

Score Test

- As B is a sum $-\sum_{i=1}^{n} \frac{d}{d\theta} \log f(x_i|\theta)$ – it is asymptotically normally distributed.
- For large n and small θ

$$B \sim N(\theta V, V) \qquad \text{and} \qquad \frac{B}{\sqrt{V}} \sim N(0,1)$$

- B is the efficient score statistic for θ
- For various response types B and V can be derived

Example: Normal data

treatment	E	C
mean	μ_E	μ_C
standard deviation (known)	σ	σ

- $\theta = \mu_E - \mu_C$
- $B = \frac{n_C n_E}{n\sigma^2}(\bar{X}_E - \bar{X}_C)$
- $V = \frac{n_C n_E}{n\sigma^2} = \frac{n}{4\sigma^2}$ for $n_E = n_C$

Example: Normal data

$$
\begin{aligned}
Z = \frac{B}{\sqrt{V}} &= \frac{\bar{X}_E - \bar{X}_C}{\sigma}\sqrt{\frac{n_C n_E}{n}} \\
&= \frac{\bar{X}_E - \bar{X}_C}{\sigma\sqrt{\frac{1}{n_E} + \frac{1}{n_C}}}
\end{aligned}
$$

And hence the Score test is equivalent to the Z-test in this situation.

Sample size

$$
\begin{aligned}
\mathbb{P}\{B > c \mid \theta = 0\} &= \alpha \\
\mathbb{P}\left\{\frac{B}{\sqrt{V}} > \frac{c}{\sqrt{V}} \mid \theta = 0\right\} &= \alpha \\
1 - \Phi\left(\frac{c}{\sqrt{V}}\right) &= \alpha \qquad \text{as } \frac{B}{\sqrt{V}} \sim N(0,1)
\end{aligned}
$$

so that $c = z_{1-\alpha}\sqrt{V}$, where z_γ is the γ percentile of the standard normal distribution.

Sample size

Similarly

$$\begin{aligned} \mathbb{P}\{B > c \mid \theta = \theta_R\} &= 1 - \beta \\ 1 - \Phi\left(\frac{c - \theta_R V}{\sqrt{V}}\right) &= 1 - \beta \end{aligned}$$

as for $\theta = \theta_R$, $\frac{Z - \theta_R V}{\sqrt{V}} \sim N(0, 1)$.

Therefore

$$\begin{aligned} c - \theta_R V &= z_\beta \sqrt{V} \\ V &= \left(\frac{z_{1-\alpha} + z_{1-\beta}}{\theta_R}\right)^2 \end{aligned}$$

when combining the results.

Sample Size

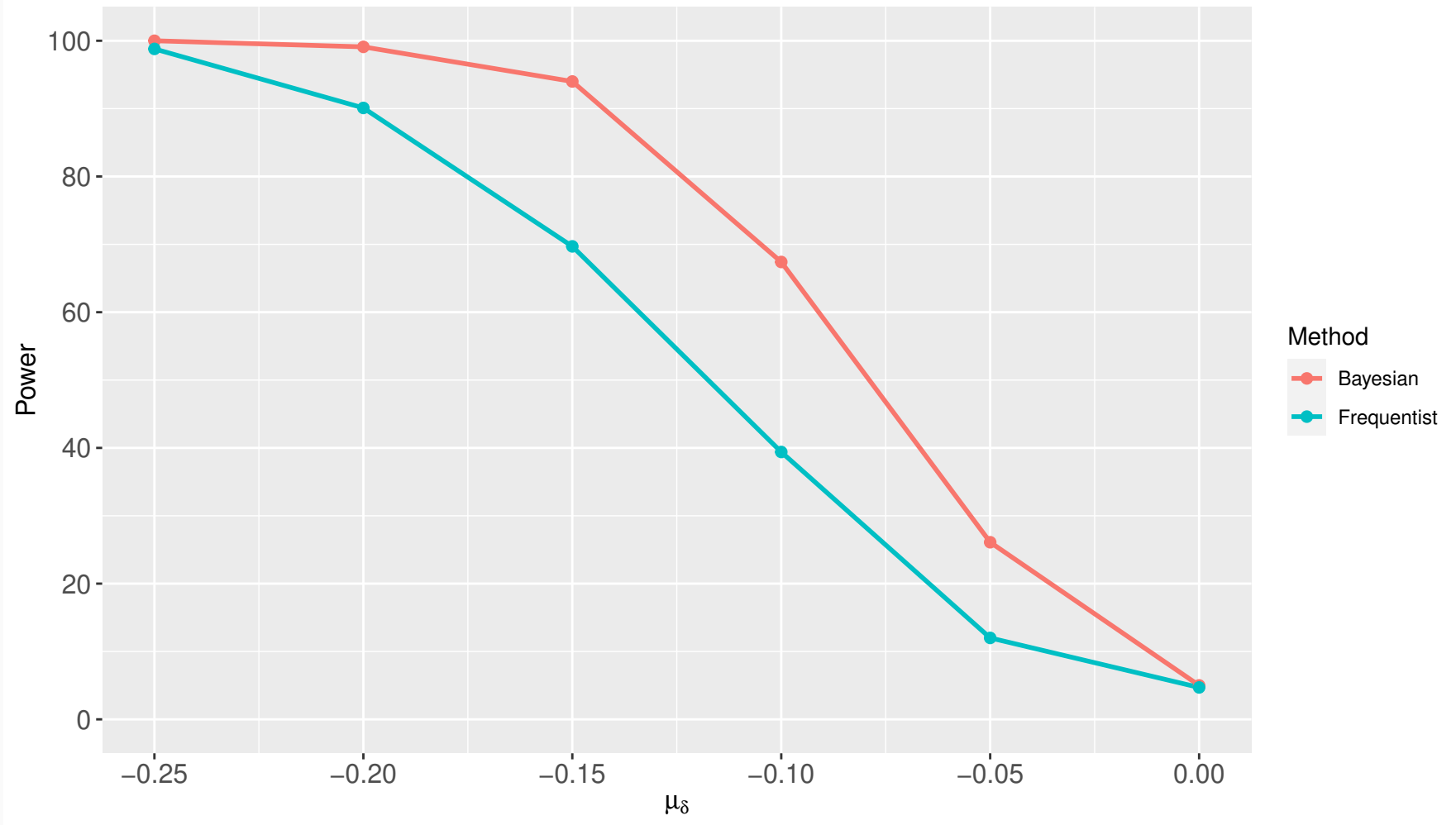
$$V = \left(\frac{z_{1-\alpha} + z_{1-\beta}}{\theta_R} \right)^2$$

- This formula has general validity
- V is a function of n and unknown parameters, which have to be estimated to obtain a sample size
- The relationship of V to n is the most approximate part of the procedure

When do traditional trials struggle: Rare diseases

- Neuroferritinopathy is an ultra-rare disease
- Fewer than 100 cases reported since its identification in 2001
- Some observational data available

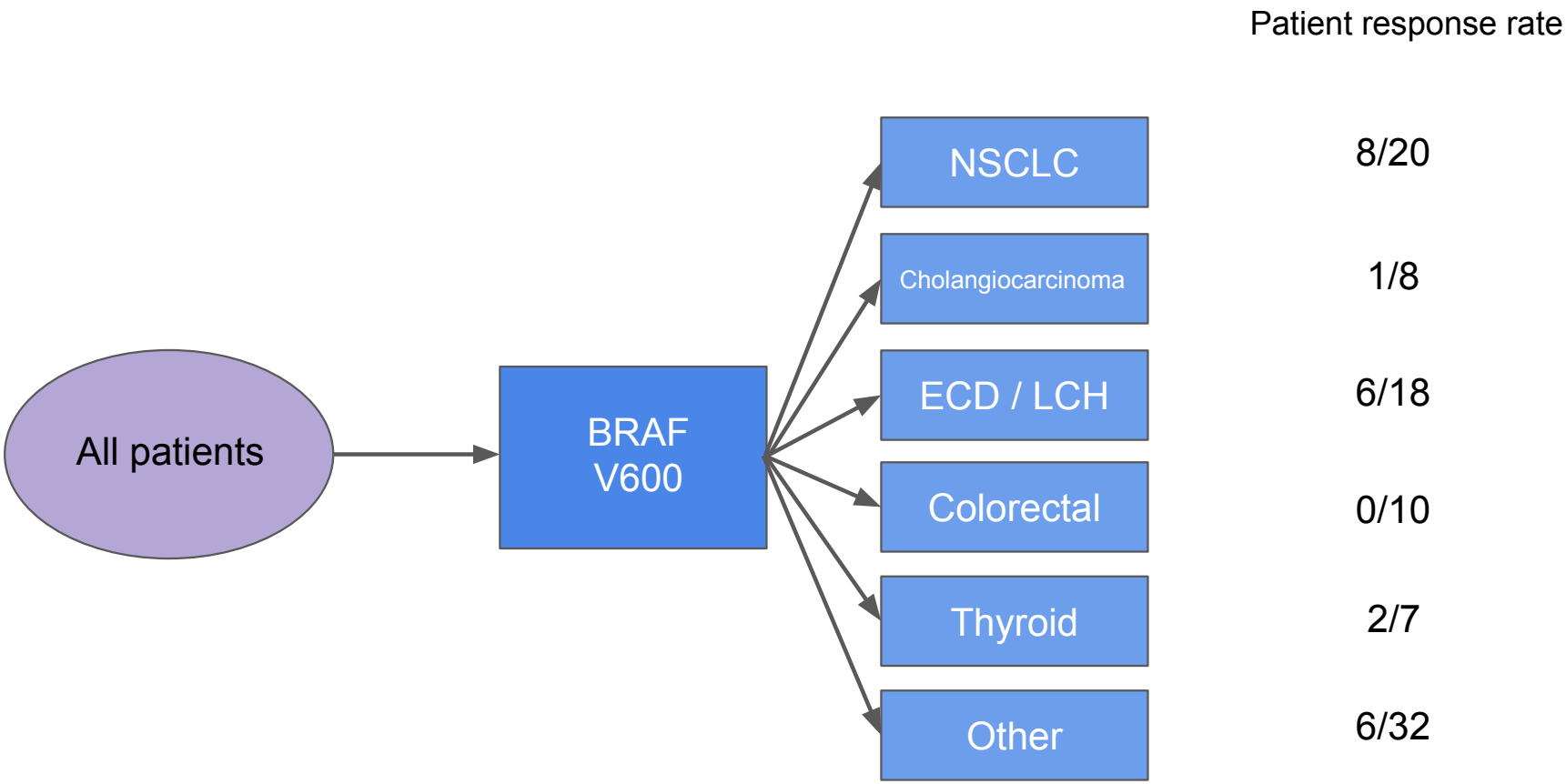
When do traditional trials struggle: Rare diseases



Basket trials in oncology – An example

Hyman *et al.* (2015) reported a recent basket trial, which has been designed to evaluate the efficacy of vemurafenib in BRAF-V600.

A total of 122 patients with BRAF-V600 mutations were enrolled, of which 95 entered the 6 modules.



References

Hyman D, Puzanov I, Subbiah V, et al. (2017) Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. New England Journal of Medicine. 373(8):726-736.

Wong CH, Siah KW, Lo AW (2019). Estimation of clinical trial success rates and related parameters. Biostatistics, 20:273-286.