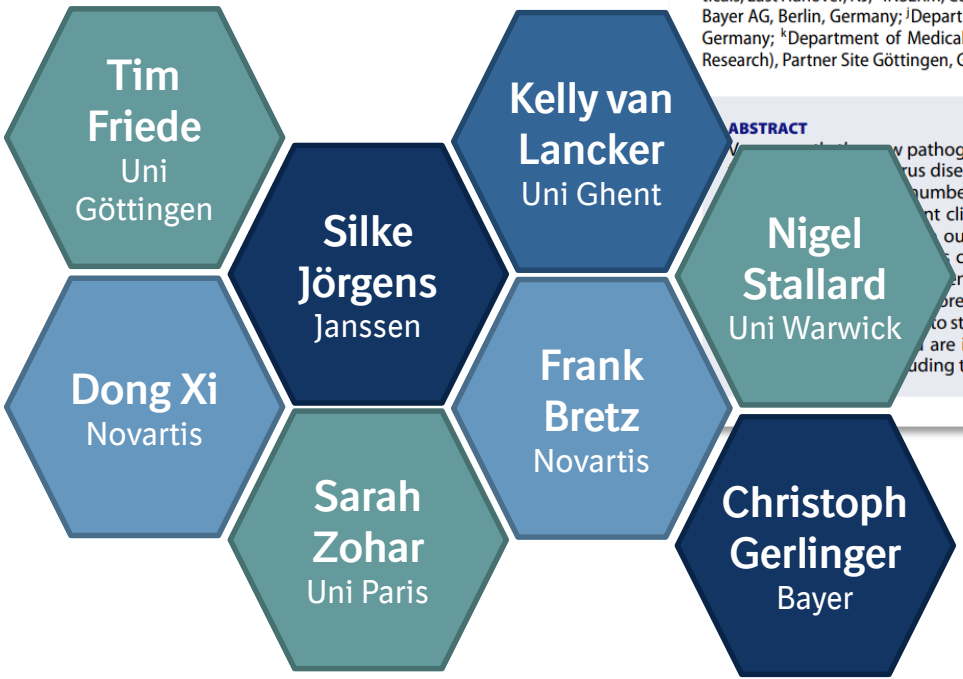
# Clinical trials impacted by the COVID-19 pandemic: Adaptive designs to the rescue?

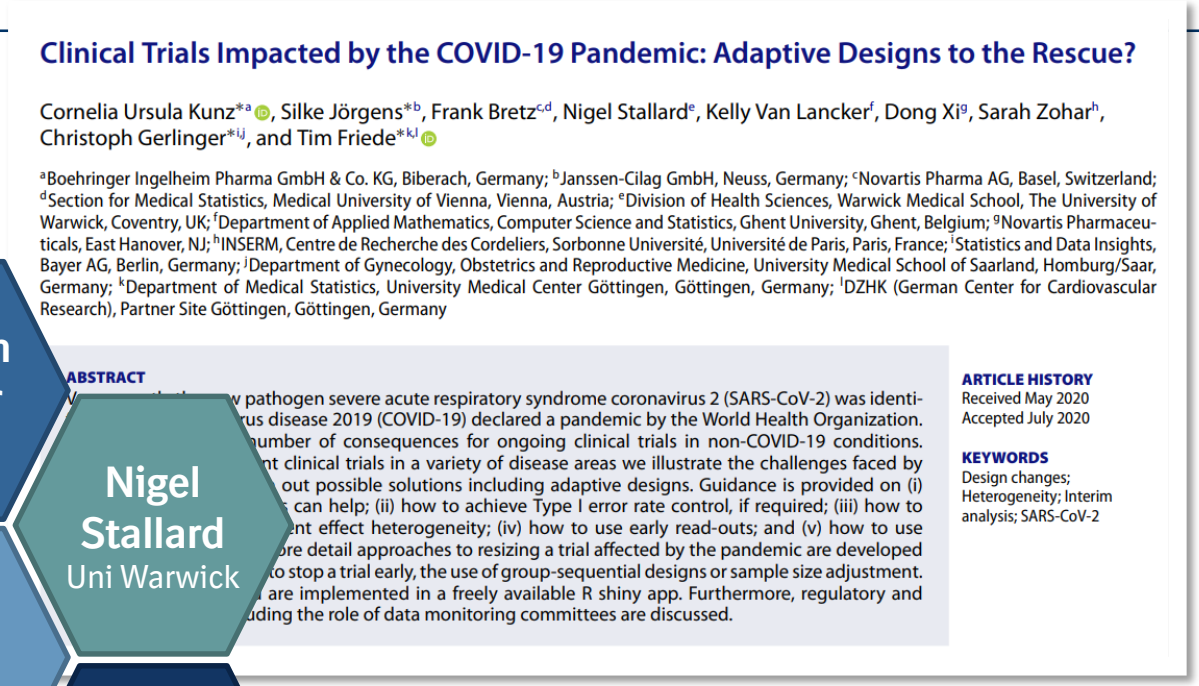
Cornelia Ursula Kunz

Boehringer Ingelheim

# Thank you to Chris Jennison for the invitation

# Thank you to…



## Clinical Trials Impacted by the COVID-19 Pandemic: Adaptive Designs to the Rescue?

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**ABSTRACT**

…w pathogen severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identi-…us disease 2019 (COVID-19) declared a pandemic by the World Health Organization. …umber of consequences for ongoing clinical trials in non-COVID-19 conditions. …nt clinical trials in a variety of disease areas we illustrate the challenges faced by … out possible solutions including adaptive designs. Guidance is provided on (i) … can help; (ii) how to achieve Type I error rate control, if required; (iii) how to …nt effect heterogeneity; (iv) how to use early read-outs; and (v) how to use …re detail approaches to resizing a trial affected by the pandemic are developed …o stop a trial early, the use of group-sequential designs or sample size adjustment. … are implemented in a freely available R shiny app. Furthermore, regulatory and …uding the role of data monitoring committees are discussed.

**ARTICLE HISTORY**
Received May 2020
Accepted July 2020

**KEYWORDS**
Design changes; Heterogeneity; Interim analysis; SARS-CoV-2

**Disclaimer**

The opinions presented are solely those of the presenter and do not reflect those of Boehringer Ingelheim or other members of the working group and their respective employers.

# A disrupted trial (completely fictitious)

Second line therapy for Type 2 Diabetes, first line treatment with Metformin unsuccessful

Two-arm trial:
A: Metformin + Sulfonylurea
B: Metformin + New drug

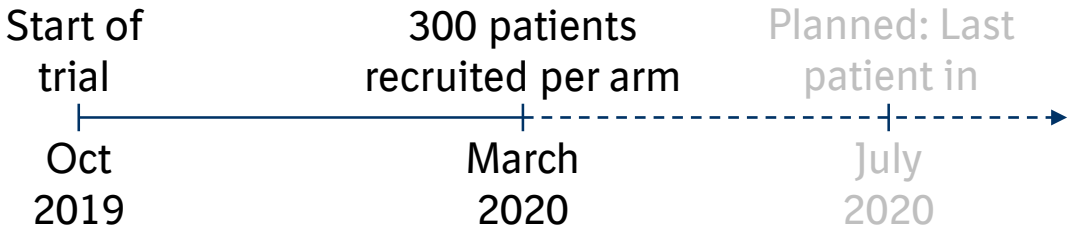
Sample size: 500 patients per arm

# Trial design

- Planning assumptions

| | |
|---|---|
| Significance level $\alpha$ (one-sided) | 0.025 |
| Power $1 - \beta$ | 0.90 |
| Assumed effect size $\delta$ | 0.20 |
| Assumed variance $\sigma^2$ | 0.95 |
| Randomization ratio | 1:1 |
| Sample size per arm | 500 |

***COVID-19***




- **No patients** have been admitted **since that** time, but follow-up has continued, so the 6-month **endpoint** has been **recorded** for all **300 patients** on each treatment.

# The questions

- **Analyze the data** and draw conclusions
- **Re-start recruitment**, but perhaps **change** the target for the **final sample size**
- **Change trial design** to adaptive/group-sequential design

Two scenarios:

(1) The data are currently **blinded**.

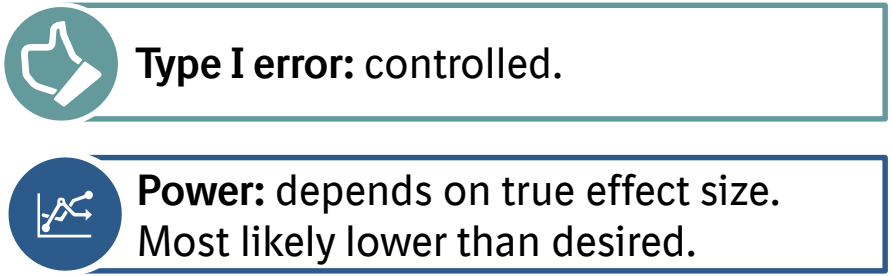
(2) The investigators have **taken a look** at the current data.

You are asked to **advise** the investigators on how they might **proceed**.

# Analyze the data

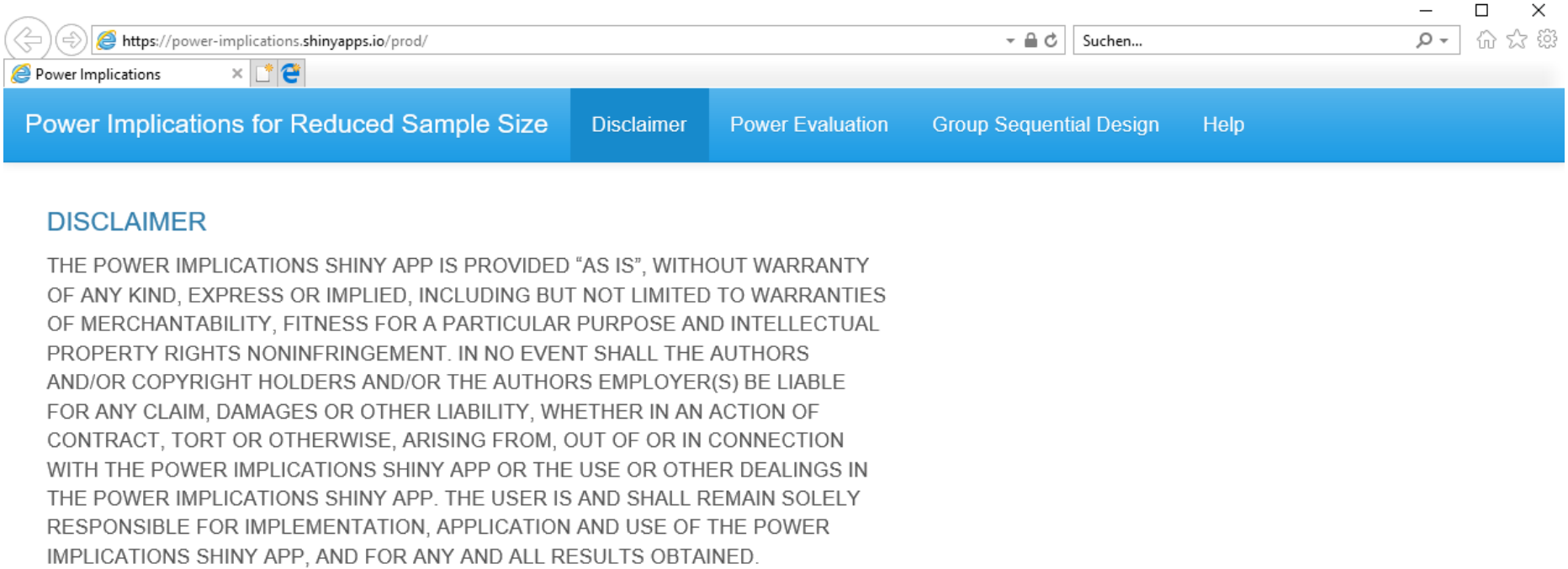
# Analyze the data

- **Stop trial** and **analyze data** collected so far



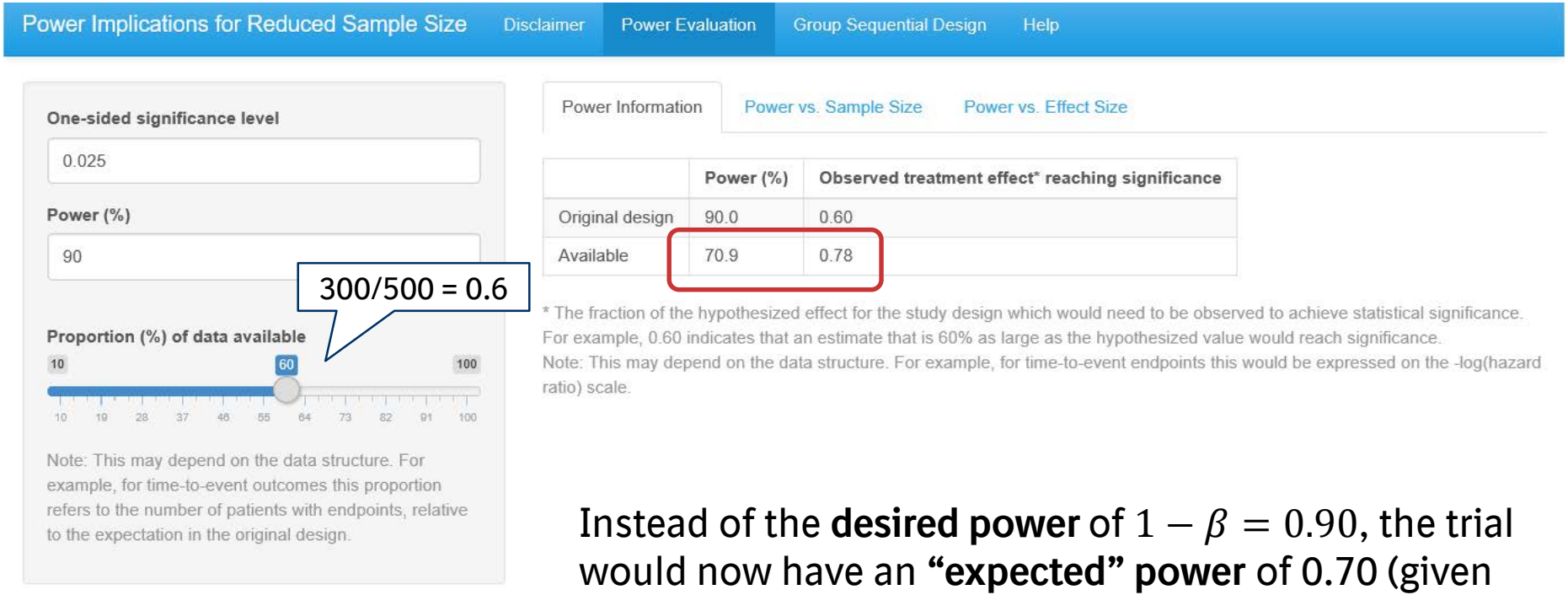

- **Statistically** it can be regarded as having (a lot of) **missing** data.
- The pattern is truly **MCAR** in this case.

# R Shiny App – Power Implications



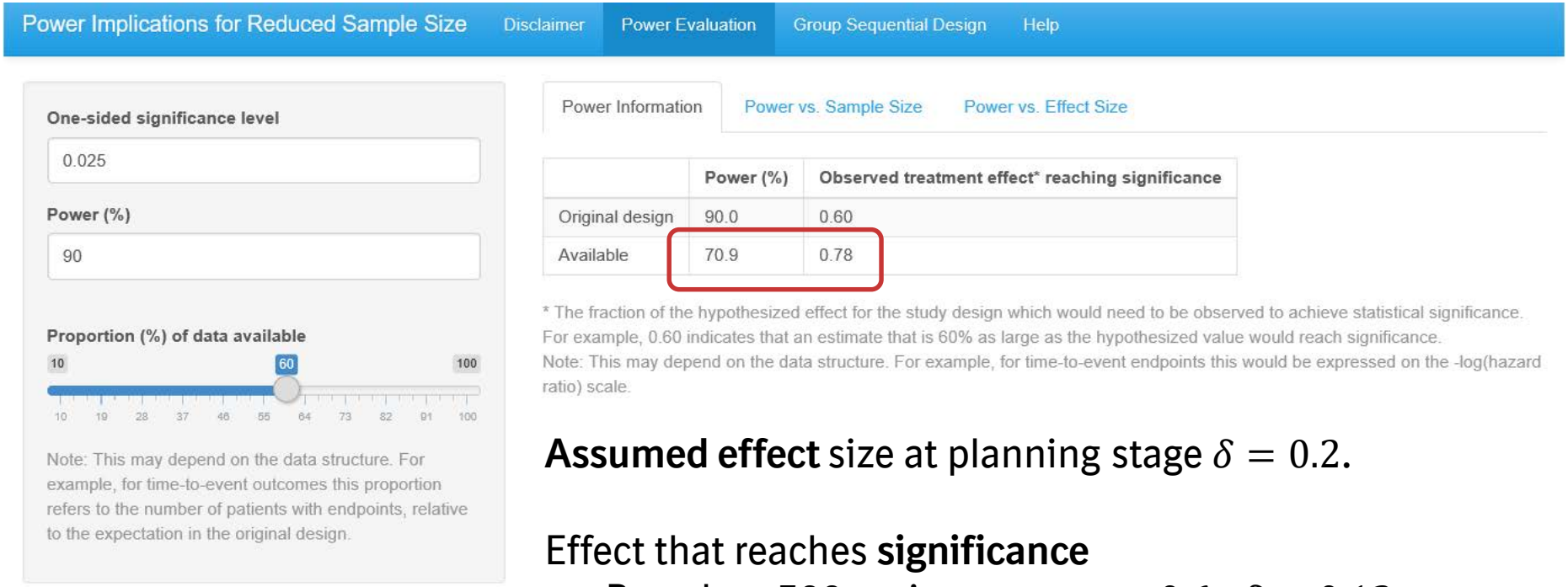

https://power-implications.shinyapps.io/prod/

# Power implications




Instead of the **desired power** of $1 - \beta = 0.90$, the trial would now have an **"expected" power** of 0.70 (given the true effect size is as assumed). The **true power** depends on the true effect size/variance.

# Power implications

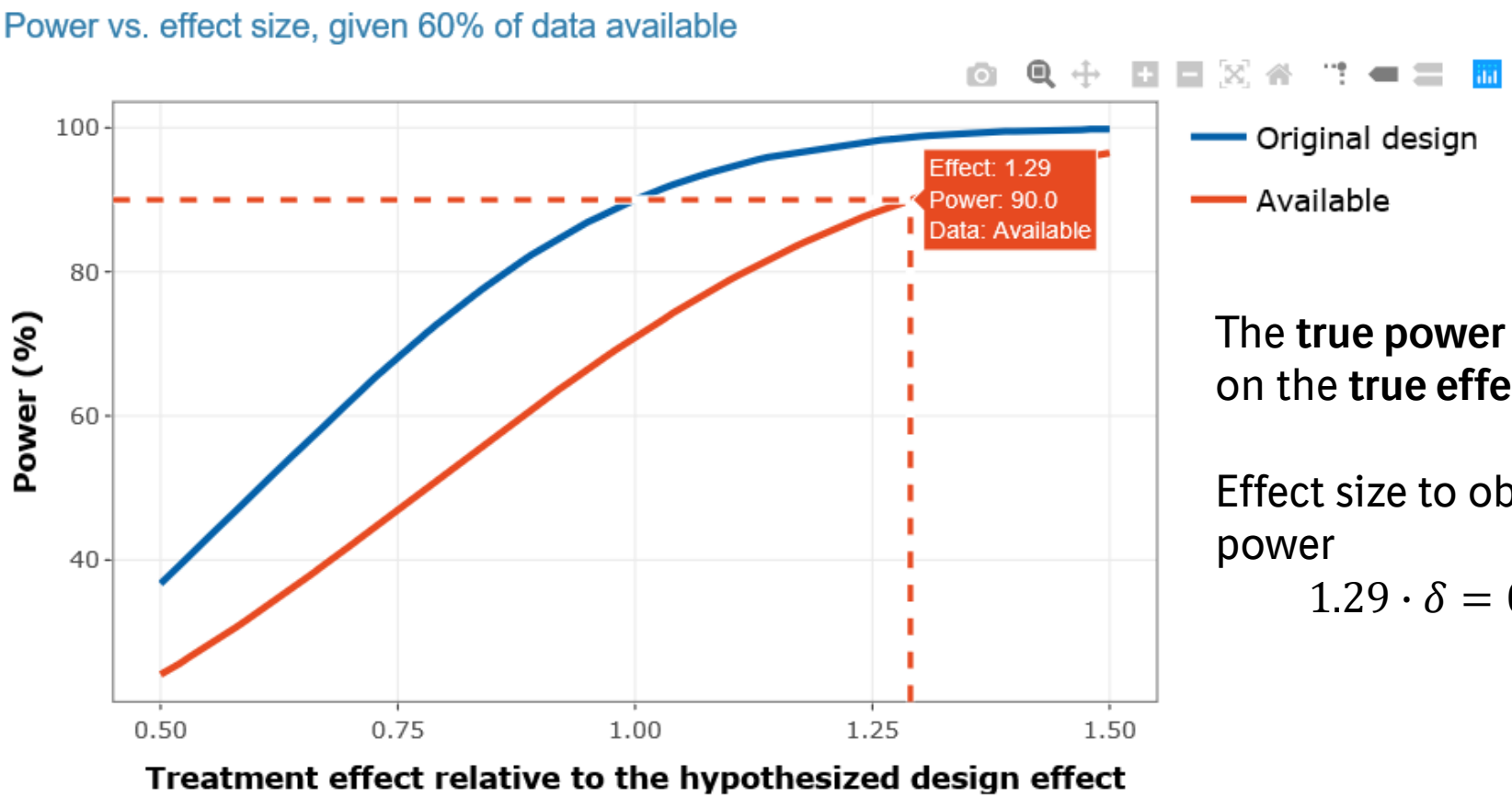



**Assumed effect** size at planning stage $\delta = 0.2$.

Effect that reaches **significance**

- Based on 500 patients per arm: $0.6 \cdot \delta = 0.12$
- Based on 300 patients per arm: $0.78 \cdot \delta = 0.156$

# Power versus effect




The **true power** depends on the **true effect** size.

Effect size to obtain 90% power

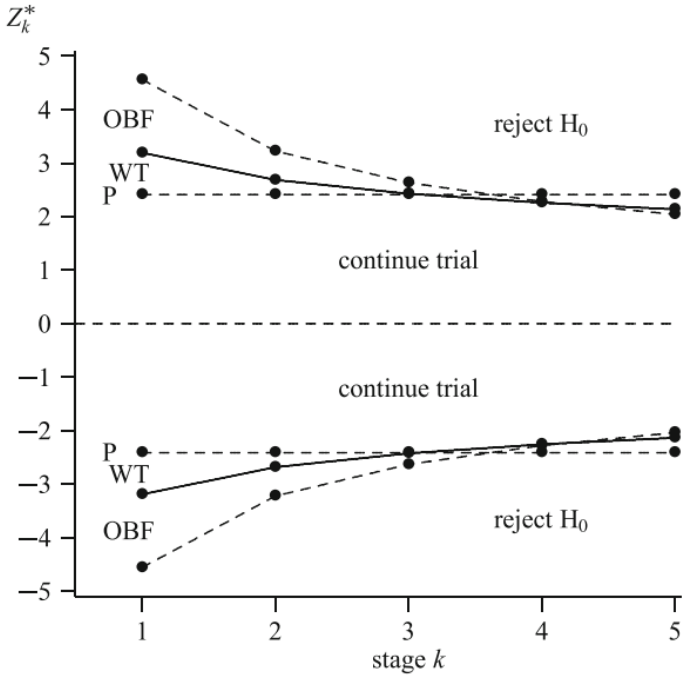
$$1.29 \cdot \delta = 0.258$$

# Change trial design

# Adaptive Design / Group Sequential Designs (GSD)

- **Changes** are possible including (non-)comparative **sample size re-estimation** and (adaptive) **group-sequential design** (GSD)

- Changes need to be **pre-specified**




**Wasser G and Brannath W** (2016): Group Sequential and Confirmatory Adaptive Designs in Clinical Trials. *Springer,* page 38.

**Type I error:** controlled as long as the specific design changes are pre-specified, i.e. have been written down (and are adhered to) before any data is analyzed.

**Power:** depends on true effect size and the specific changes of the design.

# Group-sequential design (GSD)

Power Implications for Reduced Sample Size | Disclaimer | Power Evaluation | Group Sequential Design | Help

**One-sided significance level**

0.025

**Power (%)**

90

**Proportion (%) of data available**

10 60 100

10 19 28 37 46 55 64 73 82 91 100

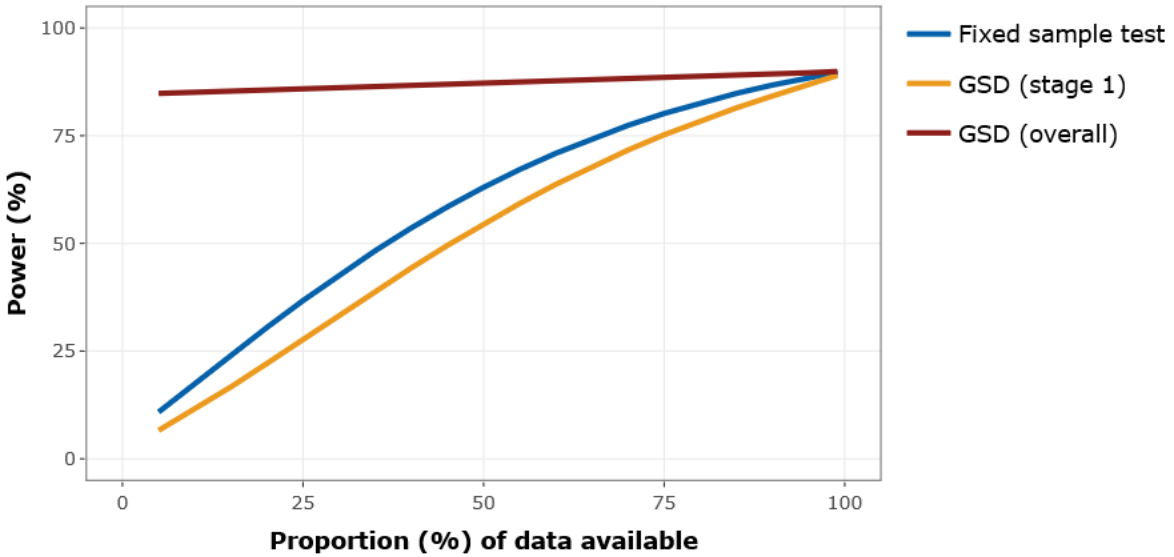
**Type of group sequential design**

Pocock

☑ **No dilution effect for second stage**

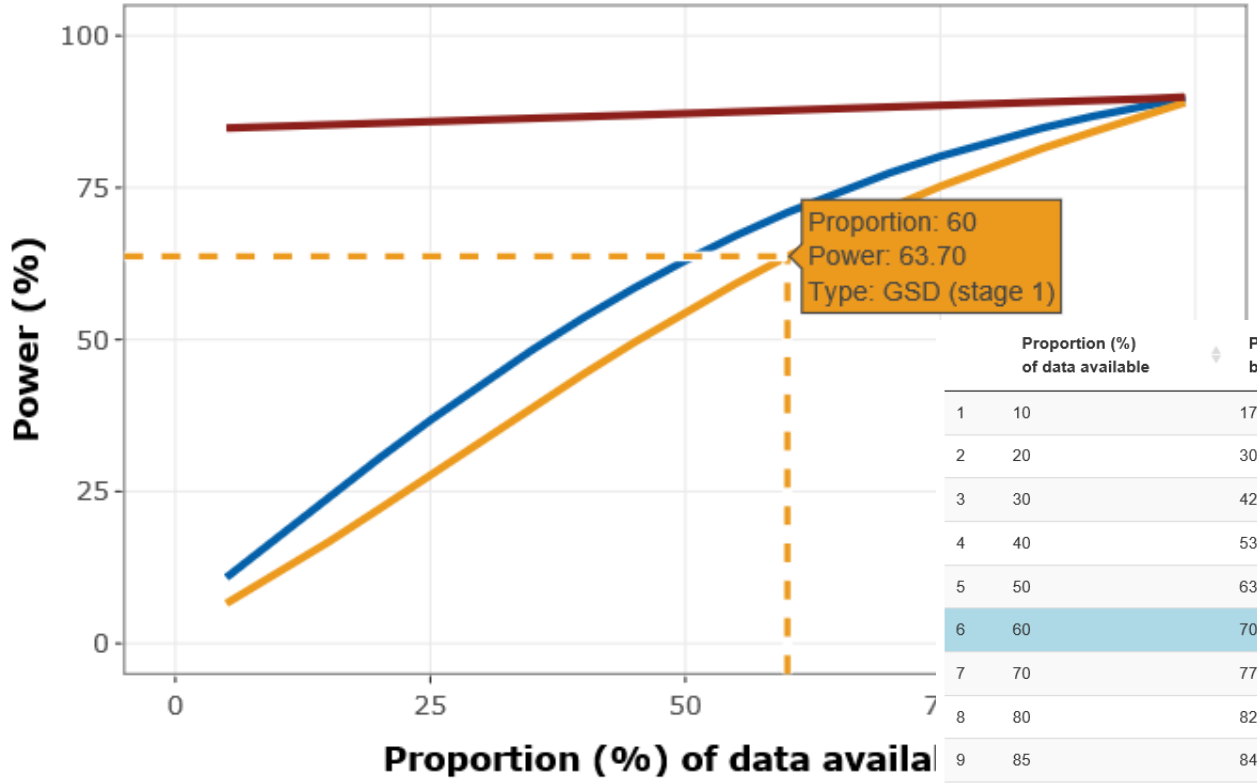
☑ **Equal variances for second stage**

Achieved Power | Sample Size Adjustment




☐ Show results in table format

# Power for first stage

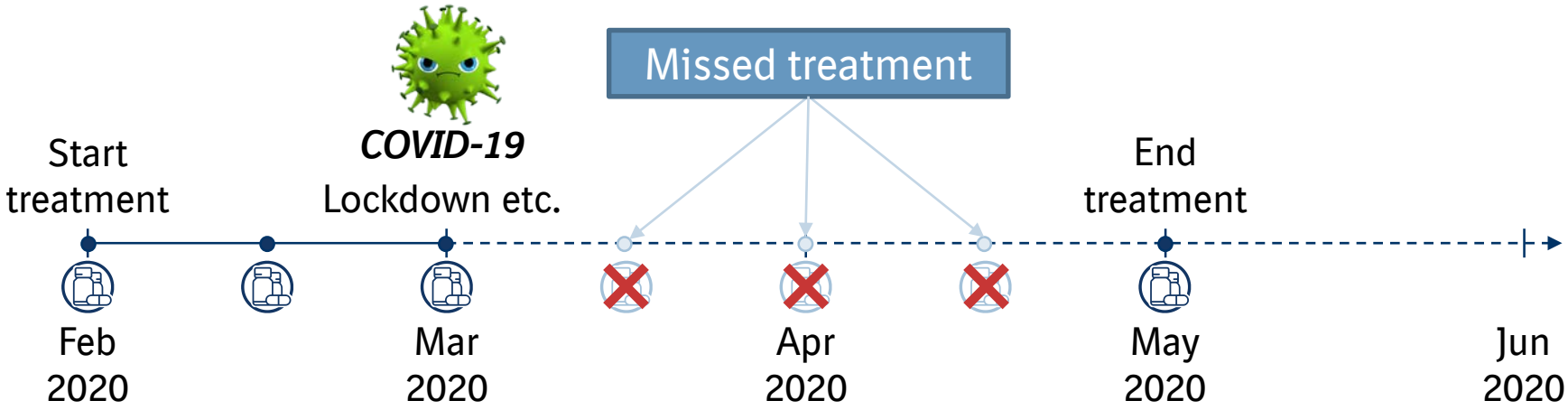



☐ Show results in table format

| | Proportion (%) of data available | Power based on available data | Power GSD Stage 1 | Power GSD overall |
|---|---|---|---|---|
| 1 | 10 | 17.49 | 11.45 | 85.07 |
| 2 | 20 | 30.49 | 22.13 | 85.55 |
| 3 | 30 | 42.68 | 33.33 | 86.02 |
| 4 | 40 | 53.59 | 44.31 | 86.50 |
| 5 | 50 | 63.01 | 54.53 | 86.99 |
| 6 | 60 | 70.91 | 63.70 | 87.50 |
| 7 | 70 | 77.40 | 71.67 | 88.04 |
| 8 | 80 | 82.62 | 78.46 | 88.61 |
| 9 | 85 | 84.82 | 81.45 | 88.92 |
| 10 | 90 | 86.76 | 84.21 | 89.25 |
| 11 | 95 | 88.48 | 86.81 | 89.60 |

# Dilution effect

- Concern from clinicians, (for example, oncologists) that due to lockdown and other restrictions, **patients miss treatments**.




- **Important:** The **mode of action**, endpoint etc. is **not affected** by the COVID-19 virus but the **treatment effect** is **"diluted"** due to having received less of the treatment.

# Assumed dilution $\eta = 0.1$

Power Implications for Reduced Sample Size | Disclaimer | Power Evaluation | Group Sequential Design | Help

One-sided significance level

0.025

Power (%)

90

Proportion (%) of data available

10 50 100

10 19 28 37 46 55 64 73 82 91 100

Type of group sequential design

Pocock

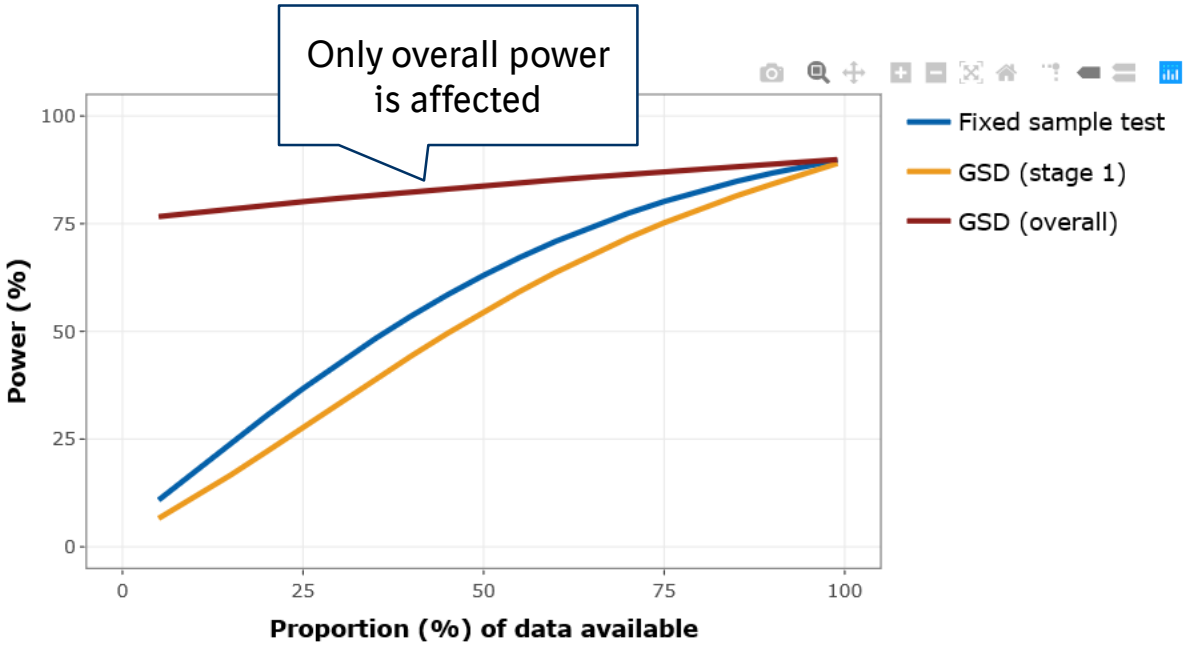
☐ No dilution effect for second stage

Dilution effect η

0.1

☑ Equal variances for second stage

Achieved Power | Sample Size Adjustment




☐ Show results in table format

# Results in table format

$\eta = 0$ $\eta = 0.1$

| Proportion (%) of data available | Power based on available data | Power GSD Stage 1 | Power GSD overall | Power GSD Stage 1 | Power GSD overall |
|---|---|---|---|---|---|
| 10 | 17.49 | 11.45 | 85.07 | 11.45 | 77.57 |
| 20 | 30.49 | 22.13 | 85.55 | 22.13 | 79.29 |
| 30 | 42.68 | 33.33 | 86.02 | 33.33 | 80.89 |
| 40 | 53.59 | 44.31 | 86.50 | 44.31 | 82.39 |
| 50 | 63.01 | 54.53 | 86.99 | 54.53 | 83.82 |
| 60 | 70.91 | 63.70 | 87.50 | 63.70 | 85.17 |
| 70 | 77.40 | 71.67 | 88.04 | 71.67 | 86.45 |
| 80 | 82.62 | 78.46 | 88.61 | 78.46 | 87.67 |
| 85 | 84.82 | 81.45 | 88.92 | 81.45 | 88.26 |
| 90 | 86.76 | 84.21 | 89.25 | 84.21 | 88.84 |
| 95 | 88.48 | 86.81 | 89.60 | 86.81 | 89.41 |

# Change trial design and/or sample size

# Sample Size Adjustment

Power Implications for Reduced Sample Size | Disclaimer | Power Evaluation | Group Sequential Design | Help

**One-sided significance level**

0.025

**Power (%)**

90

**Proportion (%) of data available**

10 60 100

10 19 28 37 46 55 64 73 82 91 100

**Type of group sequential design**

Pocock

☑ **No dilution effect for second stage**

☑ **Equal variances for second stage**

Achieved Power | Sample Size Adjustment

The trial was originally planned as an one-stage design with a fixed sample size for the following parameters:

| Treatment effect δ | Variance $\sigma^2$ | Randomization ratio 1:r (plc:trt) |
|---|---|---|
| 0.2 | 0.95 | 1 |

The originally planned fixed sample size was $N = 999$.

Assuming a dilution effect of $\eta = 0.00$ and a variance in-/deflation of $\psi = 1.00$, the adjusted sample sizes are

| | dilution effect η | Available data | Sample size for second stage (fixed design) | Sample size for second stage (GSD) | Total sample size (fix) | Total sample size (GSD) |
|---|---|---|---|---|---|---|
| 1 | 0 | 599 | 399 | 491 | 998 | 1090 |

☐ Show results for range of dilution effect η in table format

**Repowering** the trial to 90% accounting for the change to a GSD.

# With dilution effect

Power Implications for Reduced Sample Size | Disclaimer | Power Evaluation | Group Sequential Design | Help

One-sided significance level

0.025

Power (%)

90

Proportion (%) of data available

10 60 100

10 19 28 37 46 55 64 73 82 91 100

Type of group sequential design

Pocock

☐ No dilution effect for second stage

Dilution effect η

0.1

☑ Equal variances for second stage

Achieved Power | Sample Size Adjustment

The trial was originally planned as an one-stage design with a fixed sample size for the following parameters:

| Treatment effect δ | Variance $\sigma^2$ | Randomization ratio 1:r (plc:trt) |
|---|---|---|
| 0.2 | 0.95 | 1 |

The originally planned fixed sample size was $N = 999$.

Assuming a dilution effect of $\eta = 0.10$ and a variance in-/deflation of $\psi = 1.00$, the adjusted sample sizes are

| | dilution effect η | Available data | Sample size for second stage (fixed design) | Sample size for second stage (GSD) | Total sample size (fix) | Total sample size (GSD) |
|---|---|---|---|---|---|---|
| 1 | 0.1 | 599 | 496 | 603 | 1095 | 1202 |

☐ Show results for range of dilution effect η in table format

We can decide to just change the sample size based on an **assumed dilution** effect or also change to GSD

# Summary of the approaches discussed so far

**None** of the different approaches discussed so far requires a **look at any data** (neither **blinded** nor **unblinded**)

The **changes** to the trial design are **purely based** on assumptions about the **future**.

- One could argue that it makes **no sense to look** at the (blinded or unblinded) **data** that was observed **before** the pandemic.
- The **data collected** so far will **not tell** us anything about the **future** data.
- **Without COVID-19**, we would **never** have introduced any **changes** to the trial design at all.

**The investigators had taken a look at the current data…**

**… and then asked for your advice.**

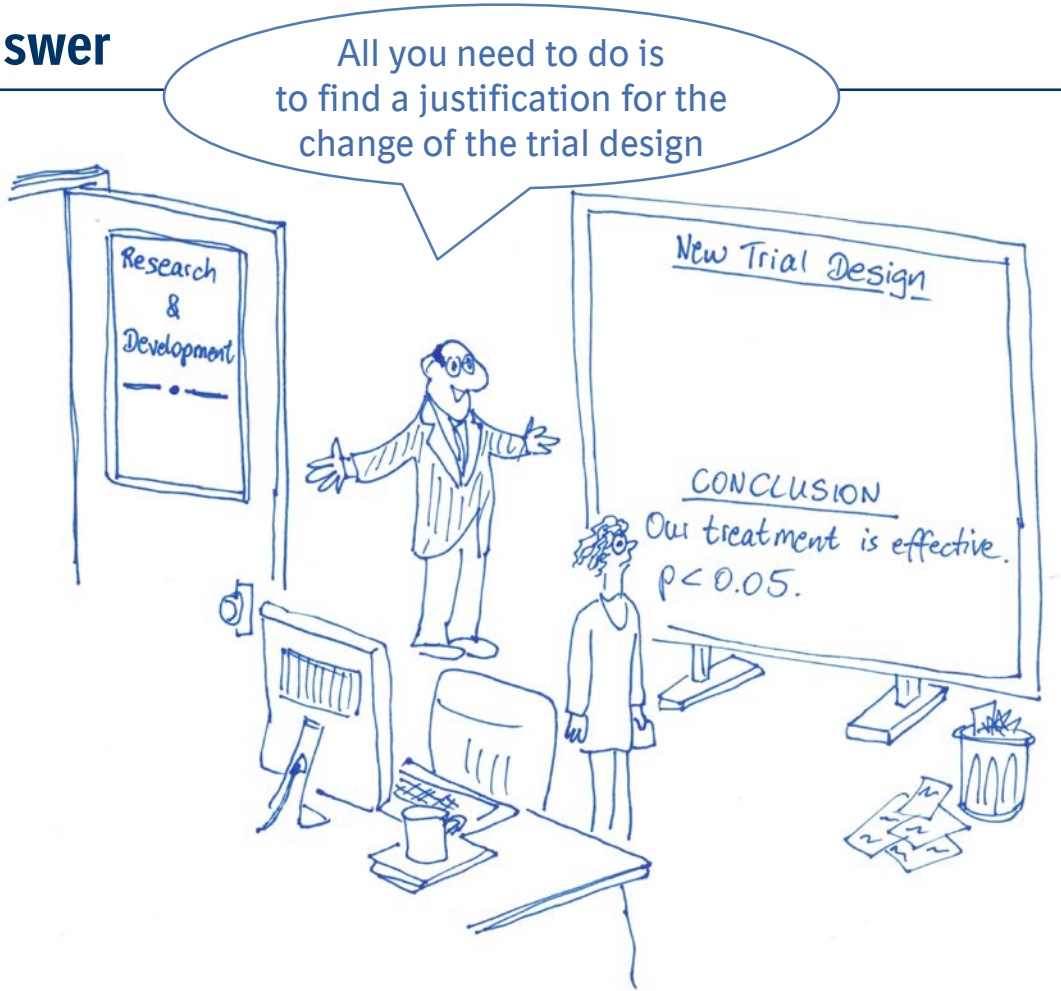
# A short answer

*"To consult the statistician after an experiment is finished is often merely to ask him to conduct a post mortem examination. He can perhaps say what the experiment died of."*

*Sir Ronald Fisher*

Presidential Address to the First Indian Statistical Congress
(1938, *Ind. J. Stat.* 4: 14–17)

# A fun answer






Kunz 2020: Clinical trials impacted by the COVID-19 pandemic: Adaptive designs to the rescue?

# A fun answer


All you need to do is
to find a justification for the
change of the trial design
Research
&
Development
New Trial Design
CONCLUSION
Our treatment is effective.
p<0.05.
Type I
error
...out of the window

# A statistical answer

The conditional error principle thus enables a trial planned with a single final analysis to be modified at any point prior to that analysis to have a sequential design, with this constructed in such that the Type I error rate is not inflated. It should be noted, however, that it is necessary to specify how any data before and after the interim analysis are combined before the first interim analysis is conducted. Modification of the design to include initially unplanned interim analyses will also generally lead to a reduction in the power of the trial, as considered in more detail below.

**Kunz CU** et al. (2020): Clinical Trials Impacted by the COVID-19 Pandemic: Adaptive Designs to the Rescue? *Statistics in Biopharmaceutical Research*, 12:4, 461-477. DOI: 10.1080/19466315.2020.1799857

# Maximum type I error rate for unplanned changes

- Investigator did **not pre-specify** the adaptation rule
- Analysis of the data is based on **conventional (naïve) test** statistics

Maximum **type I error** rate

$$Err_{max}(u) = \underbrace{1 - \Phi(u)}_{\alpha} + \underbrace{\frac{1}{4} exp\left(-\frac{u^2}{2}\right)}_{\text{inflation}}$$

With $\alpha = 0.025$, we get $u = 1.96$ and $Err_{max}(u) = 0.061625$.

To **control** type I error, we need to find $u$ so that $Err_{max}(u) = \alpha$ yielding $u = 2.353$ (**adjusted significance** level $\alpha' = 0.00931$).

**Wasser G and Brannath W** (2016): Group Sequential and Confirmatory Adaptive Designs in Clinical Trials. *Springer,* page 163.

# Comparison to Group Sequential Design

| | Critical values | |
|---|---|---|
| Design | Stage 1 | Stage 2 |
| Unplanned changes | | 2.353 |
| Pocock | 2.161 | 2.161 |
| O'Brien-Fleming | 2.572 | 1.992 |

Calculations were done using **`rpact`**:

```
design <- getDesignGroupSequential(typeOfDesign = "P",
informationRates = c(0.6, 1), beta = 0.1)
summary(design)
```

RPACT - Confirmatory Adaptive Clinical Trial Design and Analysis (shinyapps.io)

# Points to consider


- **How much** data is available?
- How **realistic** were the planning assumptions?
- Is a **dilution** effect to be expected?
- How much **missing** data is to be expected?
- …

Explore different **design options** and their **pros** and **cons.***

*This includes to run a new trial after the pandemic; to conduct the second stage after the pandemic to avoid a dilution effect, etc.

# Final advice

**Changes** to ongoing trials due to COVID-19 are **unplanned but external** to the trial. However, they will still be **viewed critically.**

Many **design changes** are **possible** if they are **pre-specified**, i.e. if the decision to change the trial is done **before any data is analyzed**.

**Consult an expert** if you are unsure **before** you analyze **any data** and before you change the trial design.

Note that there is **no right or wrong. Every trial is different** and what might be the **right choice** for one, is **not necessarily** the **right choice** for another trial.

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