Wilhelmina Children's Hospital

HIT-CF

New clinical trial design in Cystic Fibrosis

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- Difficulties of clinical trials in Cystic Fibrosis population

- Our solutions to these difficulties

Wilhelmina Children's Hospital

Difficulty 1: CF patient population

> 2000 CFTR-mutations

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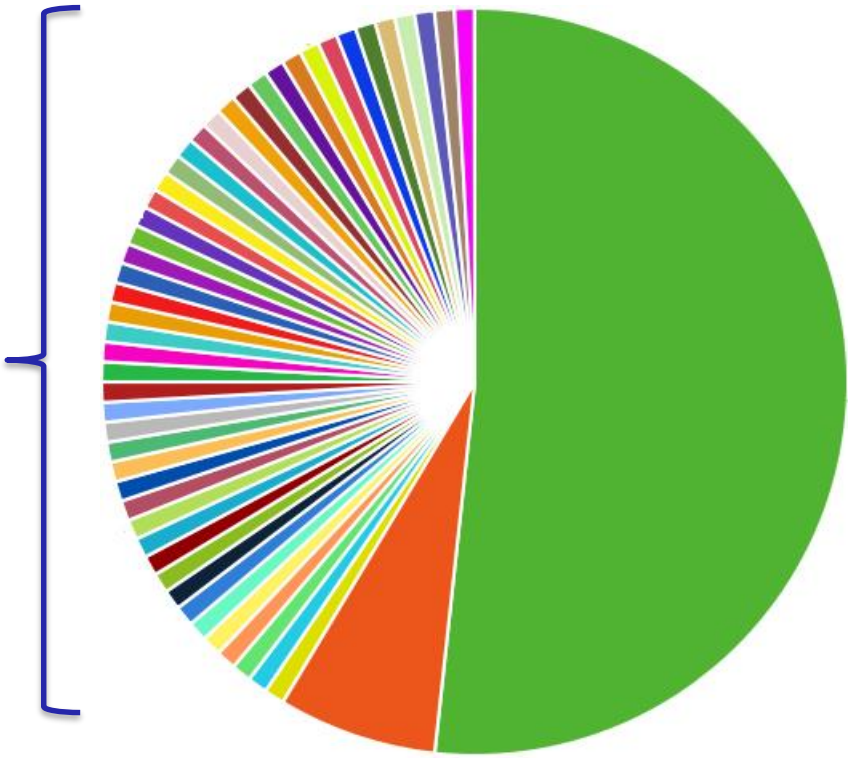


F508del/F508del

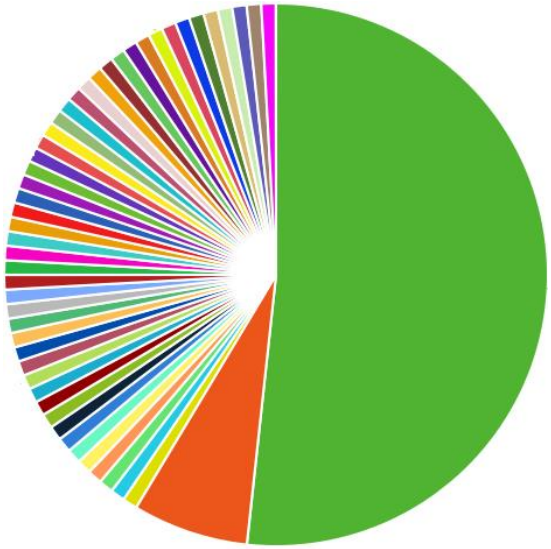
Lumacaftor/Ivacaftor
(Triple therapy)

Gating

Ivacaftor
(Novel potentiators)

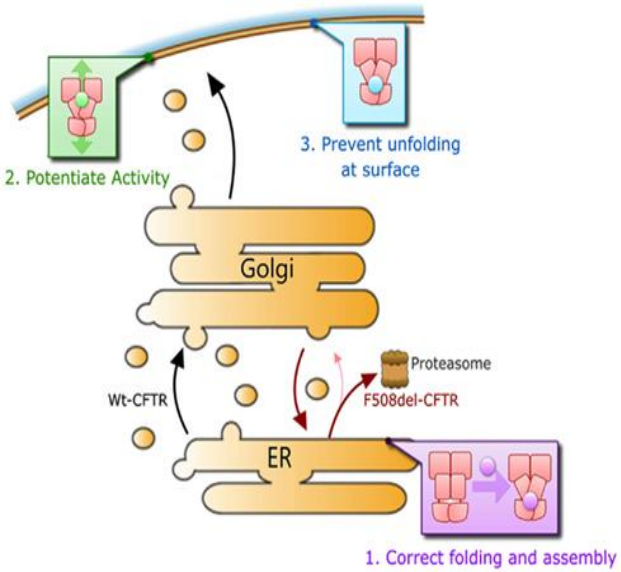
Rare disease, considerable heterogeneity

- Disease severity
  - Differs per mutation
  - Considerable differences within genotype



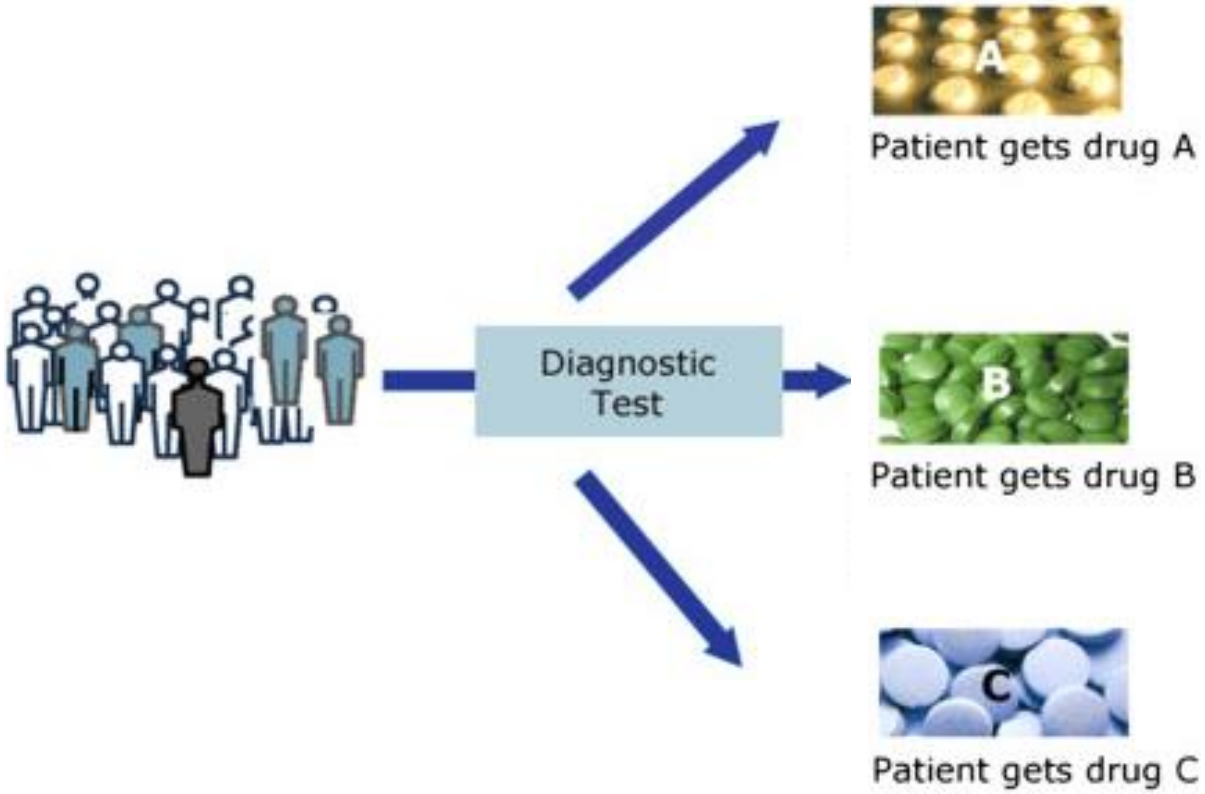
Drug efficacy

- Target is different per CFTR-mutation
  - **Target is unknown for rare mutations**
  - **Efficacy of drugs cannot be predicted in these patients**

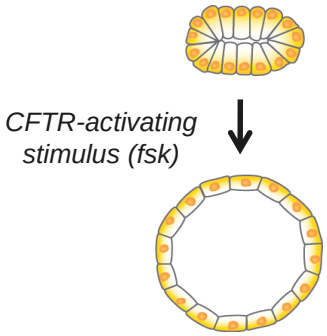


Heterogeneity in treatment response makes clinical trial very difficult

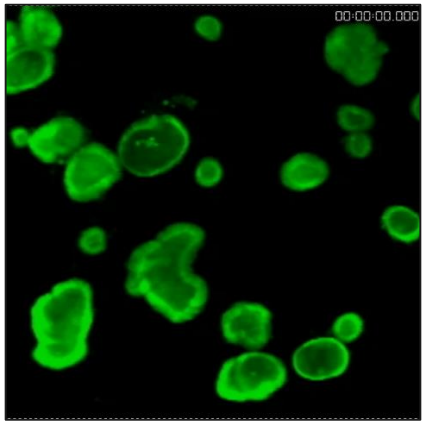
Solution: stratifying patients



Organoid model to identify drug response



Healthy control



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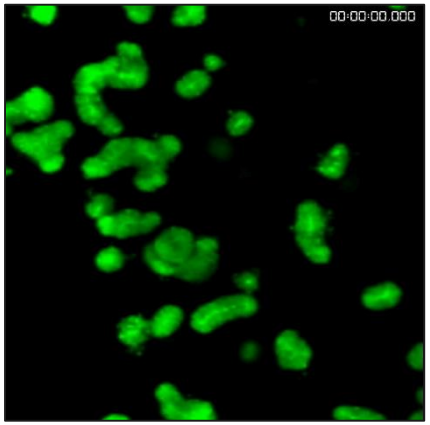

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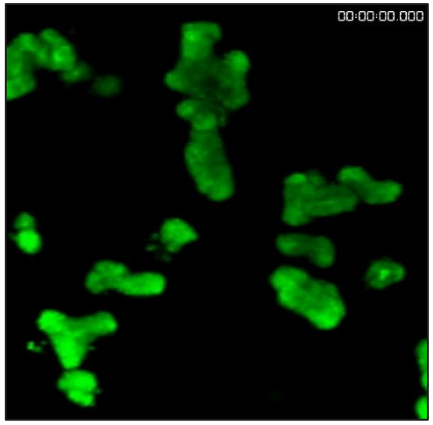
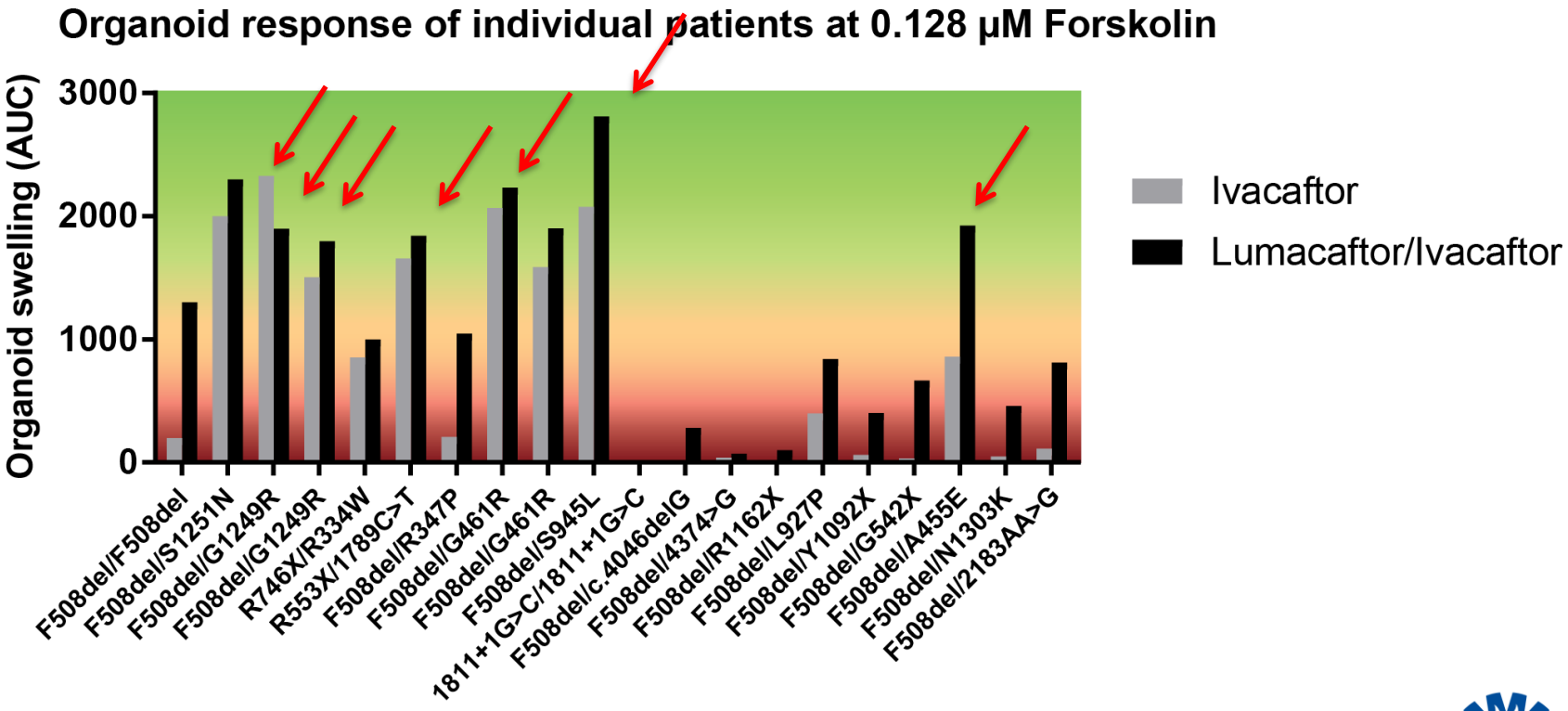
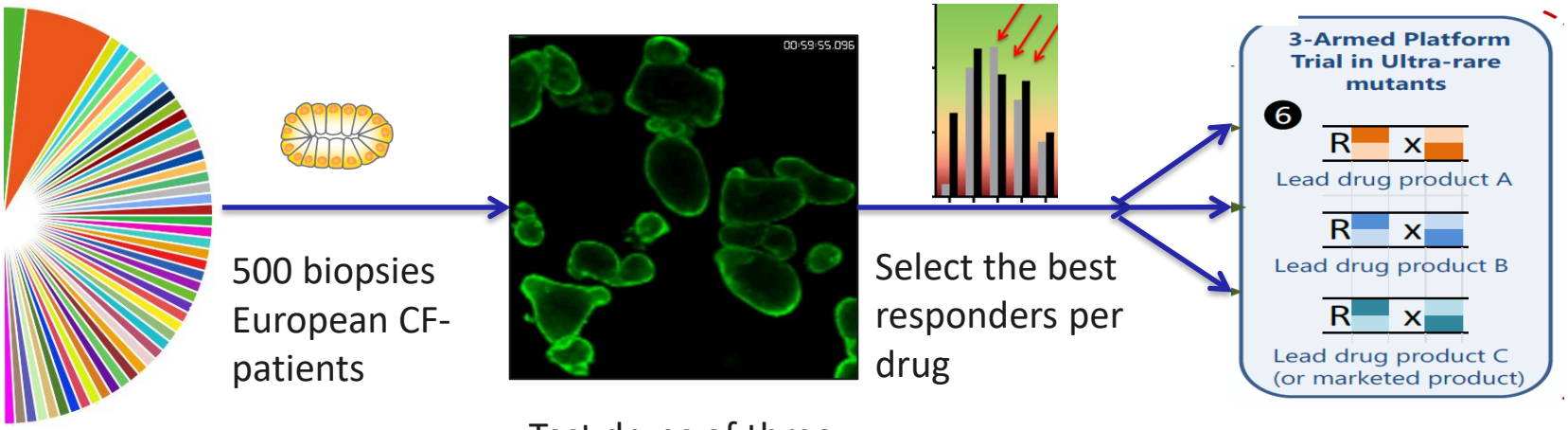
Lumacaftor/Ivacaftor



Using organoids to select the best responding patients



Identifying our patient population

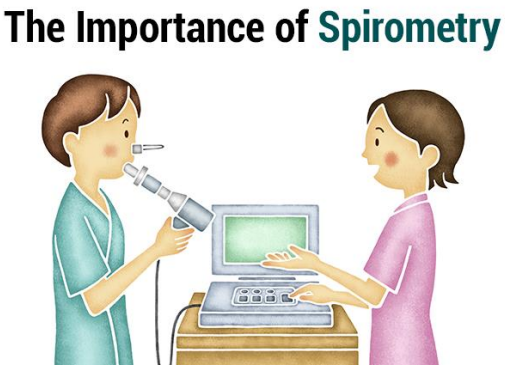


500 biopsies European CF-patients

Test drugs of three pharmaceutical companies on these organoids

Select the best responders per drug

Difficulty 2: FEV1 as EMA-approved endpoint



Forced Expiratory Volume in 1 second

"FEV1 as surrogate for mortality usually required by EMA as primary endpoint for most pulmonary indications."

"At present, FEV1, despite its major limitations, still remains an important outcome measure for clinical efficacy."

Report of the workshop on endpoints for cystic fibrosis, European Medicines Agency, 2012

Difficulties of spirometry (FEV1)

- Baseline value influences the potential for change

Starting with 100% predicted FEV1 -> less potential to increase by another 10%

- Within subject standard deviation of 4.5%-6.3% ppFEV1

- Efficacy of known drugs: 4-8% ppFEV1 improvement

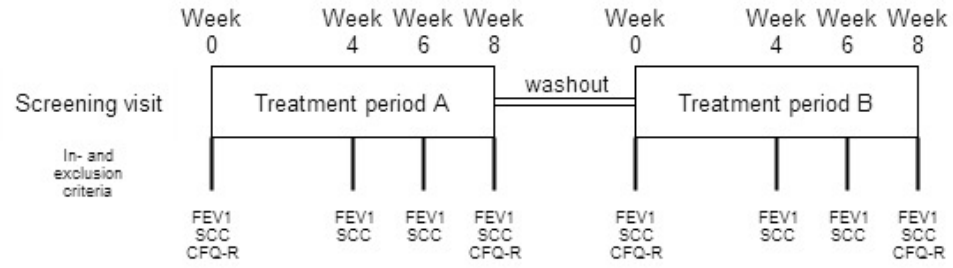
- Limited patient population

Stanbrook 2004, Chest
Cooper 1990, Pediatr Pulmonol
Taylor-Robinson 2012, Thorax

Solution (1): Tackling the high endpoint variability

- Placebo-controlled crossover design
  - Decreasing the influence of within-patient variability
  - Decreasing the influence of between-patient variance

- Repeated measurements
  - Decreasing the influence of within-patient variability



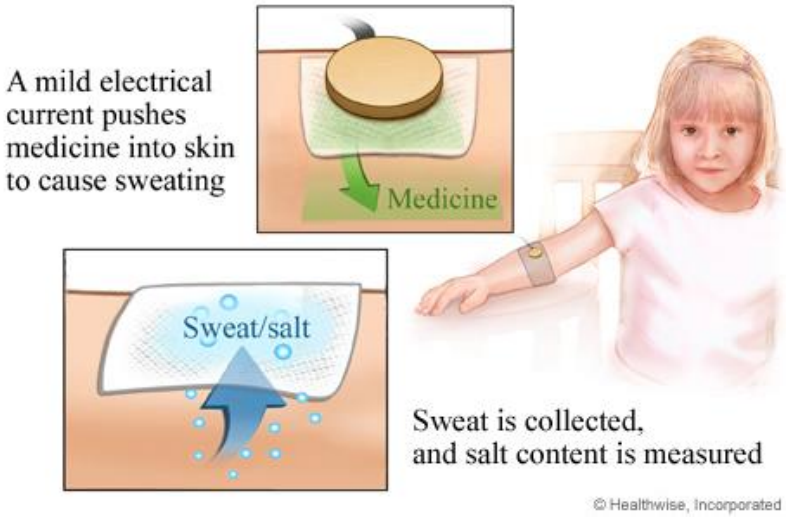
Solution: Other valid primary endpoints?

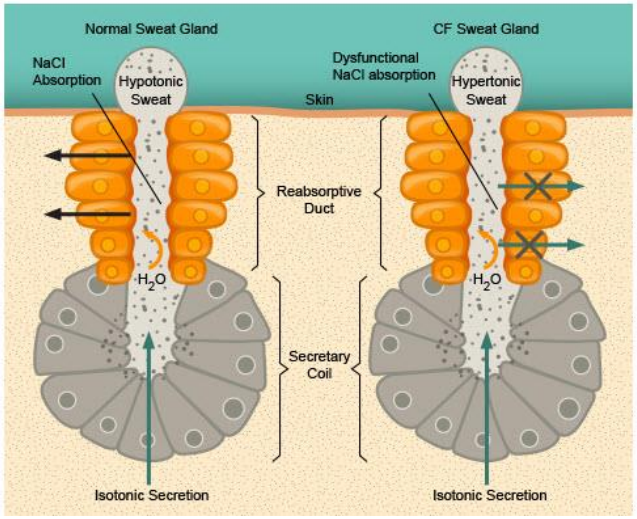
Sweat Chloride Concentration

- In-vivo measurement of CFTR-function could confirm the expected mechanistic effect at patient level
- In theory representative of systemic drug effects
- Could be used as intermediate endpoint (or biomarker)

Sweat chloride concentration

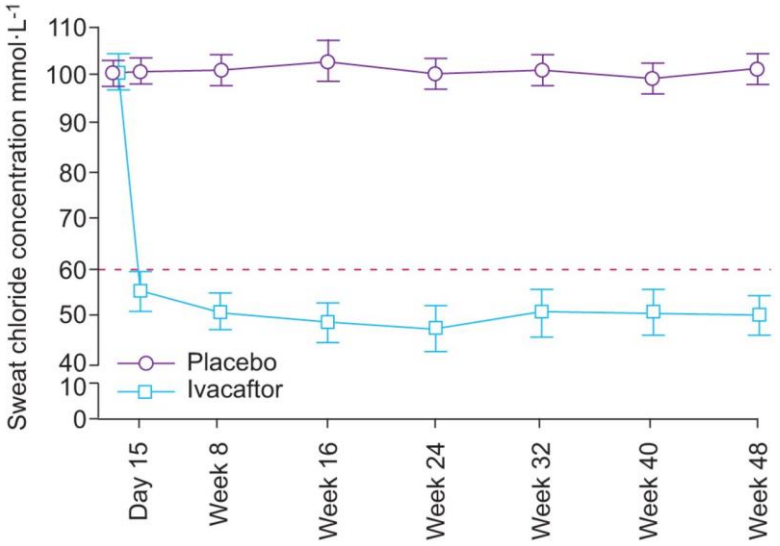
In-vivo measurement of CFTR-function





Sweat Chloride Concentration

- Elevated in CF-patients, normal in healthy subjects
- Large potential for change



Effect of Ivacaftor on SCC – STRIVE-trial

- What is a 'Clinically significant' change?

"the effect of the compound on biomarkers such as sweat chloride that directly measure CFTR function, can be considered as intermediate proof of efficacy."

Vermeulen 2016, Journal of Cystic Fibrosis

Report of the workshop on endpoints for cystic fibrosis, European Medicines Agency, 2012

Correlation between Sweat Chloride and FEV1

- ***Sweat chloride is useful*** *in multicenter trials as a biomarker of CFTR activity and to test the effect of CFTR potentiators.*

- ***Sweat chloride is not a useful*** *marker of clinical response to Ivacaftor*

- *Sweat chloride level changes in response to potentiation of the CFTR protein by Ivacaftor* ***appear to be a predictive*** *pharmacodynamic biomarker of lung function changes on a* ***population basis*** *but* ***are unsuitable*** *for the prediction of treatment benefits for* ***individuals***.

Accurso 2014, Journal of Cystic Fibrosis
Barry 2014, Thorax
Fidler 2016, Journal of Cystic Fibrosis

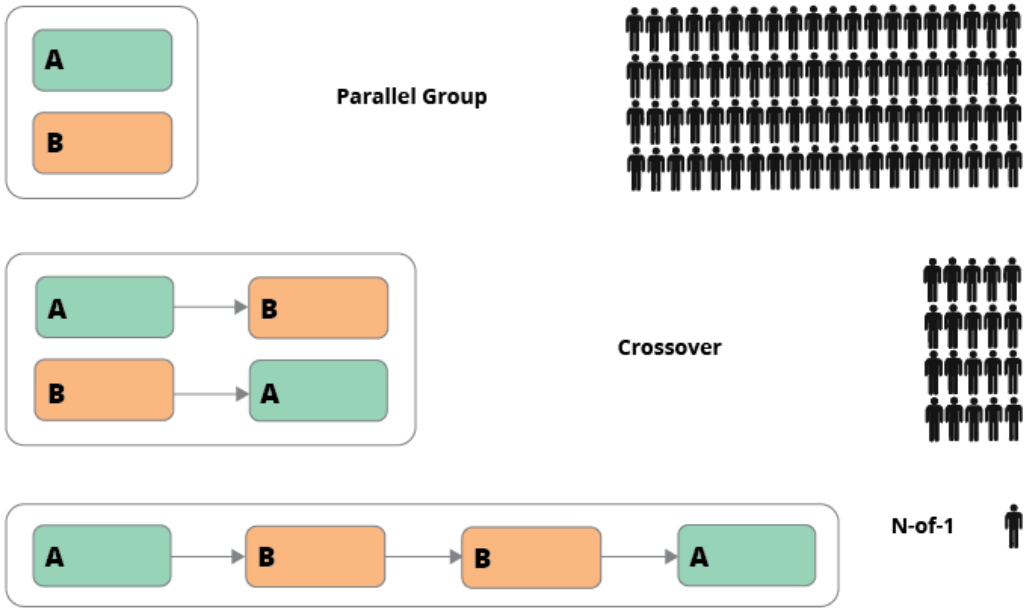
Sweat Chloride as co-primary outcome

- Provide mechanistic evidence of efficacy

- Useful for future trials in smaller populations
  - FEV1 effect possibly not large enough

Difficulty 3: increasingly small trial population

- CF-patient population becomes more dispersed
- Need for effective n-of-1 trial design/outcome parameters



HIT-CF exploratory endpoint

Within-patient comparative assessment of response to treatment

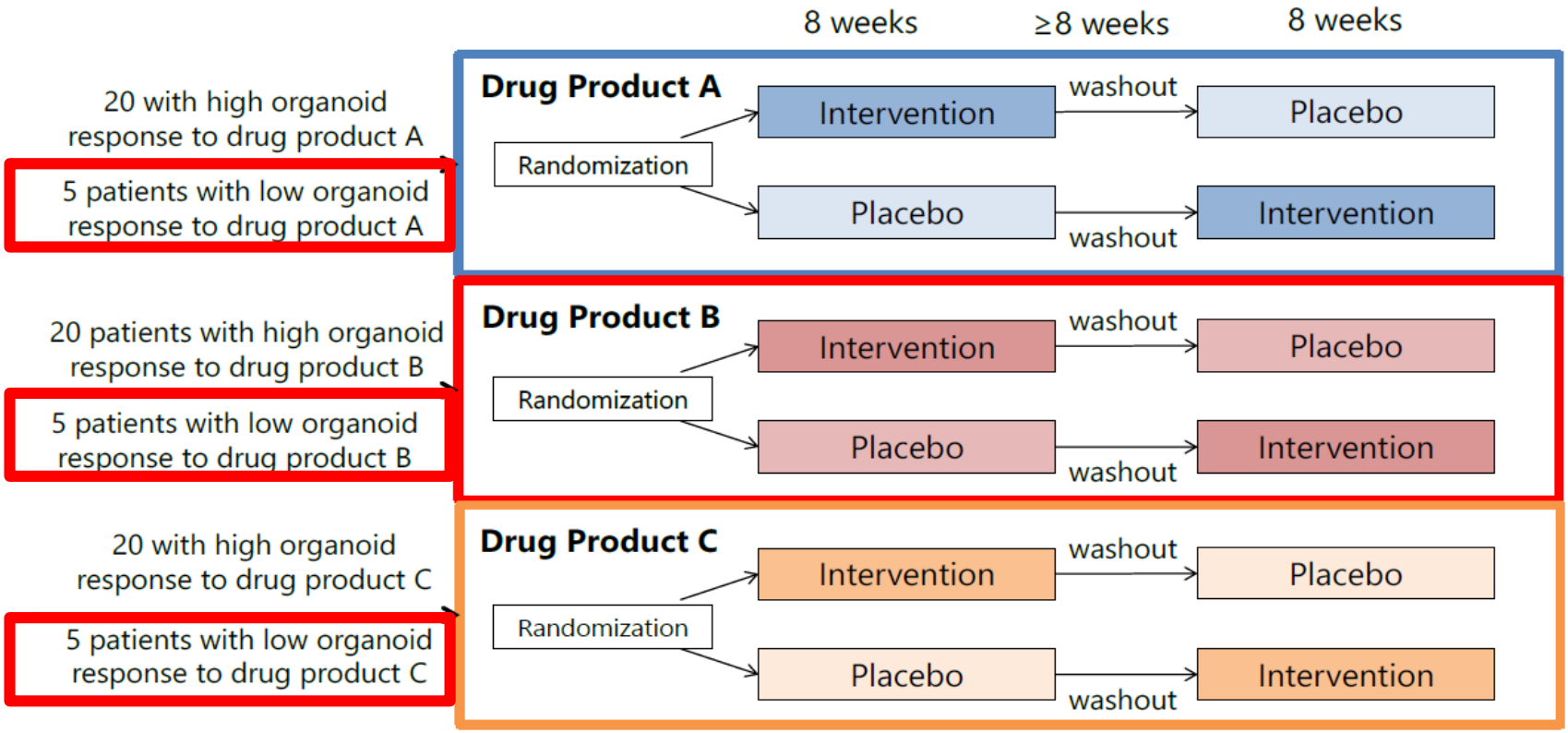
→ assess whether the **observed difference between treatment and placebo** for an individual patient is sufficiently **larger than the measurement uncertainty for an individual patient.**

These data can be used for the design of future n-of-1 trials

Difficulty 4: Validate organoids as predictive model

- Several trials are running to evaluate the predictive capacity of organoids
- If we only include ‘in vitro responders’, we cannot evaluate predictive potential
- Ethically problematic to include large numbers of predicted non-responders?

Solution 4: platform trial for overarching analysis



15 ‘low organoid responders’ can be compared to 60 ‘high organoid responders’ because of platform design

HIT-CF: enhanced clinical trial design in a heterogeneous, small population

- Using in-vitro model to **stratify patients**
- **Cross-over design with repeated measurements** to increase power
- Generating **data** to be used **for future n-of-1 trials**
- **Validating in-vitro model**

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