Regulatory perspective on (alternative) endpoints

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Perspectives

Perspective of market authorisation of a new drug

Evidence based decision of allowing physicians to add a new drug to their treatment options *(does it work and is benefit/risk positive?).*

Provide information to guide the prescribing physician.

Perspective of payers (in very diverse systems)

Evidence based assessment whether treatment (& policy) is cost-effective.

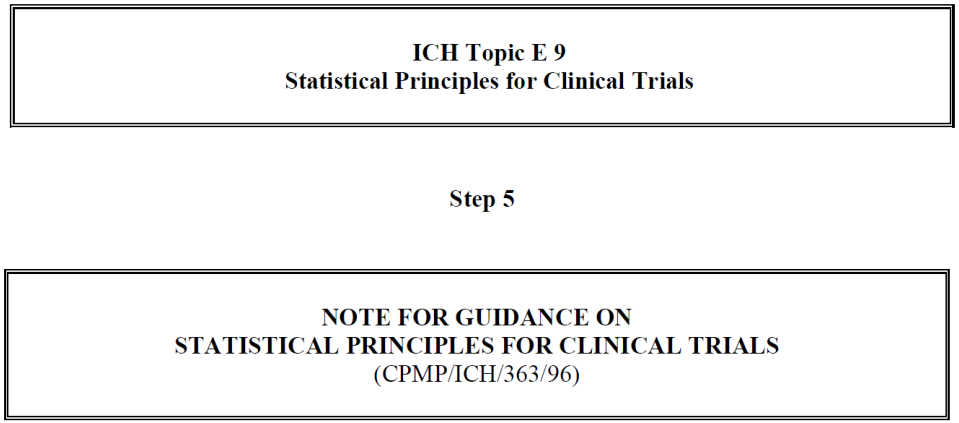
Perspective of treating physician

Evidence based decision for the (next) patient to treat, selecting from the available treatment options.

Is it "best" for the individual patient?

(Primary) Clinical endpoints

- Measure how a patient *feels, functions or survives.*
- Matter to patients (most important)
- (Phase III) clinical trials to provide confirmatory evidence on *clinical* benefit.
- May be single or composite (e.g. MACE).
- Affected by treatment.



Surrogate endpoints

- Predictive of clinical endpoint (substitute)
- Well validated
- Increase efficiency of trials
  - Viral load in HIV
  - Lipid lowering & statins (but maybe not drugs that lower lipids through other mechanism) for CV outcomes.
- True surrogacy rare: shades of grey.

Clinical endpoints and trial design

A clinical trial has: one primary objective, one primary endpoint.

Failure to demonstrate effect on primary endpoint complicates interpretation.

Primary endpoint success is only part: understand biology, combination of effects, benefits and risks.

Careful selection of set of endpoints matters.

Example: 6 Minute Walking Test

In *cardiac related diseases* (chronic heart failure, pulmonary arterial hypertension,..)

- *Valid* measure of *functional* capacity ("how a patient functions").

- Considered progonostic / predictive of clinical outcome (but not always) -> *Surrogate for clinical endpoint ("survives")*.

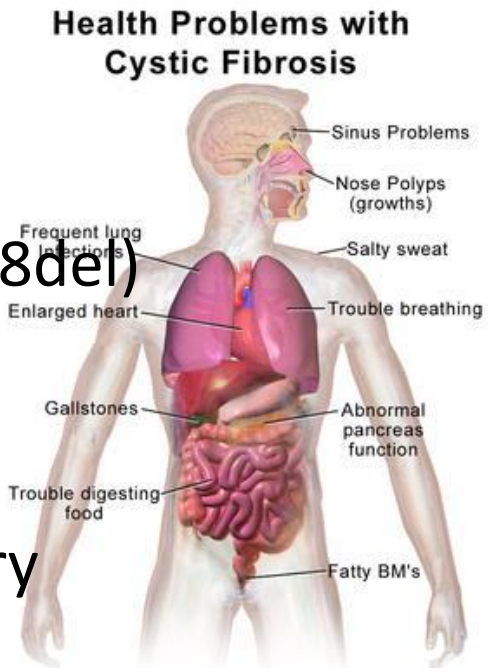
6MWT in Duchenne and Becker MD

"No specific recommendations ……can be given."

- Selection of measures across the functional domains affected, as well as ADL, quality of life.
- 6MWT validated in pediatric population, key problems indicated.

- Change in 6MWT cannot be determined in every patient.
- Recent development:
  - Upper Limb PROM tested in 194 subjects from 8 centres in 6 countries (Klingels et al. Dev Med Child Neurol 2017)

Example: Cystic Fibrosis



Genetic disease with a common variant (F508del) and many (ultra-)rare variants.

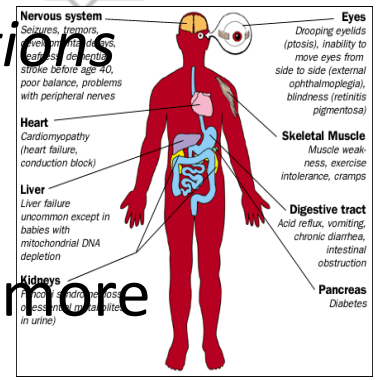
Recommended primary endpoint: Respiratory Function: FEV1.

- Standard of care improved substantially.
- Disease modifying drugs given before lung function is impaired.
- Focusing on patients with FEV1 impaired (for whom improvement possible) may lead to substantial selection.

Acknowledged need for new endpoint to evaluate drugs.

Rare diseases & patient centered outcomes

There is a great need in heterogeneous conditions



Market authorisation

- We can establish treatment effect, possibly more sensitive.
- Can we estimate benefit – risk?
- Can we see consistency across different treatments?

Payers

- Can we translate treatment effects into impact?
- Could it be sufficient to grant access early?

The next patient to treat

- Can we inform patients on what to expect?

Concluding

- Patient centered outcomes are integral to regulatory evaluation.

- Subject to same key principles as other outcomes as (primary or secondary) endpoints in clinical trials.

- (Ultra) rare diseases may require unconventional approaches
  - That need to be well motivated (exceptions)
  - That need to be validated (qualified)