Difficulties/challenges encountered – look into the future: academia perspective

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Academia perspective

- Funding of research in rare diseases
  - ➔ How to achieve the best value for money
- New surrogate outcome measures..
  - ➔ Loosen the brake
  - ➔ Specific focus on the young age
- Time for new trial designs
  - ➔ Modelling/individualized medicine
- Assessing drug safety in a rare disease
- The unnecessary admin complexity of trials

Funding of research in rare diseases:

- **Health authorities**
  - ➔ **Balance healthy competition and focused progress**
  - ➔ **Agree with academia on research priorities, including progress for outcome measures**
  - ➔ **Assign some budget to chosen priorities**
- **Industry**
  - ➔ **Franchise research on outcome measures**
  - ➔ **Supply academia with placebo arm data**

Surrogate outcome measure catch 22

- Surrogate outcomes provide ‘faster’ answers
- FEV_1 is only approved surrogate outcome
  - Insensitive unless large treatment effect
  - When normal baseline -even large treatment effect won’t help

- We need new surrogate outcomes
- Criteria for surrogate outcome are very stringent
  - Validate new outcome to clinical efficacy measure or to another surrogate outcome

New surrogate outcome measures must meet stringent criteria

- ‘Clinimetrics’
  - Reliability: consistent and free from error
  - Validity:
    - Concurrent with gold standard
    - Convergent with measure reflecting same aspect
    - Discriminative between groups, ‘sensitive’
    - **Predictive of prognosis**
  - Responsiveness: to an intervention
  - Normal values
- Feasibility
- ‘Track record’

De Boeck 2012, ERJ

180° change:
agree on markers of beneficial outcome

- Normal/improved nutritional status
- Improved lung disease
  - ➔ Delay chronic *P aeruginosa* infection
  - ➔ No/less bronchiectasis
  - ➔ Less (IV treated) pulmonary exacerbations
  - ➔ Less airway obstruction
- Improved CFTR function
  - ➔ Lower sweat chloride

Compelling data from natural history, registries

The outcome measure used for the claim must still meet stringent criteria

- **‘Clinimetrics’**
  - **Reliable: consistent and free from error**
  - **Valid**
    - **Concurrent: with gold standard**
    - **Convergent: with measure reflecting same aspect**
    - **Discriminative: between groups, ‘sensitive’**
  - **Responsive to intervention/less progression: grading.**
  - **Normal values**
- **Feasible**
- **‘Track record’ in short/medium term studies**

AND measure the claimed outcome

The main question then becomes:
How large and sustained should the effect size be?

- Significantly larger than placebo
  - ➔ Group differences
  - ➔ Explore individual treatment responses
    - ➢ In parallel groups
    - ➢ In cross-over design *Dolmage 2011, AJRCCM*
- Can we agree on a minimal threshold
  - ➔ ‘Clinically meaningful’
- Preserving normality
- What can we afford?

In preschool children with a rare, serious disease and slow disease progression

Accept as proof of efficacy in phase 3 trials, a change in a (surrogate) outcome parameter

- **closely linked to the disease's causal pathway**
  - **sweat chloride, nasal PD, lung clearance index, imaging**
- ***especially* if efficacy is proven in another age category**
- **proof of clinical benefit can follow in phase IV trial**
  - **pharmacovigilance**

To see what is right, and not do it,
is want of courage

Confucius

EMA guideline on clinical trials in small populations

Time to explore new trial designs

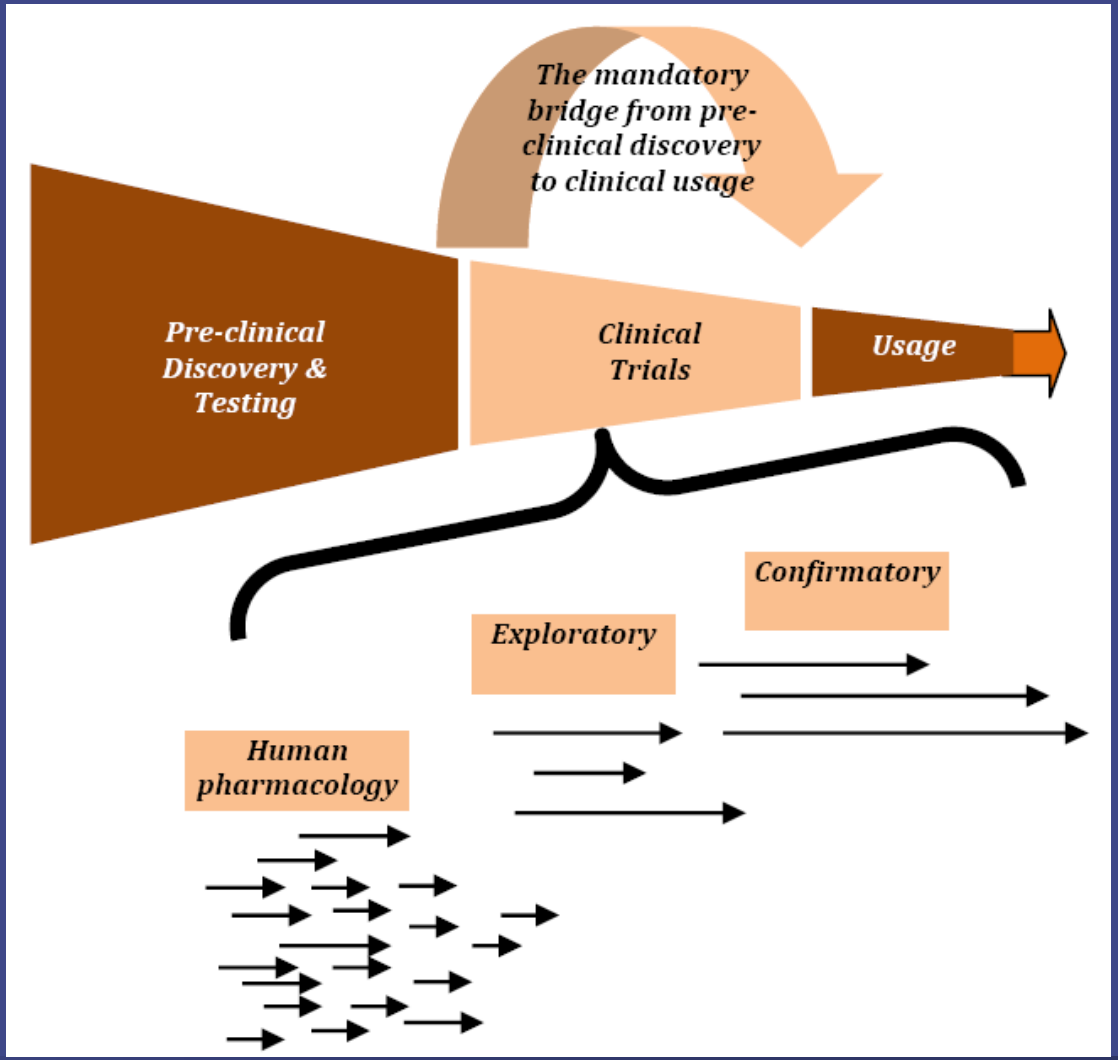
- Randomized controlled trials should not be the only option
- Explore data modelling
  - ➔ Use existing databases
  - ➔ Can modelling be used to better predict treatment responses
  - ➔ Compare to ‘usual approach’
  - ➔ Link to individualized medicine

Clinical trials assess risk/benefit

Safety

versus

efficacy



Safety assesment requires:

- **Sufficient exposure**
  - ➔ **duration : at least 12 mo (*EMA/ CF*)**
  - ➔ **numbers: ? N= 100's (im)possible in rare disease**
- **In rare diseases especially**
  - ➔ **ongoing assesment past licensing**
  - ➔ **phase 4 pharmacovigilance**
    - ➢ **spontaneous adverse drug reaction reporting…**
    - ➢ **a systematic proactive approach is better**

Pharmacovigilance via CF registries

- Continuous online database
  - → e.g. CFF-clinical database
- Add-on modules
  - → to large national registries
    - ➢ colimycin safety data
  - → to ECFSPR
  - → to ECFS-CTN center data bases

Opportunities: all ages, long duration, need pharma
EMA- CF community

Challenges: time lag to results, ?causality, cost

The importance of CF registries

- define important medical needs
- identify optimal patient cohorts for interventional studies
- power calculations
- feasibility
- data modelling techniques
- pharmaco-economic data
- real life long term outcome data

But how to fund them?

Industry please decrease the administrative complexity of trials

- Admin burden will decrease the focus on patient safety and accuracy
- Too many vendors and too many different procedures for
  - ➔ Ordering supplies, sending samples, recording data
  - ➔ Licensing and relicensing
- Overcommunication:
  - ➔ E-mails, faxes, queries, notifications..
- Competitive inclusion/reasonable timeline

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