EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Workshop on endpoints for cystic fibrosis clinical trials

Clinical trials in CF - regulatory perspective: Endpoints for added clinical benefit in view of HTA

Paolo D. Siviero

Head of Economic Strategy and Pharmaceutical Policy

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Consultancy for a company	X				
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Public Health and Burden of CF

- ✓ In Europe, the average prevalence of CF is 0.737/10 000.
- ✓ Between 2004 and 2008 infants screened in European countries increased from 1.6 to 3 million and this number is expected to increase over the next few years.
- ✓ Most children with CF now can expect to survive into adulthood and life expectancy has improved achieving average survival of over 30 years.
- ✓ Recent advances in treatment (introduction of new antibiotics, gene therapy, administration of pancreatic enzymes, lung and liver transplant) can further improve life expectancy and quality of life of CF affected persons: the predicted median survival for newborns in 2000 with CF is likely more than 50 years.

Farrell PM. J Cyst Fibros. 2008 Sep;7(5):450-3.

Socioeconomic aspects

- CF care is expensive
- Best survival in specialized centers
- Costs increase with age
- Increase in costs when chronic pulmonary infection *Pseudomonas aeruginosa*
- Home care is less expensive and can be as effective as hospital treatment in selected patients
- Separated budget for CF care
- Focus on economic aspects of care

- Many new pharmaceutical products, specifically designed to treat a given disease, are more expensive than the older treatments they replace and there is a need to generate evidence on their value for money.

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New Cystic Fibrosis Drug Offers Hope, at a Price

Science
AAAS

Last week, the news that U.S. regulators had approved a new drug for cystic fibrosis (CF) cheered patients and the biomedical research community. The drug, called Kalydeco and made by Vertex Pharmaceuticals, is the first to target the genetic defect discovered 23 years ago that causes a protein to malfunction in cystic fibrosis, resulting in a sticky buildup of mucus in the lungs and digestive tract that eventually causes fatal health problems.

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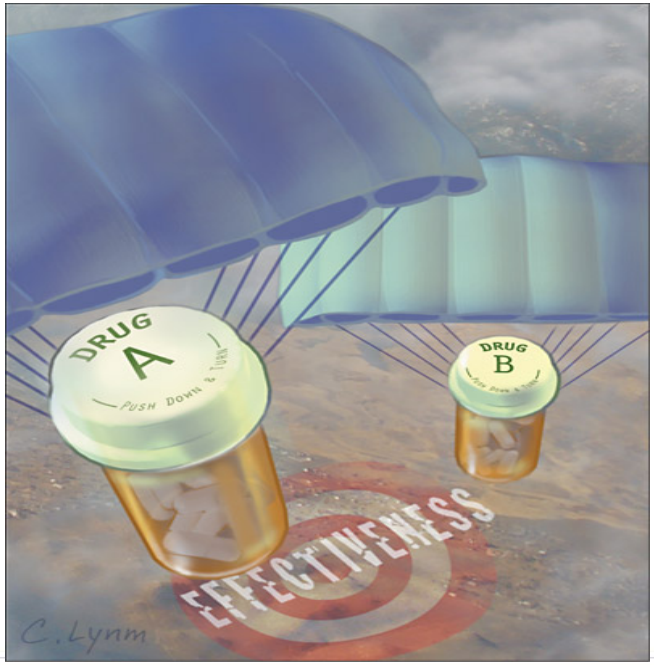
The management of CF
is an expensive commitment

Health economic analysis for CF therapeutic technologies

- Health care policy makers and funders expect rigorous assessments of the cost-effectiveness of new treatments.

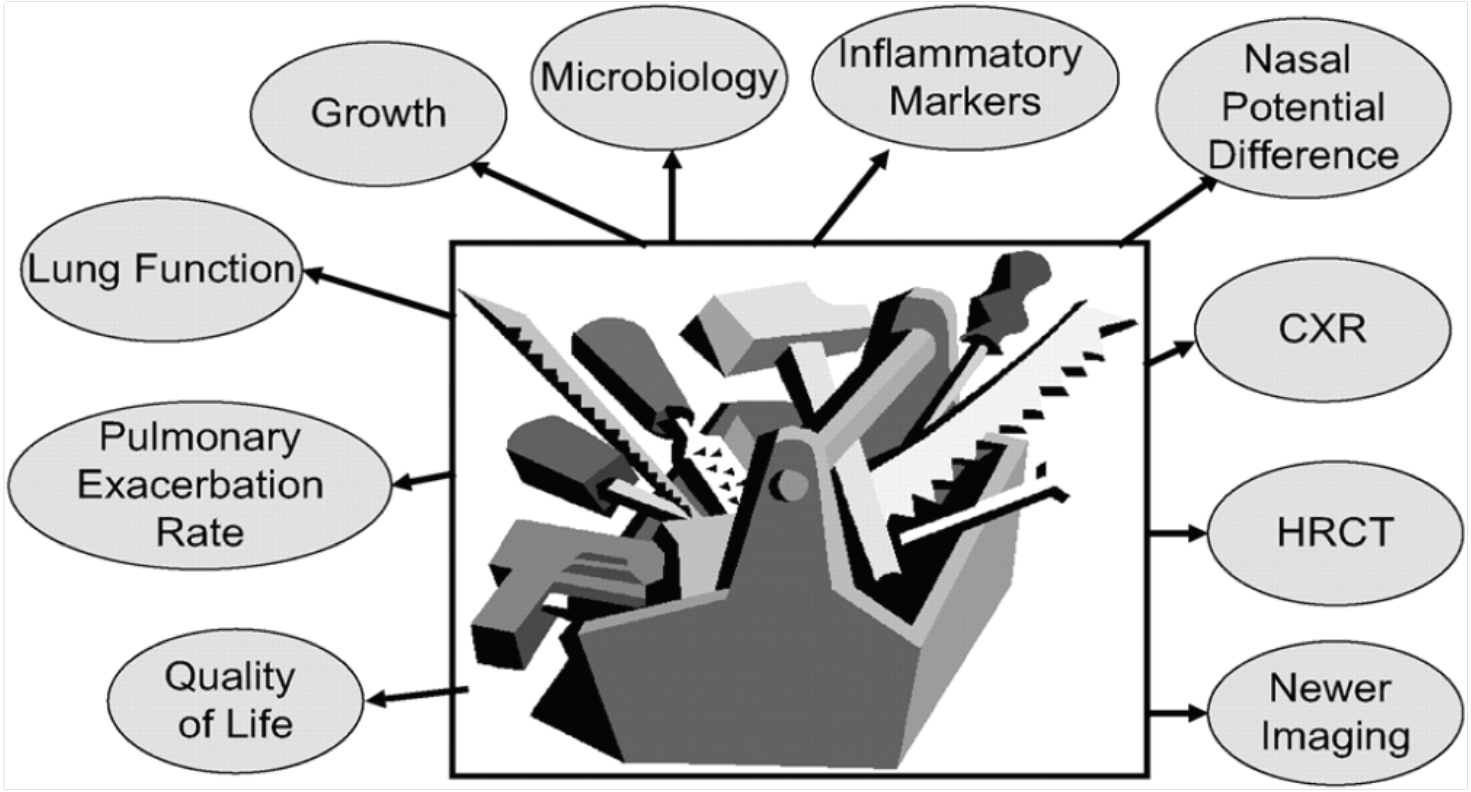
- In an increasing number of countries decisions to reimburse medicines, medical devices and medical procedures are based on health economic evaluations (e.g. cost effectiveness analyses (CEA) or cost-utility analyses (CUA)) and/or budget impact estimation.



Clinical trials in CF

- Clinical trials (CTs) in CF investigate a widening array of new therapeutics (gene therapy, anti-inflammatories, anti-infectives), but often explicit data for the health technology assessment are missing.
- A small number of CTs examined the cost of care associated with CF.
- There is a raising awareness among healthcare professionals and regulators of the need for CTs in different categories of CF patients.
- Health economics data and patient perspective related information should be included in future clinical trials in CF patients in order to obtain health economic data already within CTs for MAA registration.
- A wide range of clinical trial endpoints is needed to adequately evaluate these agents.

The existing “toolbox” of CF clinical trial endpoints



One Size Does Not Fit All

CXR = chest X-ray; HRCT = high-resolution computed tomography.

Rosenfeld M. Proc Am Thorac Soc Vol 4. pp 299–301, 2007

Pathogenesis, treatments and outcome measures for CF lung disease

Step in pathogenesis	Treatment	Biomarker/outcome measure
CFTR mutation	Gene therapy	Transgene/protein expression
CFTR protein absence/dysfunction	Read-through of stop mutations (PTC 124) Correctors (Vertex 809) Potentiators (Vertex 770)	Sweat chloride Nasal potential difference Rectal potential difference Tissue expression of mature CFTR
Abnormal ASL/mucociliary clearance	Mannitol dry powder Dornase alfa Hypertonic saline Airway clearance treatments	Mucociliary clearance
Infection colonization–exacerbation	Antimicrobials: IV, inhaled PA eradication	Number of exacerbations Bacterial quantification Molecular diagnostics/ microbiome shifts Antimicrobial susceptibility Serology for pathogens
Inflammation	Macrolides (azithromycin) NSAIDs (ibuprofen)	Serologic/sputum inflammatory markers
Lung destruction Lung Structural Abnormalities	All of the above	FEV_1, lung volumes and other measures of lung function High resolution CT scan Biomarkers of lung tissue breakdown Lung clearance index
Morbidity/mortality	All of above	Patient-reported outcomes Hospitalizations Measures of treatment burden

ASL = airway surface liquid; CFTR = Cystic Fibrosis Transmembrane Conductance Regulator; CT = computed tomography; FEV_1 = forced expiratory volume in 1 second; IV = intravenous; NSAIDs = nonsteroidal anti-inflammatory drugs; PA = *Pseudomonas aeruginosa*.

E.T. Zemanick et al. / Journal of Cystic Fibrosis 9 (2010) 1–16.

Health Economic Evaluation

CUA and CEA: Compare relative value (costs and outcomes) of different interventions

Cost-Utility Analysis (CUA)

- Demonstrates differences in Health-Related Quality of Life (HRQoL) between the intervention and comparators.
- Outcomes are measured as health-related preferences, which are most often expressed as Quality of Life Years gained in health state (QALYs).

Cost-Effectiveness Analysis (CEA)

- The outcomes are measured in natural (health) units, such as Life years Gained, lives saved, or clinical event avoided or achieved.

Incremental Cost Effectiveness Ratio

$$ICER = \frac{\text{Costs Differences}}{\text{Outcomes Differences}}$$

CUA

$$\frac{\Delta \text{ Costs}}{\Delta \text{ QALY}} \qquad \frac{T_a\text{Cost} - T_b\text{Cost}}{T_a\text{QALY} - T_b\text{QALY}}$$

CEA

$$\frac{\Delta \text{ Costs}}{\Delta \text{ LYG}} \qquad \frac{T_a\text{ Cost} - T_b\text{ cost}}{T_a\text{LYG} - T_b\text{ LYG}}$$

CF Outcomes relevant for HTA

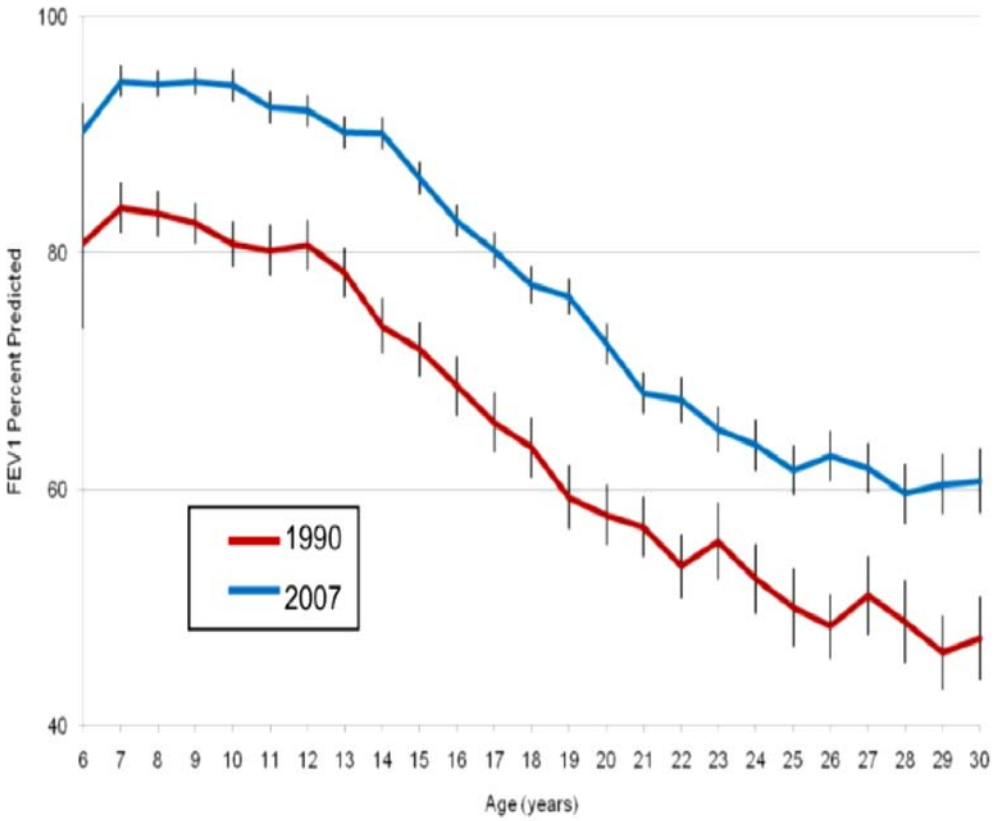
- Lung function measured in terms of forced expiratory volume (FEV_1)
- Rate and extent of microbial response (for example sputum density of *P. aeruginosa*)
- Respiratory symptoms relief
- CFTR function (sweat chloride concentration and transepithelial potential difference);
- Chest imaging (standard chest radiography and high-resolution computed tomography [CT]);
- Frequency and severity of acute exacerbations
- Growth parameters
- Inflammatory markers;
- Microbial biomarkers

- Health-related quality of life (HRQoL)
- Other PRO
- Compliance

- Measurement of treatment burden
- Use of antibiotics
- Hospitalisation
- Adverse events of treatment (including rate of resistance to antibiotics) and related costs

Pulmonary function decline and modelling the relationship with survival in CF patients

- ✓Forced expiratory volume in 1 second (FEV1) and pulmonary exacerbation rate are the most commonly used outcomes in CF clinical trials.
- ✓As improvements in treatment slow pulmonary function decline, the utility of FEV1 and exacerbation rate as outcome measures may decrease.
- ✓Modelling the relationship between pulmonary function and survival in CF is complicated by FEV_1 measurement errors and death censoring of patients with the poorest lung function.



Mean forced expiratory volume in 1 s (FEV1) percent predicted versus age with 95% confidence intervals. Lung function was higher at each age in 2007 compared to 1990. Data from CFF Patient Registry, 1990 and 2007

E.T. Zemanick et al. / Journal of Cystic Fibrosis 9 (2010) 1–16.

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Rate of lung function decline (RLFD) vs FEV1

- The most commonly used therapies have not been shown to reduce rate of FEV_1 decline, but rather to produce a sustained improvement in FEV_1 compared with placebo-treated controls.

VanDevanter DR, Konstan MW. Respir Drug Deliv 2008;1:11–8.

- Use of rate of FEV_1 decline (RLFD) as a prospective clinical trial endpoint remains a desirable but elusive goal for CF drug development in part because of individual variability in FEV_1 over time

Davis PB et al. Pediatr Res 1997;41:161–5.

- The effect of this variability is mitigated as study duration increases, which may partially explain why the only prospective controlled clinical trial in CF to demonstrate a significant reduction in the rate of FEV_1 decline to date has been a 4-year study of high-dose ibuprofen.

Konstan MW at al. N Engl J Med 1995;332:848–54.

Economic evaluations of treatments in CF

- At present, there have been relatively few economic evaluations of treatments in CF (mainly of antibiotic treatments)
- Three different areas of interest:

  (a) assessment of cost-effectiveness of Dry-Powder Inhaled antibiotics (DPIs)

  (b) the economic value of home- versus hospital-based intravenous therapy

  (c) the economic value of antibiotic eradication therapy

Nebulised Treatment Burden

- ✓ CF places large treatment burden on patients and their families with complex time intensive therapies and multiple medications during the day.
- ✓ Patient with *P. aeruginosa* infection spend several hours in assuming inhaled tobramycin and dornase alpha just to maintain the clinical stability.
- ✓ A study in adult patients with CF found that:
  - subjects reported spending an average of 108 minutes (SD±58min) on daily CF treatments;
  - the perceived treatment burden is highly associated with the number on nebulised medications prescribed (time-consuming treatment) [1,2].
- ✓ Nebulised therapy may be associated with poor adherence.

[1]] Sawicki GS et al. J Cyst Fibros. 2008
[2] Quittner AL et al. Curr Opin Pulm Med. 2008

The consequences of poor adherence

- ✓ Poor adherence is very common in CF and the likeliest cause of treatment failure.
- ✓ Families may have a poor understanding of how specific medications work or how to correctly administer them.
- ✓ The consequences of poor adherence include:
  - increased symptoms,
  - accelerated decline in lung function,
  - more frequent hospitalizations,
  - increased family stress and conflict,
  - higher healthcare costs.

Assessment of cost-effectiveness of Dry-Powder Inhaled antibiotics (DPIs)

- Inhaled nebulised antimicrobics have been in clinical practice since ’90s for the treatment of CF patients suffering from Gram negative bacteria - including *P. aeruginosa* - lung infection or colonisation

- Recently new formulations of inhaled antimicrobics, DPIs entered on the market

- DPIs are small portable devices able to deliver high loads of medicine to the lungs

- To date EMA authorised 2 DPIs:

  - *Colobreathe®* Tobramycin capsules (28 mg) of dry powder for inhalation through a portable inhaler device

  - *Tobi Podhaler ®* Colistimethate sodium -1 662 500 IU inhalation powder

Current difficulties in producing a robust Health Economic analysis of DPIs

NHS
National Institute for
Health and Clinical Excellence

Colistimethate sodium powder and tobramycin powder for inhalation for the treatment of pseudomonas lung infection in cystic fibrosis [ID342]

Assessment Report

Commercial in Confidence stripped version for consultation

1. Use of a short time horizon in RCTs
2. Absence of direct comparative evidence of DPIs upon HRQoL
3. Limited evidence relating to survival benefits for DPIs
4. Modelling and uncertainties
5. Absence of published economic evaluations and of relevant studies reporting cost-effectiveness of DPIs compared to standard treatments

1) Use of a short time horizon in RCTs

- ✓EMA recommends a 12-month FEV_1 end-point for intervention intended to slow or stop pulmonary disease
- ✓No long-term evidence is available to demonstrate the efficacy of DPIs beyond a maximum 24-week trial follow-up period;
- ✓Most patients with chronic *P. aeruginosa* will receive antibiotics for the rest of their lives
- ✓As consequences:
  - Trials durations of DPIs are insufficient to assess any treatment benefit in terms of mortality reduction;
  - Absence of long term evidence enhances uncertainties about the relationship between intermediate outcome measures (FEV_1) and final end-point (mortality)
  - Lack of data on long term adverse events and adherence to treatment

2) Absence of direct comparative evidence of DPIs upon HRQoL

- ✓ The short-term trials evidences do not include the direct measurement of HRQoL using a preference-based instrument (e.g. the Euroqol-5D).
- ✓ A mapping exercise has been used to translate the CFQ-R to the EQ-5D in order to estimate health utility (not differentiated by treatment).
- ✓ The relationship between FEV_1 and HRQoL and/or survival has not been established either in the trials of DPIs and in scientific literature

3) Limited evidence relating to survival benefits for DPIs

- ✓ The relationship between intermediate end-points (FEV1) and final outcomes (survival) has not been established

4) Modelling and uncertainties

- ✓ The results of modelling for translating from intermediate endpoints to final outcomes need to be interpreted with caution since they are not sufficient to substitute empirical evidence
- ✓ An appropriate handling of uncertainty should be considered during the evaluation

The economic value of home - versus hospital-based intravenous therapy

Table 3
Effectiveness at end of one-year study period compared with baseline "average" FEV_1 values: number of patients (%)

	All patients ($n=116$)	"Home" ($n=47$)	"Hospital" ($n=51$)	"Both" ($n=18$)
Base case: ≤0% decline				
Effective	59 (50.9%)	20 (42.6%)	30 (58.8%)	9 (50.0%)
≤2% decline				
Effective	62 (53.4%)	20 (42.6%)*	32 (62.7%)*	10 (55.6%)

* $p=0.045$.

The improved clinical effectiveness achieved with hospital-based treatment may only be achieved with the input of considerable extra resources.

Table 4
Costs to health care provider of 1 year of treatment with intravenous antibiotics (data from original sample)

	All patients ($n=116$)	"Home" ($n=47$)	"Hospital" ($n=51$)	"Both" ($n=18$)
Cost of resources per patient, mean (range)/£				
iv antibiotics and disposables	8974 (829 to 57,300)	9325 (1122 to 43,833)	7920 (829 to 57,300)	11,044 (2587 to 25,857)
Home kits	25 (0 to 96)	39 (11 to 96)	8 (0 to 64)	33 (11 to 75)
Laboratory testing	101 (0 to 424)	88 (0 to 259)	113 (0 to 424)	103 (4 to 223)
Clinic appointments	546 (0 to 1984)	789 (0 to 1984)	268 (0 to 1357)	702 (0 to 1775)
Hospital stay	8856 (0 to 50,610)	3263 (0 to 20,059)*	14,299 (617 to 50,610)*	8041 (926 to 23,762)
Total cost per patient, mean (range)/£	18,513 (1537 to 99,828)	13,528 (1537 to 51,898)	22,609 (2873 to 99,828)	19,927 (5,149 to 45,813)

* $p<0.001$.

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J. Thornton et al. / Journal of Cystic Fibrosis 4 (2005) 239– 247

How to bridge the gap

- Collaboration and communication between stakeholders (research centers, patients and physicians associations, regulators and pharmaceutical industry);
- Design together (Regulators, Payers, Manufacturers, University, Patients) clinical trials to obtain homogenous and forecasting decisions;
- Stimulating high quality research (defining consistent and transparent quality standards; harmonizing clinical trial procedures, defining endpoints for added clinical benefit in view of HTA);
- Promoting “scientific advice” model in the process of R&D shared by the Regulator and the Payer.

Thank you for your attention

Paolo Daniele Siviero
Head of Economic Strategy and Pharmaceutical Policy
Italian Medicines Agency
p.siviero@aifa.gov.it

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