Registries do have potential to be used in clinical trials

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Head of Research,
Dutch CF Foundation NCFS
Executive Committee, European CF Patient Registry

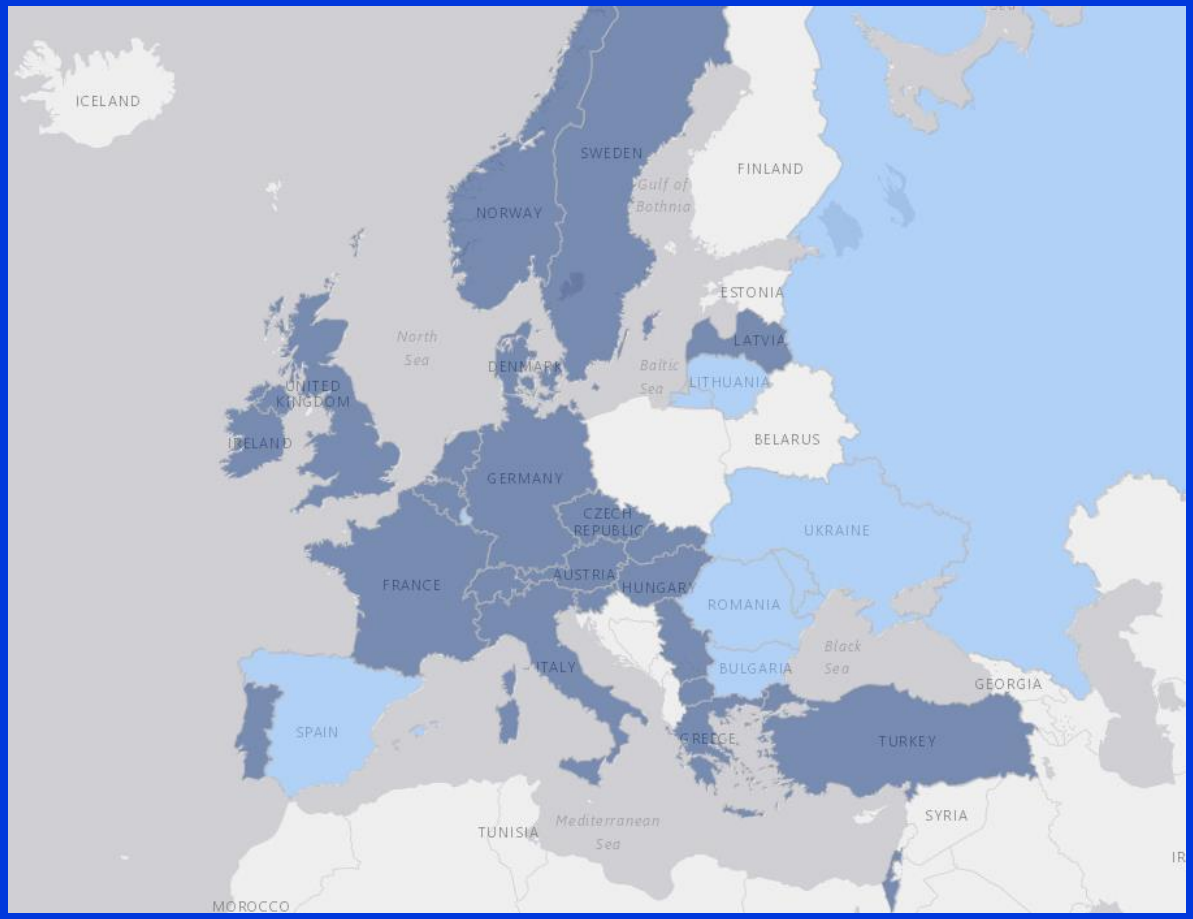
Asterix Symposium, Zaandam NL, September 18 2017

Cystic Fibrosis

- Hereditary rare disease
- Intensive treatment
- High impact on QOL
- Decreased life expectancy
- 85.000 people worldwide registered
- > 2000 mutations, including ultrarare

ECFS Patient Registry

- 31 Countries
- >42,000 pts
- 17 National Registries
- 81 centers using ECFS Registry Software



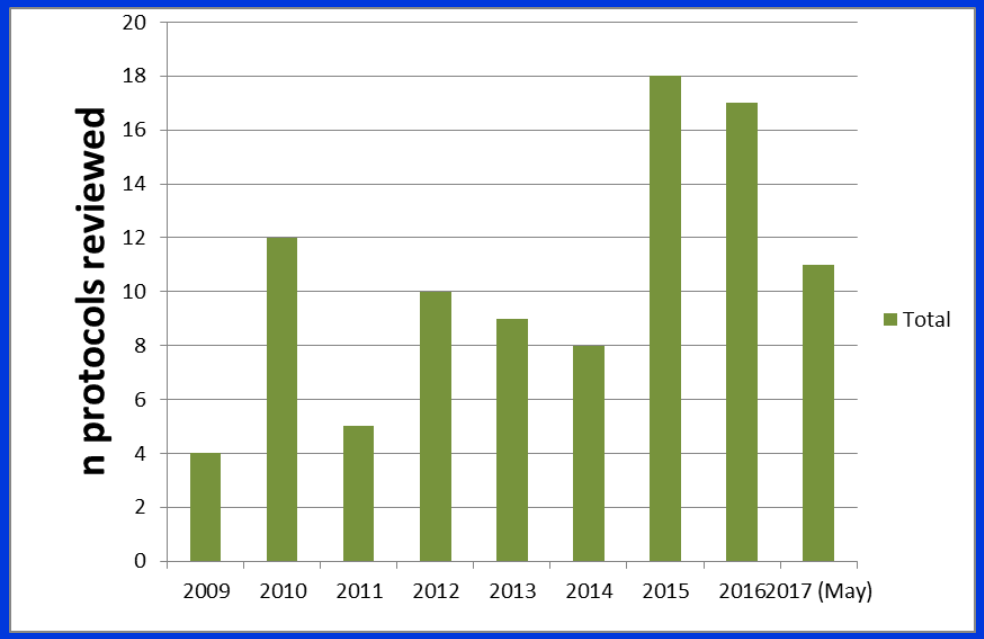
Variables Collected by ECFSPR

Demographic	Age, Gender, Status of patient, Date and cause of death
Diagnosis	Age at diagnosis, Sweat test, Meconium Ileus, Neonatal screening
Genetics	CFTR Genotype
Growth/Lung function	FEV1 & FVC, height and weight
Microbiology	Pseudomonas aeruginosa, Staphylococcus aureus, B. cepacia, NTM, MRSA
Complications	Exacerbations (IVs, hospitalisations), Diabetes, Liver disease, Pancreatic status
Therapy	Antibiotics, Bronchodilators, Mucolytics, Oxygen therapy, Pancreatic enzymes, CFTR Correctors
Transplant	Lung/Liver transplant

Registry Uses:

Need for Novel Approaches to Clinical Trials: The ECFS Clinical Trial Network

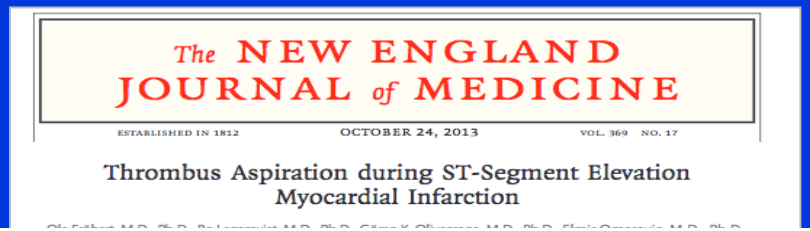
Increase in Protocols reviewed by CTN



CTN Increase in Active Studies

Courtesy of the ECFS CTN - Presented ECFS 2017

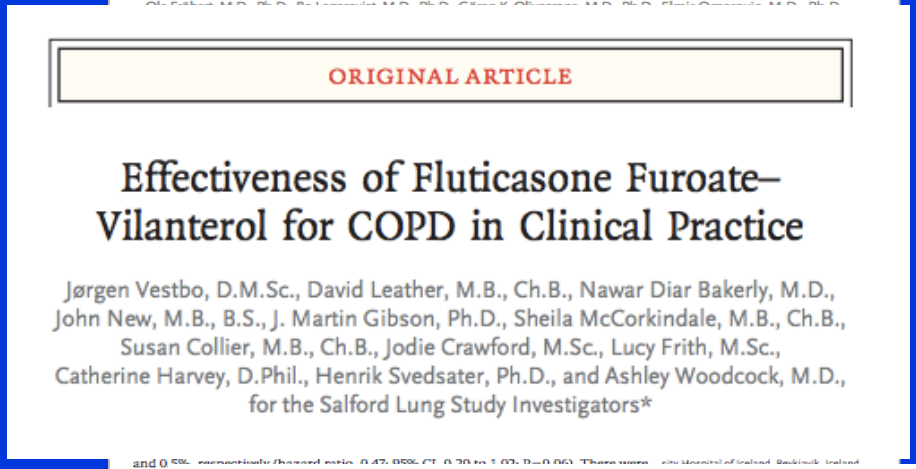
Registries and Clinical Trials



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 24, 2013 VOL. 369 NO. 17

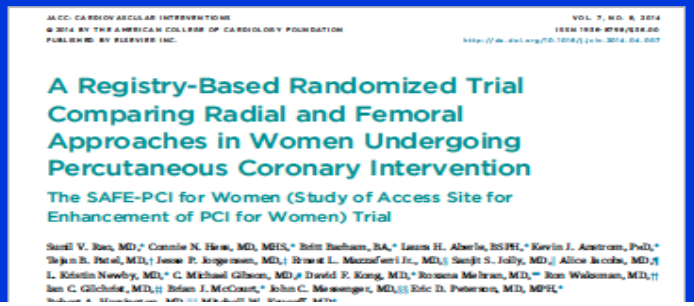
Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction



ORIGINAL ARTICLE

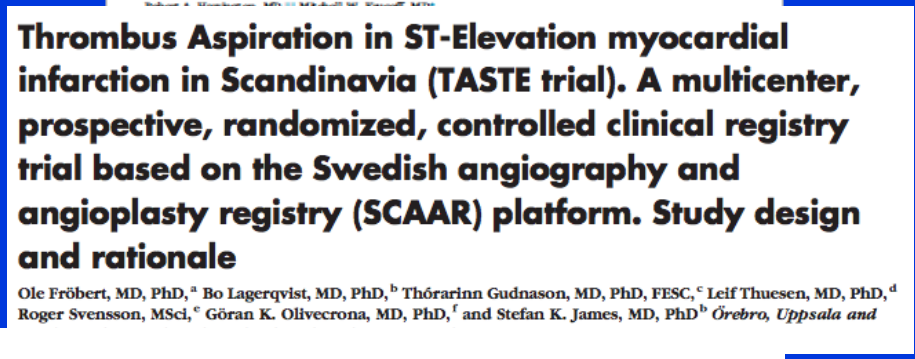
Effectiveness of Fluticasone Furoate–Vilanterol for COPD in Clinical Practice

Jørgen Vestbo, D.M.Sc., David Leather, M.B., Ch.B., Nawar Diar Bakerly, M.D., John New, M.B., B.S., J. Martin Gibson, Ph.D., Sheila McCorkindale, M.B., Ch.B., Susan Collier, M.B., Ch.B., Jodie Crawford, M.Sc., Lucy Frith, M.Sc., Catherine Harvey, D.Phil., Henrik Svedsater, Ph.D., and Ashley Woodcock, M.D., for the Salford Lung Study Investigators*



A Registry-Based Randomized Trial Comparing Radial and Femoral Approaches in Women Undergoing Percutaneous Coronary Intervention

The SAFE-PCI for Women (Study of Access Site for Enhancement of PCI for Women) Trial



Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE trial). A multicenter, prospective, randomized, controlled clinical registry trial based on the Swedish angiography and angioplasty registry (SCAAR) platform. Study design and rationale

Ole Fröbert, MD, PhD,[a] Bo Lagerqvist, MD, PhD,[b] Thórarinn Gudnason, MD, PhD, FESC,[c] Leif Thuesen, MD, PhD,[d] Roger Svensson, MSci,[e] Göran K. Olivecrona, MD, PhD,[f] and Stefan K. James, MD, PhD[b] *Örebro, Uppsala and*

The Randomized Registry Trial — The Next Disruptive Technology in Clinical Research?

Michael S. Lauer, M.D., and Ralph B. D'Agostino, Sr., Ph.D.

Related article, p. 1587

Frobert et al. Am H J 2010
Frobert et al. NEJM 2014
Laeur & D'Agostini NEJM 2014

Interaction

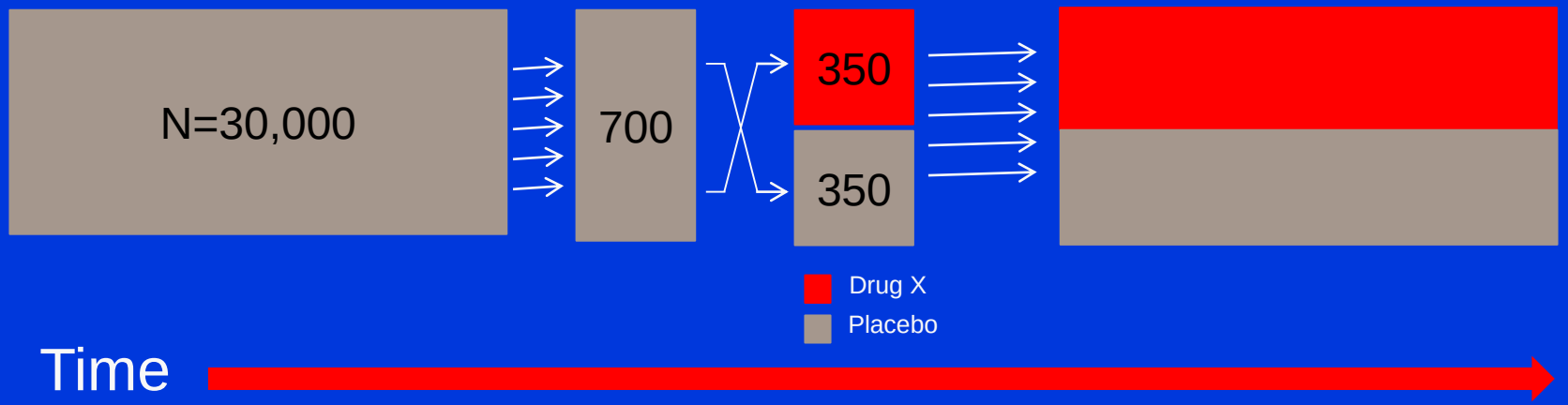
- EMA
- Pharma
- Clinicians
- Epidemiologists / Statisticians
- Patients

The Multicenter, Prospective, Randomised, Controlled Clinical Registry Trial

Clinical registry with measures of patient baseline characteristics

Patient Subgroup Selection & Randomization

Follow-up of Patient Outcomes using Patient Registry



The Multicenter, Prospective, Randomised, Controlled Clinical Registry Trial

Advantages

- Considerable savings
  - TASTE $50 per patient
- Increases ability to study more medications
- Supports & Promotes use and value of Registries
- Real-world assessments of baseline characteristics
- Opportunity to study populations difficult to recruit into RCT

Disadvantages

- Missing data fields
- Quality of data
- Choice of population to study
- Blinding?
- Standardization of measures and outcomes

Requirements for Using Registries for Clinical Trials

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

Public-Private Partnership
Co-founded by Duke University & FDA
Involves all stakeholders
80+ members

MISSION: To develop and drive adoption of practices that will increase the quality and efficiency of clinical trials

https://www.ctti-clinicaltrials.org/

Requirements for Using Registries for Clinical Trials

https://www.ctti-clinicaltrials.org/

Requirements for Using Registries for Clinical Trials

1. RELEVANCE
2. ROBUSTNESS
3. RELIABILITY
4. PATIENT PRIVACY

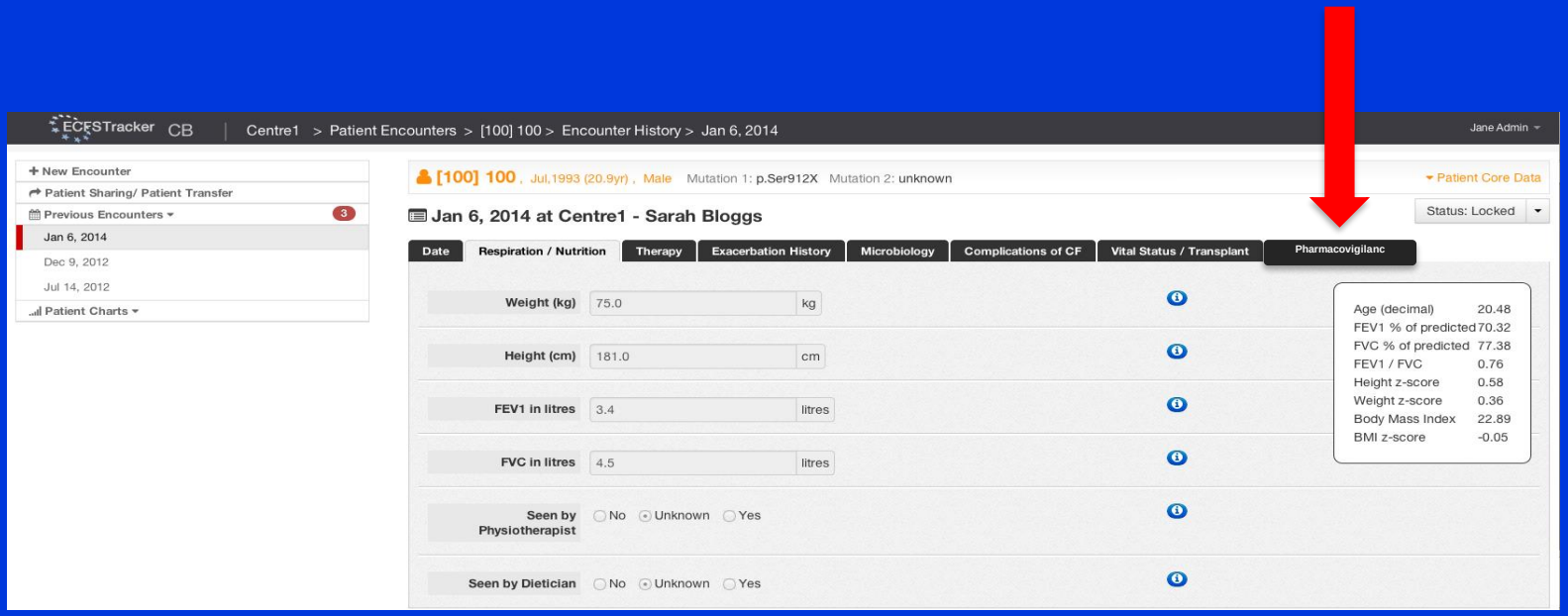
Post-approval Phase IV Studies and CF Registries

OPTIONS

1. Extension studies to RCT - “Open label study”
2. New Drug Safety/Efficacy Phase IV Product Specific Registry developed and maintained by Industry
3. Use of Existing Clinical Registries

The “Hybrid” Phase IV/Registry Trial

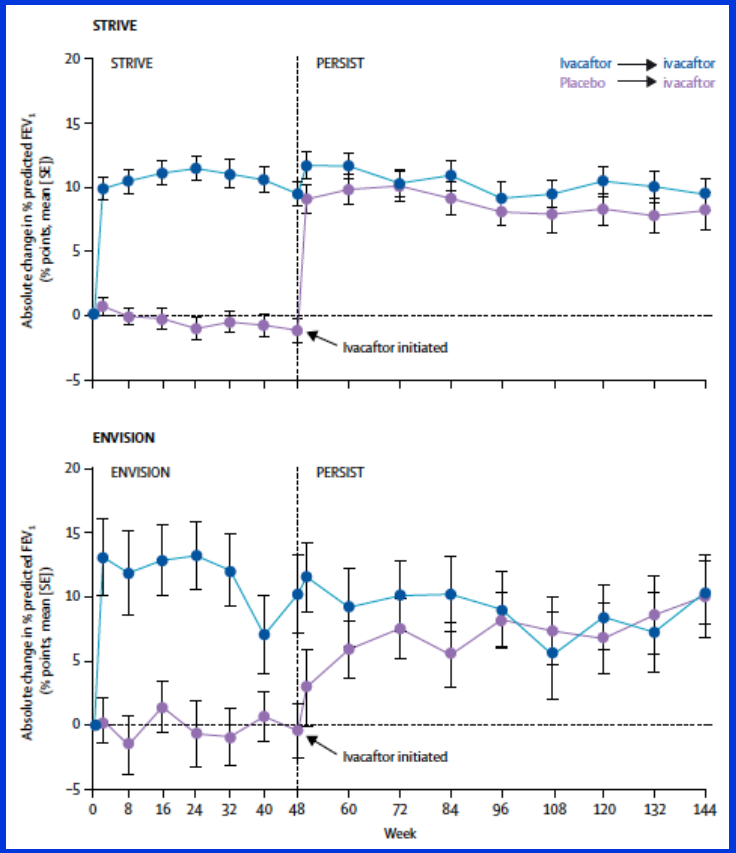
- Registry Software can be adapted to include modules suitable for monitoring new drug safety and efficacy
  - Need early discussion between Industry/Registries regarding feasibility
  - Contains PRO, specific ADRs (ECG/LFTs etc.)
  - Can be used within the structures of a monitored post-approval trial



Real World Registry Studies
How well do they work?

Example - Ivacaftor Open Label Trail

- Open-Label - 144 weeks
- Lung Function Sustained over 144 weeks
  - ~9% increase
- Exacerbation frequency remained lower than placebo
  - ~0.5-0.7 per year v 1.3



McKone et al. Lancet Resp Med. 2014

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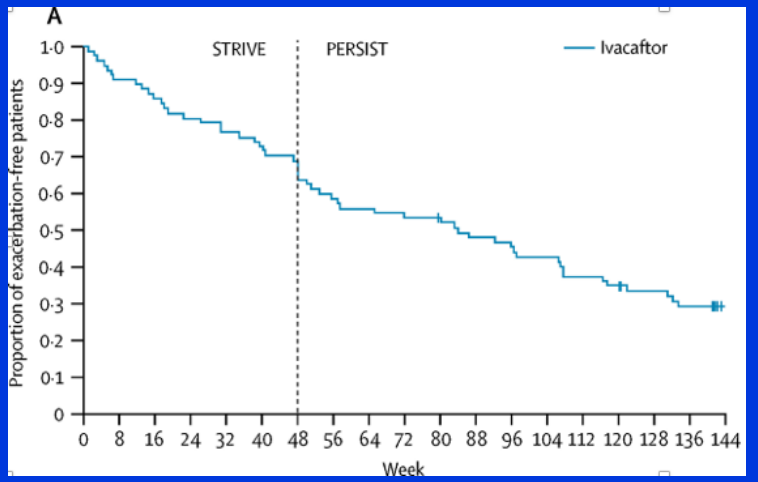

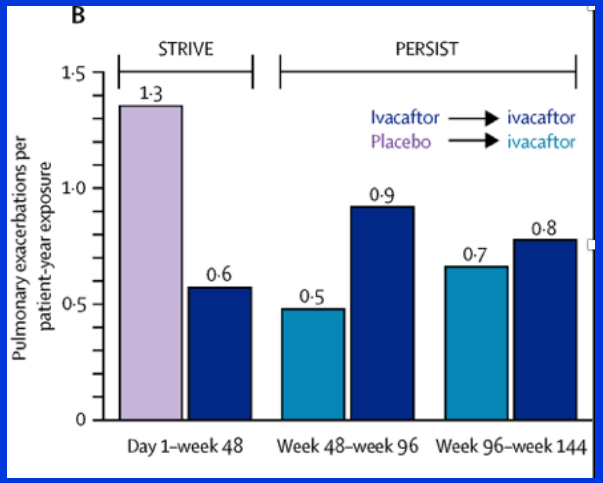

McKone et al. Lancet Resp Med. 2014

Conclusions

- CF registries have great potential and value for:
  - post-approval studies of newly approved CF therapies
  - phase lll clinical trials
  - n=1 trial designs

- Early interaction with all stakeholders is essential to maximise effective use of registries for phase lll and post-approval pharmacovigilance studies