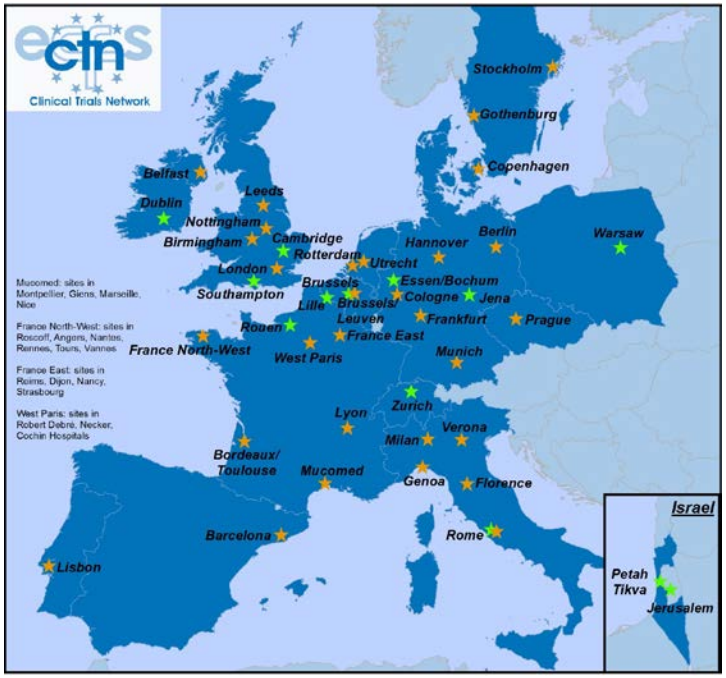
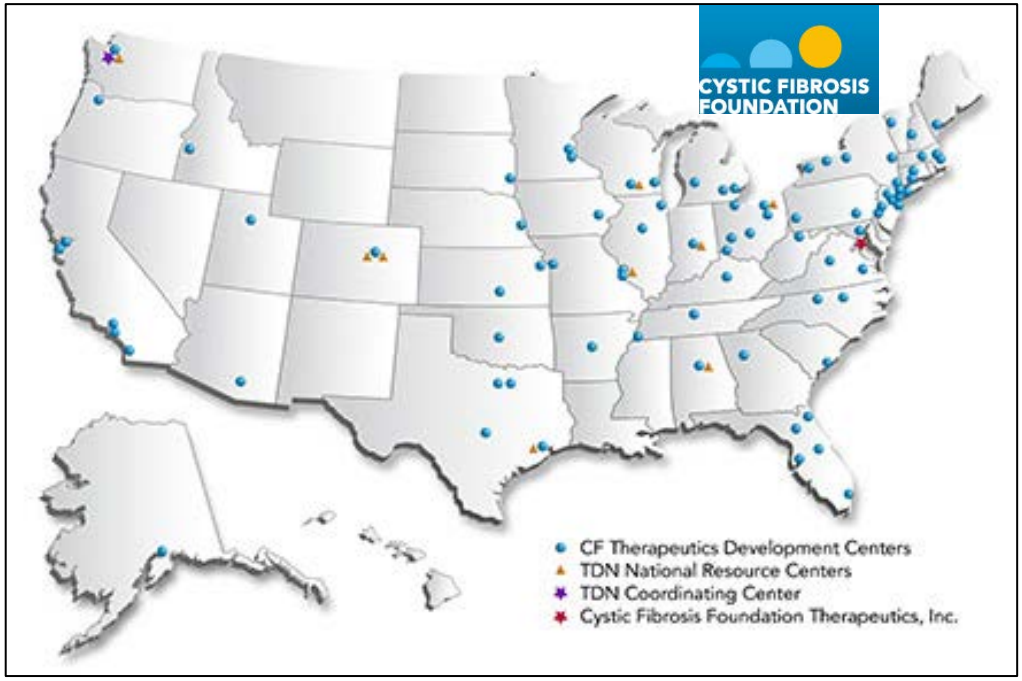




ECFS-CTN Perspective:

Interaction with Investigators – Sponsors - Regulators

Update for EnprEMA Meeting, May 16th, 2017

Tim Lee, ECFS-CTN Director

ecfs ctn
Clinical Trials Network

How do the Clinical Trial Networks add value?

- Experts in delivering clinical trials in the population in question (country and/or disease specific) – especially feasibility
- Know best countries/sites for specific study requirements
- Dealing with whole pipeline – see full context (although much of this will be confidential)
- Involve patients in prioritisation/feasibility
- No conflict of interest (other than wanting best outcome for patients)

Cystic Fibrosis Landscape

- A rare disease (75,000 affected worldwide)
- Life shortening (current UK predicted life expectancy 45.1 years[1] improving rapidly)
- Current very active pipeline from multiple pharma
  - CFTR modulator drugs (potential for considerable gains in life expectancy)
  - Mucolytics to reduce chest infections/scarring
  - Improved antibiotics including inhaled therapies
  - Anti-inflammatories to reduce lung scarring
  - Treatments for pancreatic/liver/GI disease seen in CF
- CFTR modulator drugs approved so far very expensive, not available in many countries

1) UK CF Registry 2016

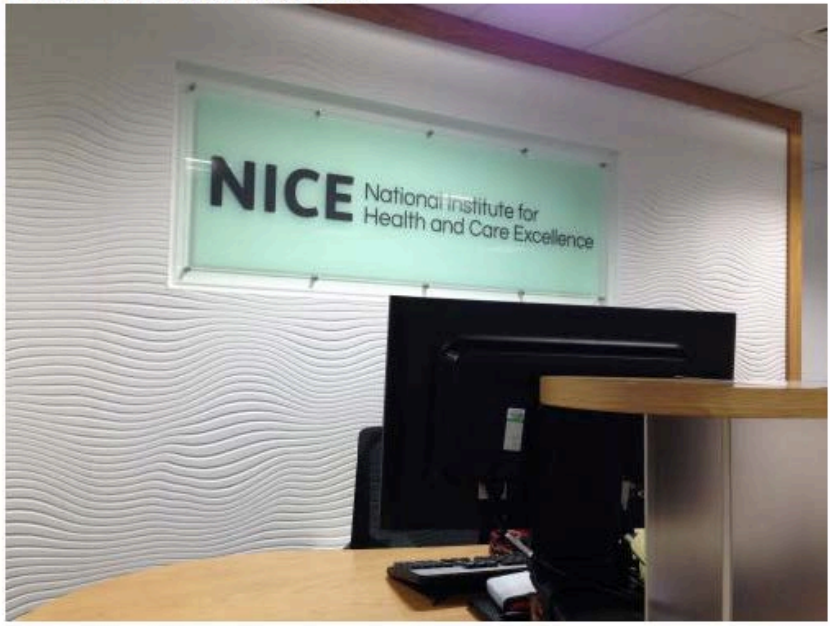
Clinical Trials Network

Current challenges (1)

- In a rare disease drug development costs can rapidly lead to new drugs being unaffordable for some Healthcare Providers

Final Nice appraisal says no to cystic fibrosis drug, Orkambi

Published on 17/06/16 at 08:21am



The National Institute for Health and Care Excellence (Nice) has issued a final appraisal determination rejecting cystic fibrosis drug, Orkambi (lumacaftor/ivacaftor), which is developed by Vertex Pharmaceuticals.

Despite describing it as a "valuable new therapy for managing cystic fibrosis", the drug will not be made available to patients on the NHS in England. The drug is indicated for people with cystic fibrosis aged 12 and over who have two copies of the F508del mutation.

http://www.pharmafile.com/news/503575/nice-draft-guidance-says-no-cystic-fibrosis-drug-orkambi

THE TIMES SUBSCRIBE

German deal sets high price for Orkambi

Aaron Rogan

January 30 2017, 12:01am, The Times

The HSE is negotiating with the makers of the cystic fibrosis drug but hopes are slim of negotiating an acceptable price

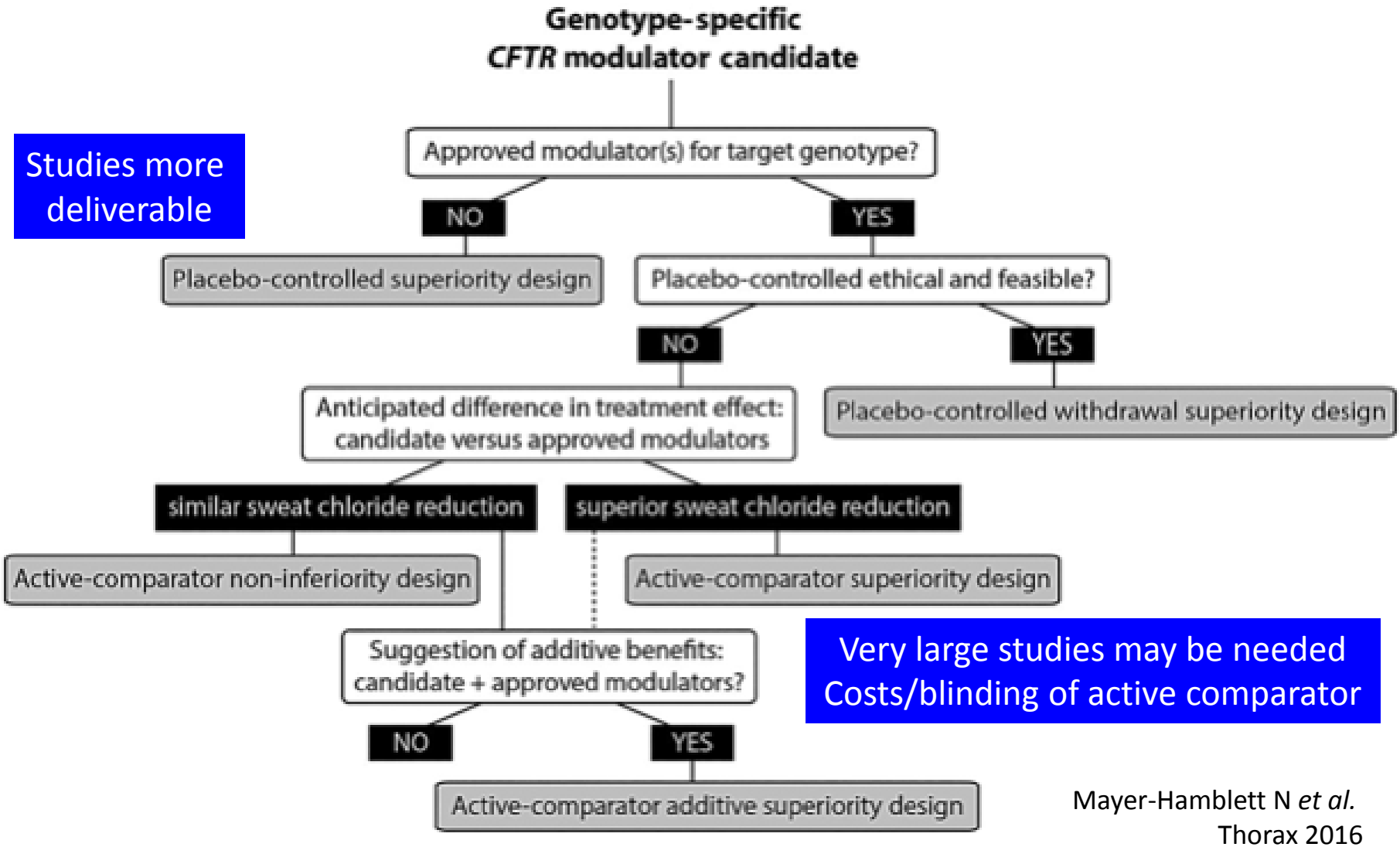
LEAH FARRELL/ROLLINGNEWS

There are unlikely to be any "drastic price cuts" in Ireland for Orkambi, the cystic fibrosis drug, after German negotiators secured only a 15 per cent discount, according to market sources.

Analysis of the German deal by Jefferies, the New York investment firm, revealed that Vertex, the Boston-based pharmaceutical company, agreed a "reasonably modest" reduction to about €133,000 per patient per year.

https://www.thetimes.co.uk/article/german-deal-sets-high-price-for-orkambi-pkkls0lc8

Current Challenges (2):We need a worldwide CF clinical trials strategy in age of CFTR modulators



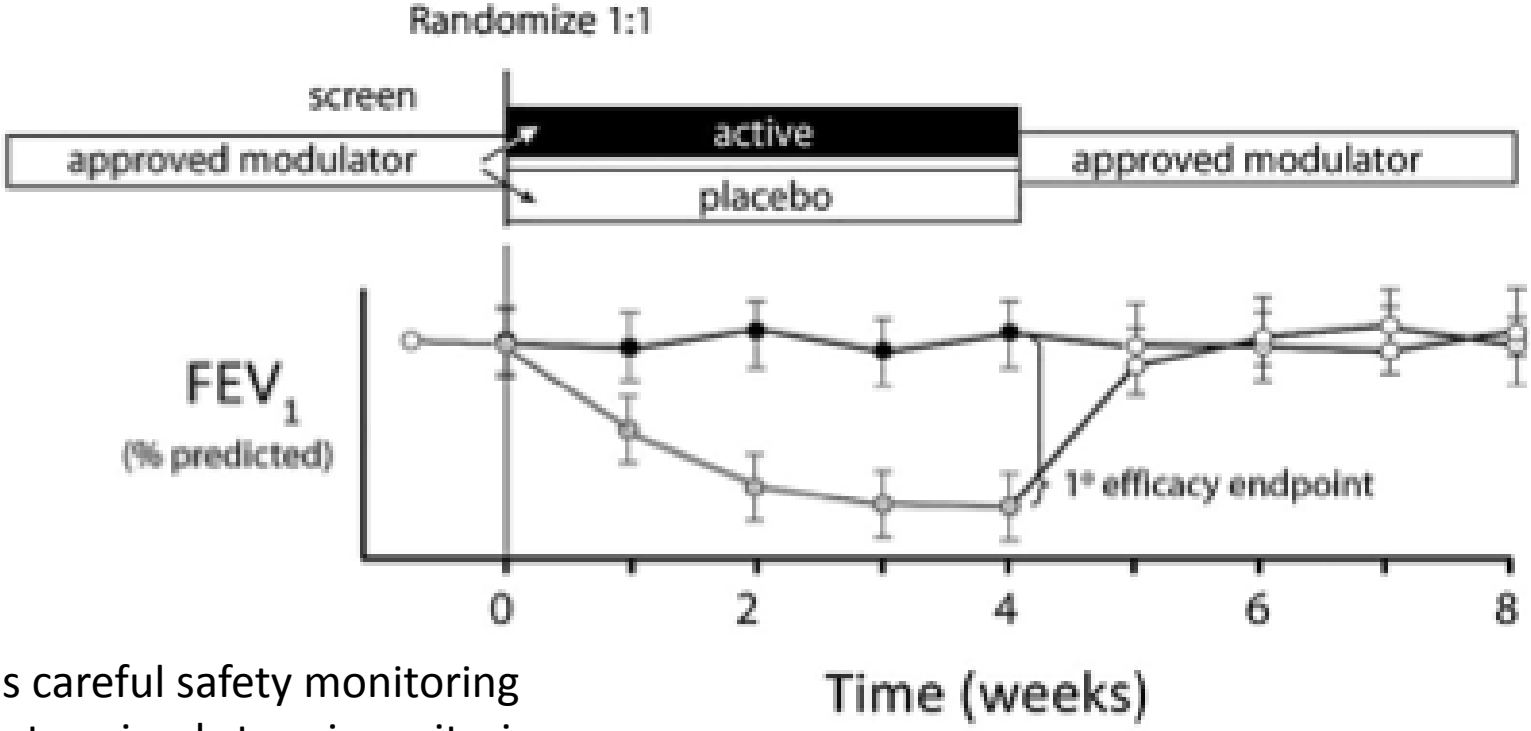
Studies more deliverable

Very large studies may be needed
Costs/blinding of active comparator

Mayer-Hamblett N *et al.*
Thorax 2016

Alternative study designs:

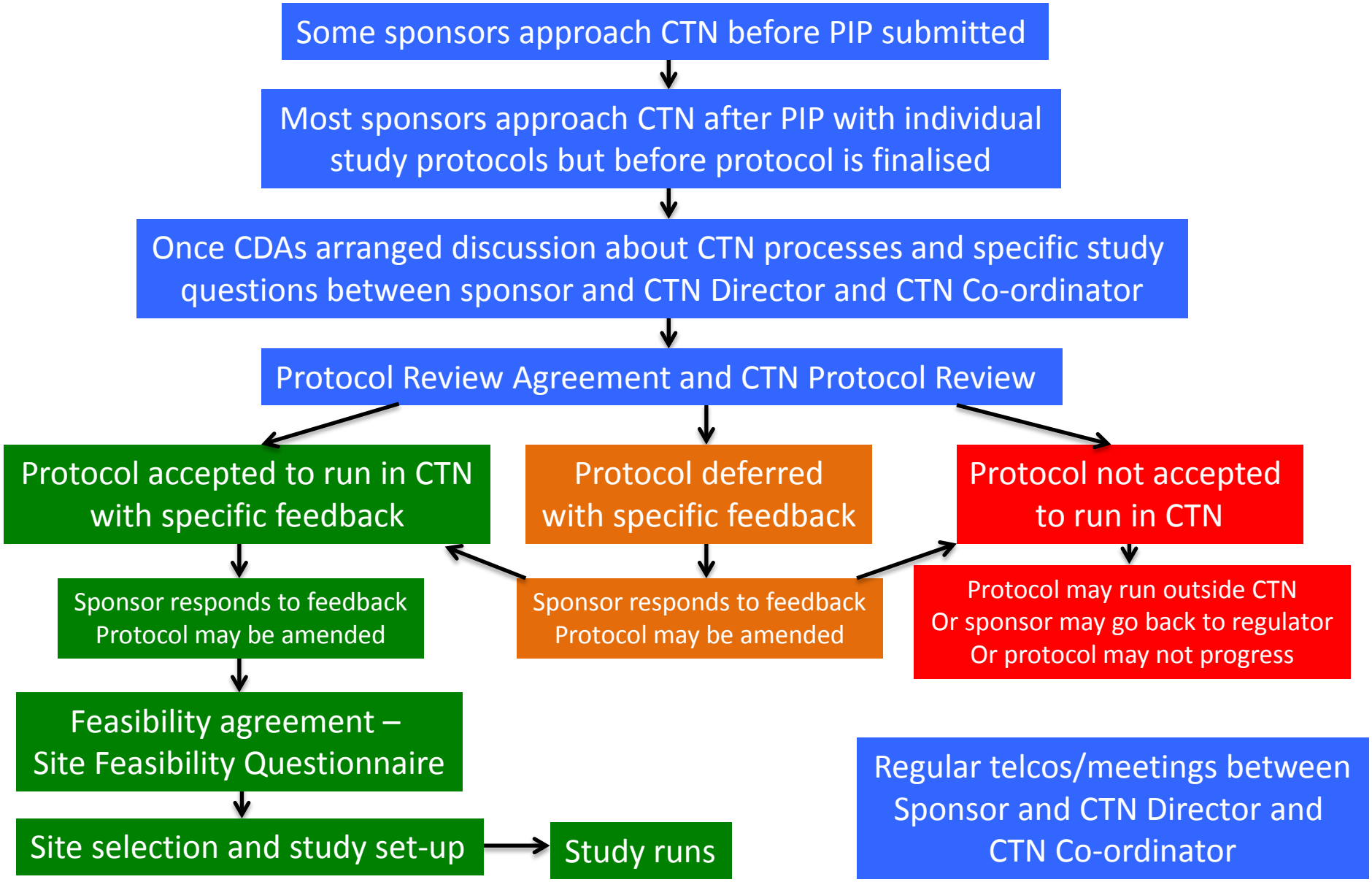
- For example: 1 month withdrawal from standard of care modulator



Needs careful safety monitoring
Pre-determined stopping criteria

Mayer-Hamblett N *et al.* Thorax 2016

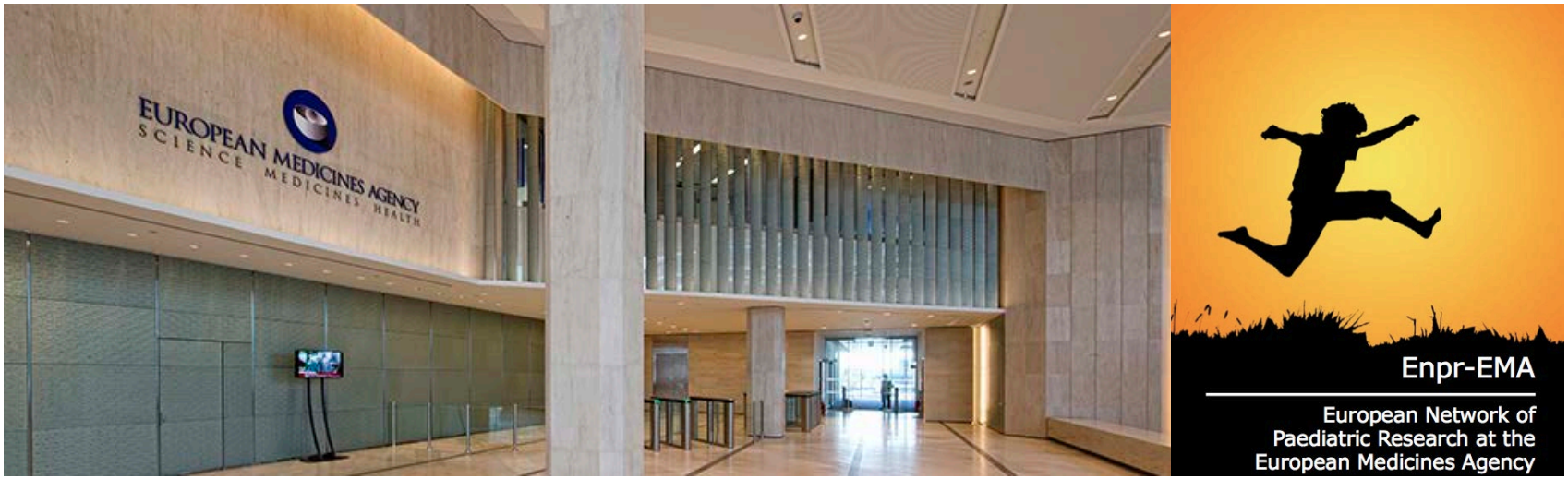
Sponsor – ECFS-CTN Interaction



Advocacy for patients to sponsors– examples

- Guaranteed Enrollment Plan for Sites – across most CFTR modulator studies
- Anti-inflammatory study: Request for further safety data
- Infant study: Request for data showing effect on lung development
- Successful lobbying that subjects involved in early CFTR modulator studies should not be excluded from later studies
- Protocol feasibility – impact on work and school attendance - endpoints that are minimally disruptive/unpleasant
- Speed of safety reporting back to sites
- Improving Screening experience and efficiency eg genotype reporting
- Suggesting Registry type studies are conducted by existing Registries
- Advised sponsors on concerns about ultimate drug costs

Interactions with Regulators



- Participation in EMA workshop to standardise outcome measures and priorities for CF Clinical Trials – and ongoing general advice/consultation (both ways)
  - Importance of In Vitro assays on Intestinal Organoids for predicting response for CF patients with rare CF mutations
- Responsed to EMA scoping Document Revision of Guideline on Clinical Development of New Treatments for people with Cystic Fibrosis (CHMP/EWP/9147/08) and encouraged responses from other stakeholders (eg Sponsors; Patient Organisations; US Cystic Fibrosis Foundation Therapeutics Development Network).
- Liaise with US Cystic Fibrosis Foundation Therapeutics Development Network over interactions with FDA
- Regularly invite speakers with regulatory expertise to our ECFS-CTN Steerco meetings to discuss changing landscape and strategic priorities
- Involvement in Enpr-EMA committees and working groups

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ECFS-CTN – Thank you

Clinical Trials Network

ECFS-CTN Site Leads, Basel June 2017

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