

BRONCHIECTASIS

Networks and Pipelines

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Aims

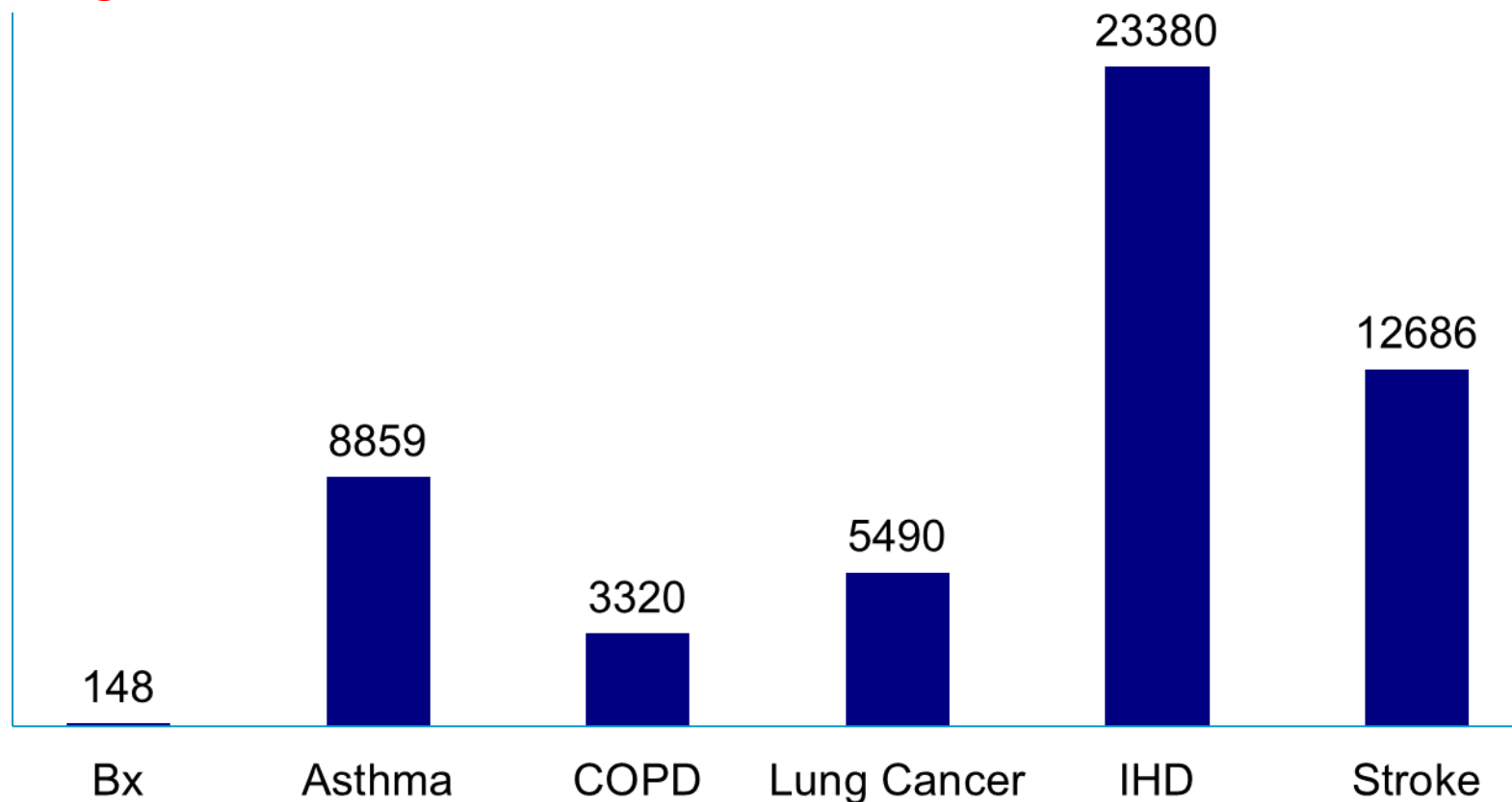
- Update on developments in Bronchiectasis
 - Infrastructures supporting R&D
- Pipelines of new studies & therapies



Why we need to advance knowledge in bronchiectasis care

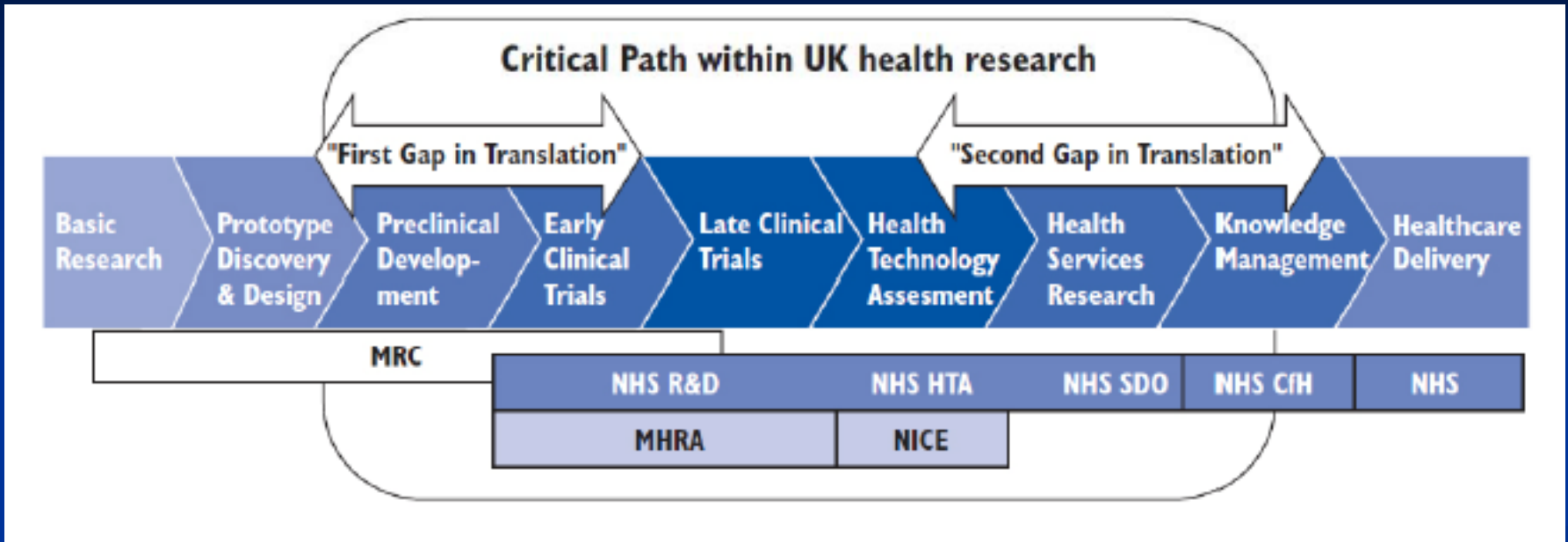
Courtesy A Hill
Edinburgh

RCTs



Our challenges

- It's a rare disease That isn't rare
 - CPRD database prevalence estimates = 0.3%
 - It's a heterogeneous disease that is probably no more heterogeneous than asthma or COPD
- We don't have a patient focus group lobbying as per CF
- Single centre approaches....



Basic scientists

Clinical trialists

Pharma

Clinical Champions

Patients

Networks

- Ideal network will have at minimum:
 - patients, clinicians, industry and basic science links
- US Registry- network of centres
- Spanish network- FACED prognostic score
- Australian network -BLESS trial- registry in set up
- German network- Tobias Welte
- Dutch network- BAT trial- registry ??

BronchUK

- Aims
 - Registry, Biobank, Attract and Design Trials
 - Prognostic models and Health Economic data
- MRC funded 9 centre recruiting 1500 pts and following up over 3-4 years
 - Clinical and basic scientists
 - PPI input
- 5 co funding pharma partners
 - Forest, Bayer, GSK, AZ, Chiesi



BRONCH-UK

The UK bronchiectasis network and biobank



BRONCH-UK
The National Bronchiectasis Network



- Microbiology – J Foweraker
- Physio- Judy Bradley
- Immunology- P Kelleher
- Mucus- J Pearson
- Genetics- B Cookson
- Epidemiology- R Hubbard/ V Navaratnam
- Health Econ- A McGuire
- Pseudomonas – Craig Winstanley & links to 1000 Pseudomonas genomes project

EMBARC

- ERS guidelines and task force committee
- Registry element (shared data platform)
- Cross europe including Eastern Europe
 - Already recruiting



EMBARC

The European Bronchiectasis Registry

Login ▾

www.bronchiectasis.eu

Home

About EMBARC ▾

NEWS

RESEARCH ▾

EDUCATION ▾

EMBARC Registry



Developing the next generation of treatments requires multinational co-operation and co-ordination. Bronchiectasis has historically been a neglected "Orphan" disease. An international network will build capacity to perform high impact clinical trials and observational studies in bronchiectasis

EMBARC is a pan-European network committed to promoting clinical research and education in bronchiectasis, through sharing of protocols, research idea and expertise. Central to this project is the creation of the European Bronchiectasis Registry, a collaboration open to all investigators around Europe caring for patients with bronchiectasis.

Derivation and multi centre validation of the Bronchiectasis severity index

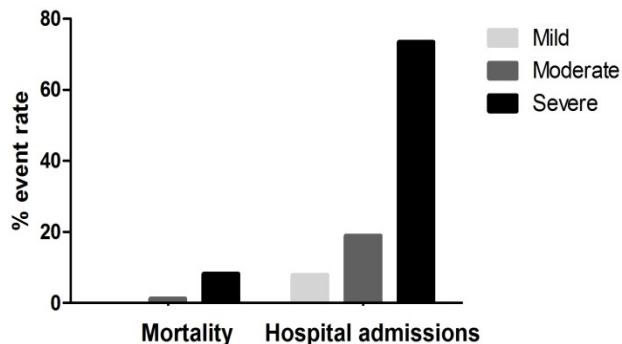
- Prospective Study Edinburgh 2008-2012
- 608 patients “derivation cohort”
- Identify independent predictors of mortality and hospitalisation over 4 years

- Validated in independent cohorts
Dundee(N=128),m Leuven (N=252),
Monza(N=105) Newcastle (N=126)

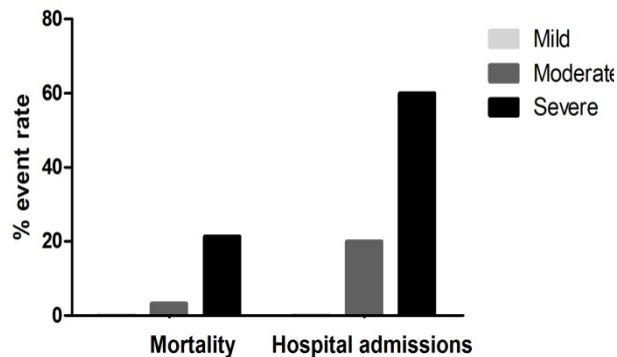
Chalmers, Aliberti.Dupont,
Goemminne, De Soyza, Hill et al
AJRCCM 2014

Bronchiectasis severity scores

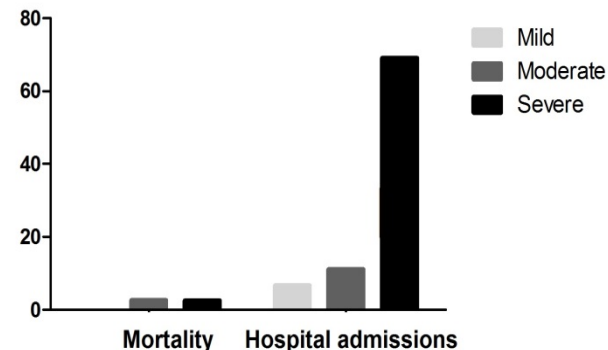
Dundee cohort



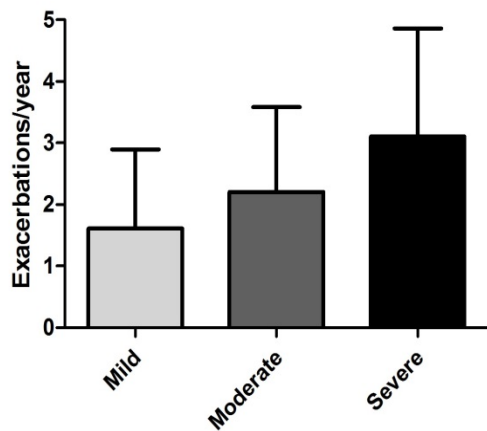
Newcastle cohort



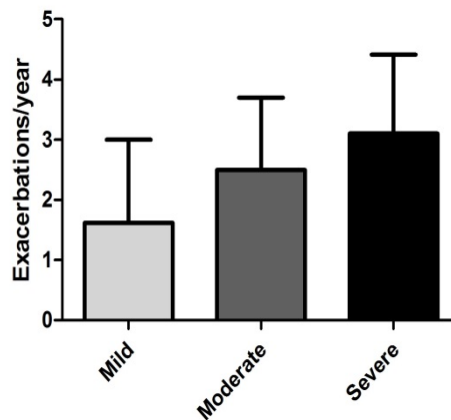
Monza cohort



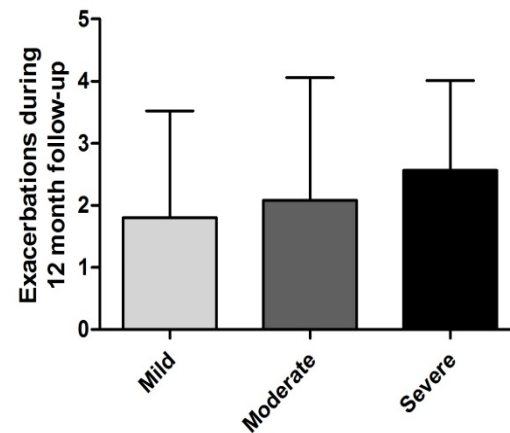
Dundee cohort-exacerbations



Newcastle cohort-exacerbations



Monza cohort-exacerbations



Innovative Medicines Initiative (IMI)

- EU Funded
- Private-Public partnership
- Novartis & Basilea (SME) with a trans-EU CF and Bronchiectasis initiative
 - Microbiology repository
 - CF trials network as model
 - EU registry (EMBARC)
 - Phase II and phase III studies (TiP in bronchiectasis)

Networks

- National Institute for Health Research (NIHR)

Academic arm

- Funders- Recently HTA commissioned call for nebulised ABX in bronchiectasis
- RfPB – Bronchiectasis Empowerment Tool

Infrastructure arm- CLRNS, LRNS and research facilitation

- =UK is a lead destination for new therapies to be developed and / or tested

Updated Study Timelines

- Last Subject Screened: 10 April 2014
- Last Subject Randomized: 17 April 2014
- Last Subject Last visit: 16 June 2014
- Database lock: 14 July 2014

Enrolment Update

Country	Total # of sites	# Actives sites	# sites with enrolled patients	# Patients screened	# Patients in screening	# Patients Screen failed	# Patients Randomized
Germany	8	8	7	22	0	9	13
Italy	6	5	6	25	0	7	18
Spain	3	2	2	19	0	10	9
UK	12	11	12	75	0	21	54
TOTAL	29	26	27	141	0	47	94

We are pleased to inform you that the randomization period was closed on 21 April 2014, according to the timelines. Thanks to your hard work, we have managed to reach and exceed our target with a total of 94 patients

So what does this all mean?

- There will be several compatible datasets across Europe/ Globe
 - Patients will be collected into registries (prognostic modelling, benchmarking, trials feasibility)
 - Biobanks and health economic data sets will allow
 - Genetics
 - Microbiology
- Massive step forwards for academic and pharma investment

BR 2010-guidelines

BTS guidelines

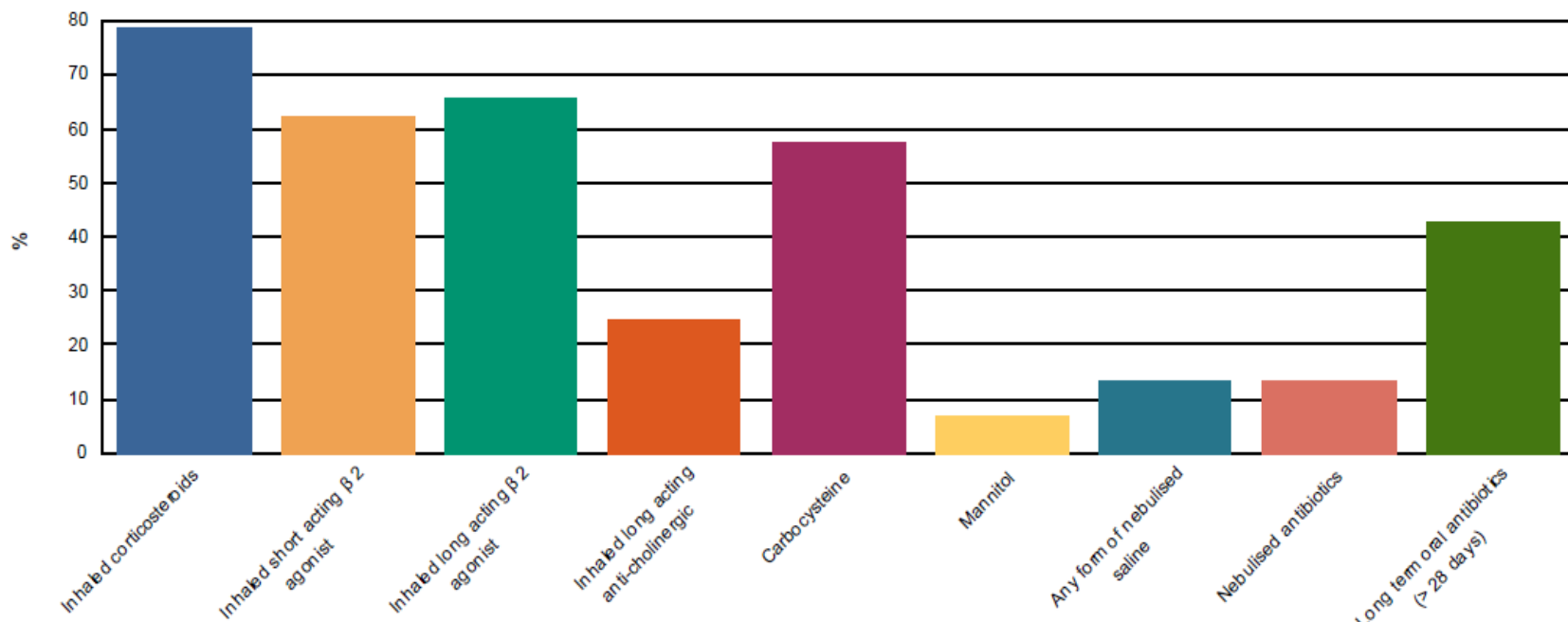
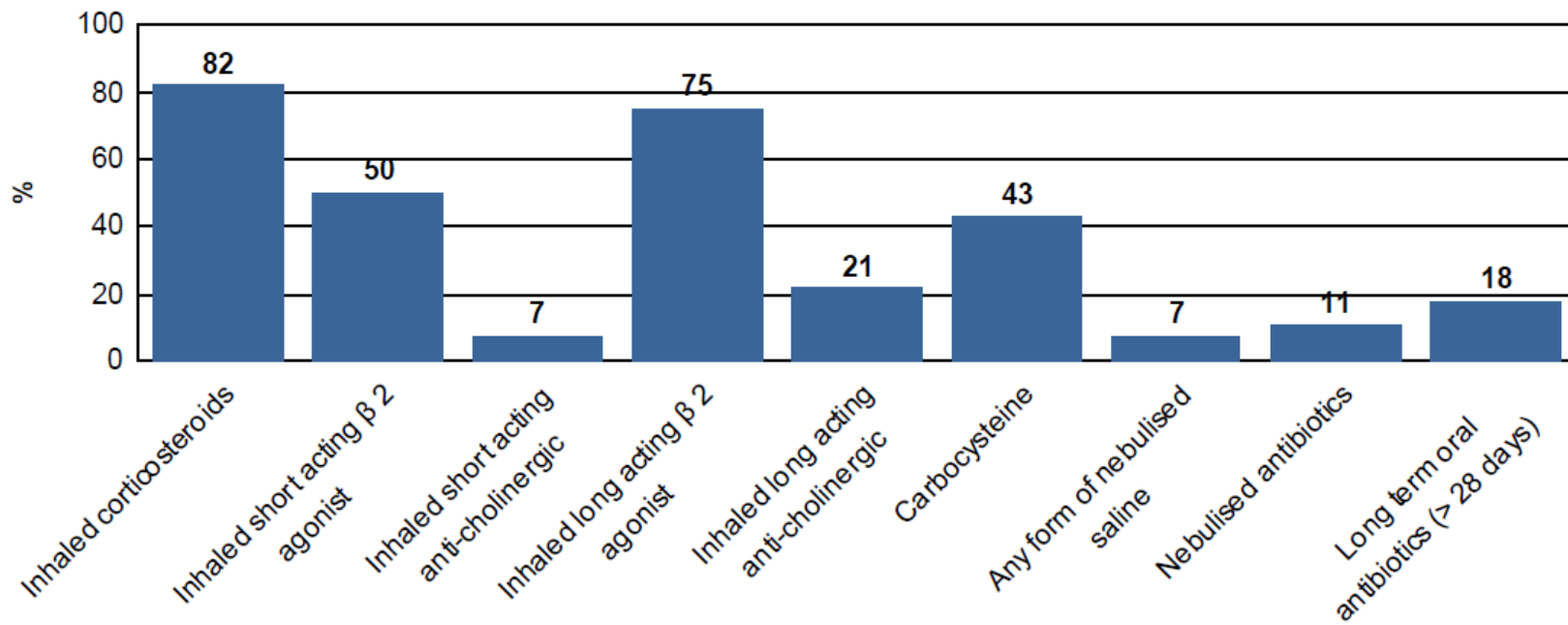
APPENDIX 3: AUDIT CRITERIA AND RESEARCH QUESTIONS

Audit criteria

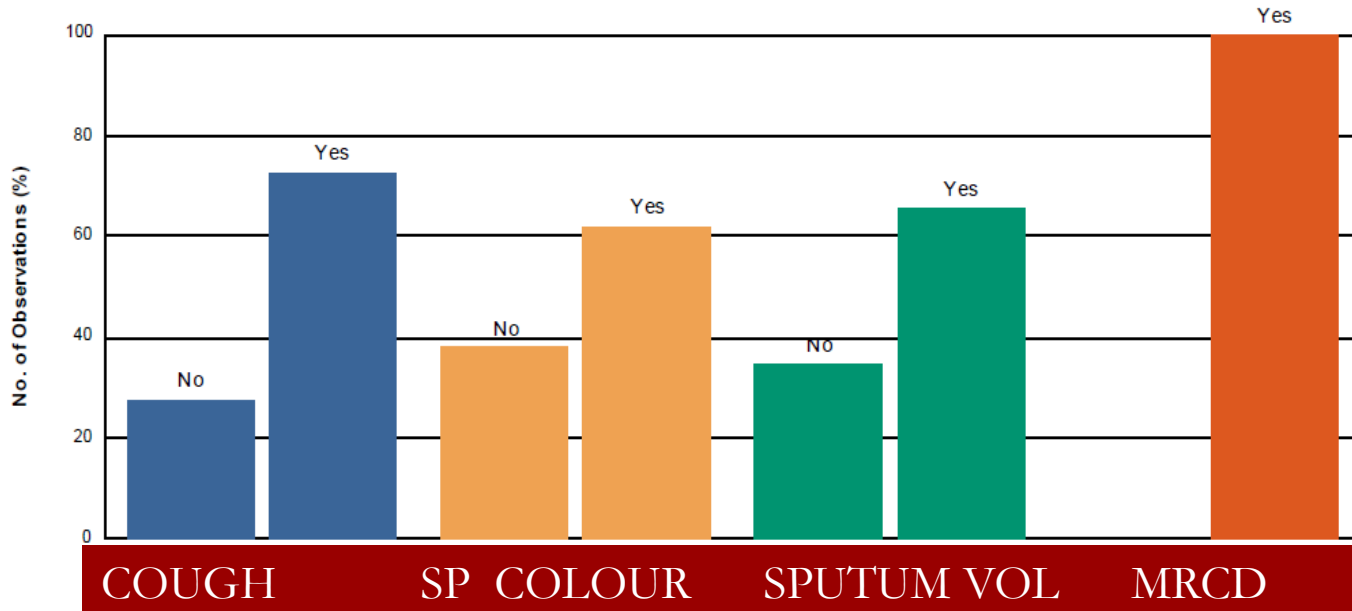
- ▶ All patients should be assessed for underlying cause(s).
- ▶ Sputum microbiology should be checked prior to antibiotics being given for exacerbations.

Summary of research recommendations

- ▶ Further studies are required to establish the link between COPD and bronchiectasis.
- ▶ Further studies in other connective tissue diseases are indicated.
- ▶ Use of carbocysteine in bronchiectasis should be the subject of a randomised control trial to establish its clinical efficacy.
- ▶ Mannitol should be investigated further in a randomised controlled trial.
- ▶ A large randomised controlled trial is required to assess the role of inhaled corticosteroids in bronchiectasis.

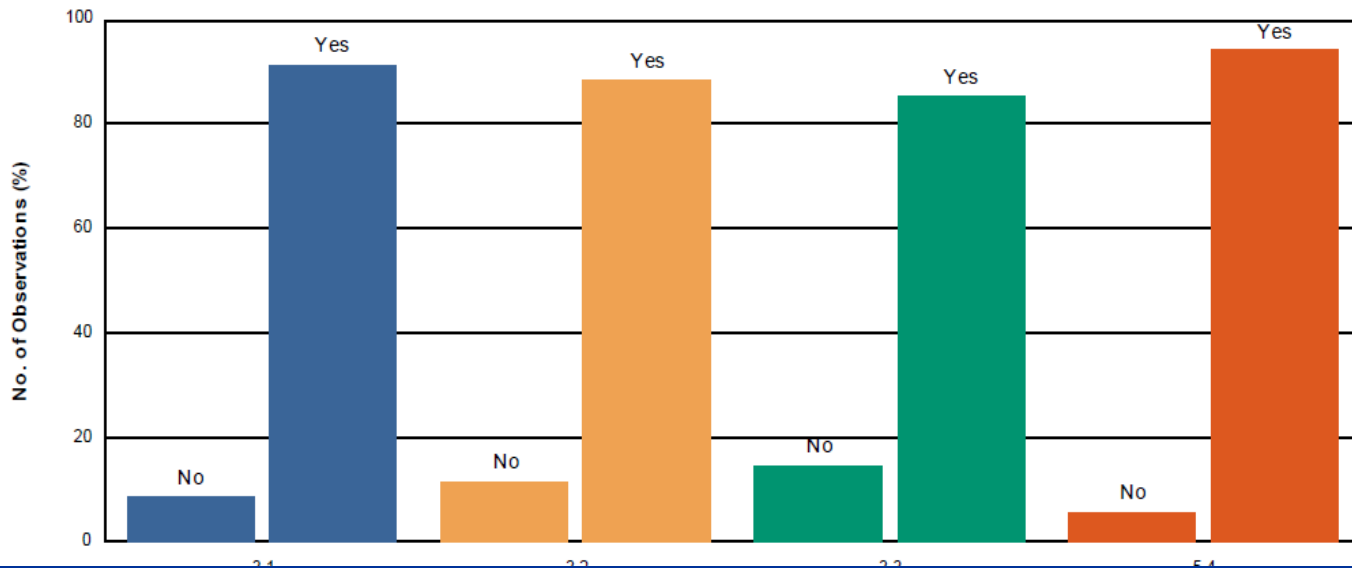


Period 1 - 29 Observations



Recording
in itself
drives
behaviour
change

Period 2 - 68 Observations



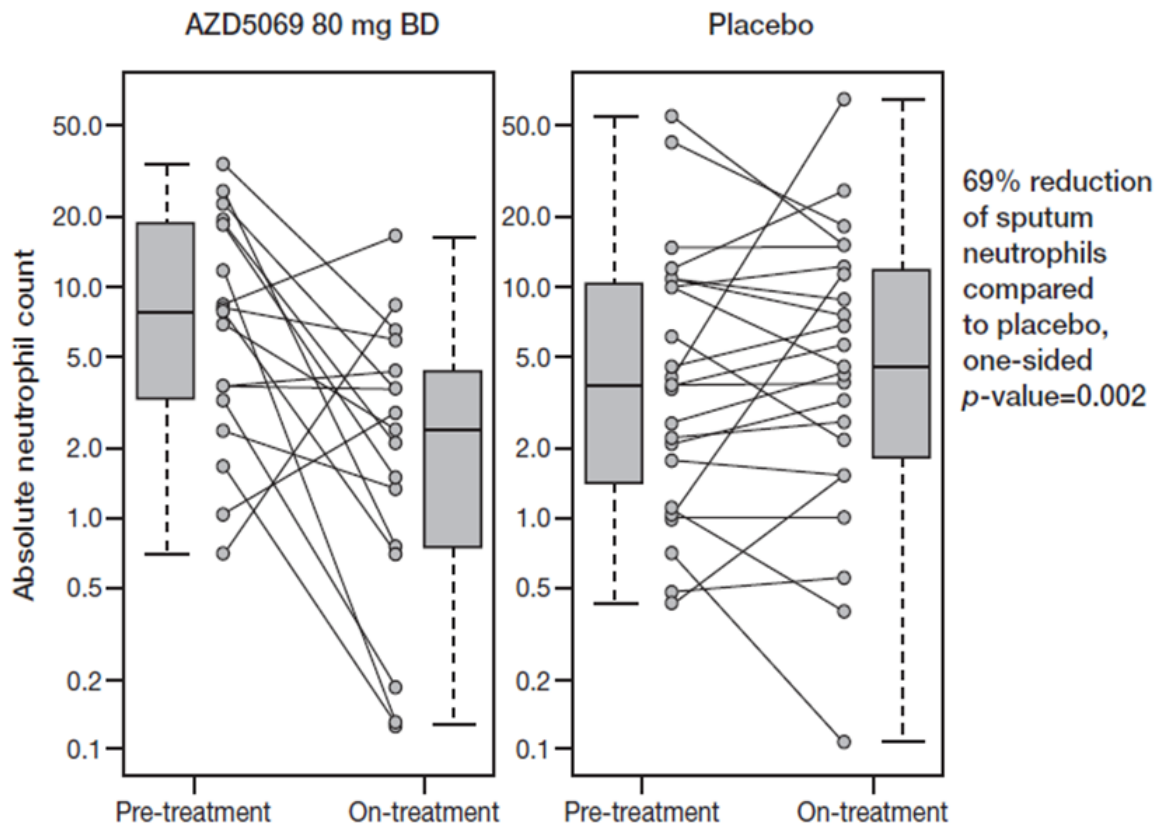
Where will this take us?

- Patient stratification
 - Opportunity to network with Asthma and COPD experts
 - BCOS and BAOS overlap syndromes
- Better trials design and outcome measures
- Database that supports day to day clinical care
(?)

Anti-inflammatory Pipelines

- Inflammation
 - Neutrophil targeting (elastase inhibition, CXCR2, apoptosis)
 - Macrolides
 - Cytokine targeting
 - Other- Theophyllines

CXCR2 inhibition drops sputum neutrophils- AZD 5069



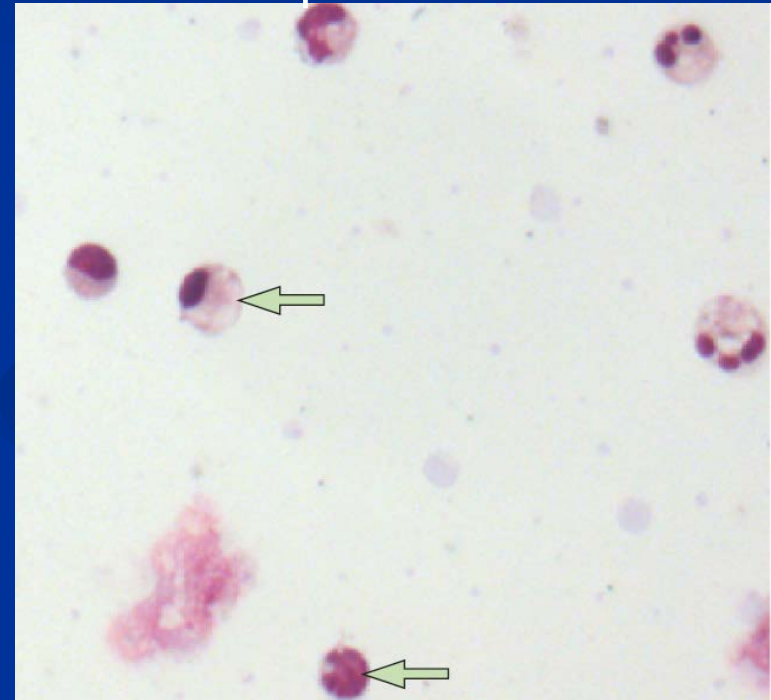
- Good- trends towards better SGRQ
- Bad (?)-
 - rise in systemic IL-8
 - Increase in infections ?

De Soyza, Stockley, Elborn, Pavord *et al* under review

Statins may affect neutrophils in bronchiectasis

- DB-RCT Atorvastatin 80mg OD vs placebo
 - N=30 each arm
- LCQ improved
- IL-8 and CRP fell vs. placebo

Mandal *et al* Lancet RespMed 2014



Pipelines- anti-infectives

- Ciprofloxacin
 - Nebulised liposomal (Aradigm) phase III
 - Dpi Cipro (Bayer)- phase III
- Tobramycin (DriPod- Novartis)- IMI study?
- Colistin –
 - Promixin via iNeb
 - Colistin dri powder inhaler (ColoBreathe)?
- Aminoglycosides and Hyaluronate ?
- Vaccines (Haemophilus, Strep & others?)

Pipelines

■ Mucus

- Mannitol- Thorax Dec 2014 “negative trial”-
 - Responder population seen in post hoc analysis
- Hyaluronate ?
- Oral Mucolytics

What it really means..

- You will have the BEST opportunities ever in bronchiectasis to
 - Collaborate
 - Recruit patients into registries
 - Participate in phase II and phase III trials
- Move from empirical therapy to evidence based treatments

Thanks



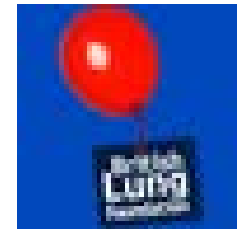
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UKRRC



Patients

Pharma collaborators

