Pulmonary Fibrosis – A Clinical Update

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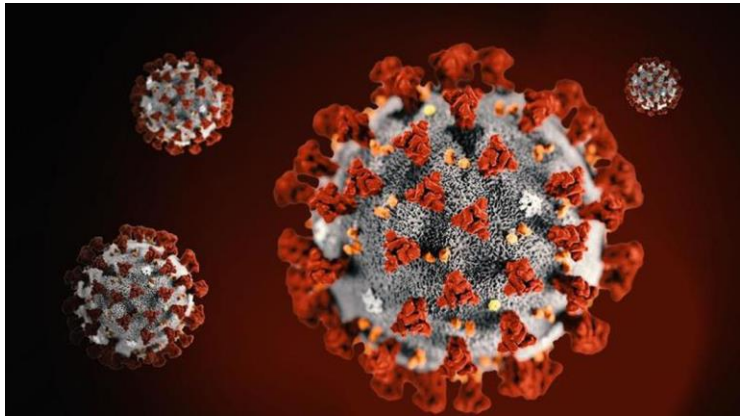
Disclosures:

- Educational grants to attend conferences from Boehringer Ingelheim, Chiesi, GlaxoSmithKlein, Intermune.
- Project grants from Intermune, BI
- Advisory board Intermune, BI and Roche.

Objectives



Guidelines

2 Sarcoid Guidelines!!
2 HSP Guidelines!!
Home Oxygen
Cryobiopsy
Apr 22 – LCH
May 22 – IPF/PPF

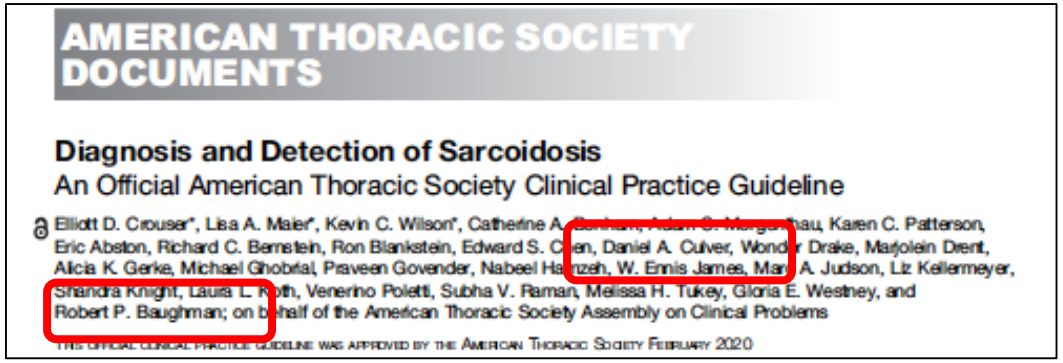
Clinical Trials
Of
Treatments

>10 RCTs!!

Guidelines:

- **ERS clinical practice guidelines on treatment of sarcoidosis.**
- **Diagnosis and Detection of Sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline.**
- **Diagnosis of Hypersensitivity Pneumonitis in Adults. An Official ATS/JRS/ALAT Clinic al Practice Guideline.**
- **Diagnosis and Evaluation of Hypersensitivity Pneumonit is: CHEST Guideline and Expert Panel Report.**
- **Home Oxygen Therapy for Adults with Chronic Lung Disease. An Official American Thoracic Society Clinical** Practice Guideline.
- **Transbronchial Cryobiopsy** for the Diagnosis of Interstitial Lung Diseases: **CHEST Guideline and Expert Panel Report.**
- **Idiopathic Pulmonary Fibrosis (Update) and Progressive Pulmonary Fibrosis** in adults **ATS/ERS/JRS/ALAT** Clinical Practice Guideline.
- International Consensus Recommendations for the Diagnosis and Treatment of **Langerhan's Cell Histioc ytosis. Annual Histiocyte Society Meeting 2019**

Sarcoidosis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Diagnosis and Detection of Sarcoidosis
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THIS OFFICIAL CLINICAL PRACTICE GUIDELINE WAS APPROVED BY THE AMERICAN THORACIC SOCIETY FEBRUARY 2020


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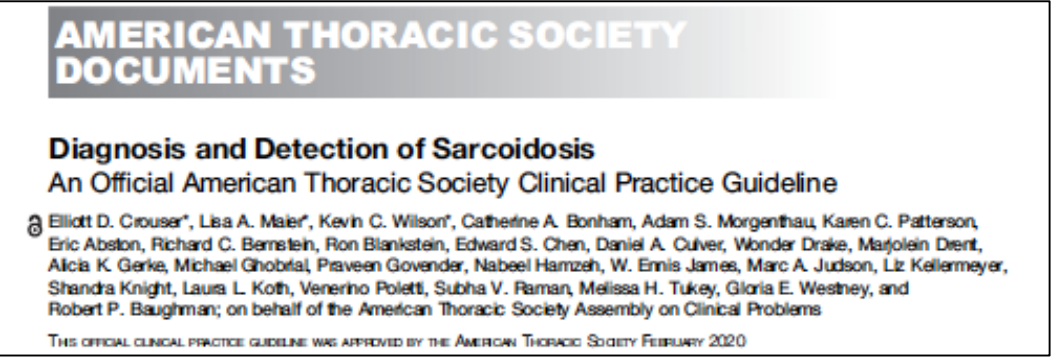
ERS clinical practice guidelines on treatment of sarcoidosis

Robert P. Baughman[1], Dominique Valeyre[2], Peter Korsten[3], Alexander G. Mathioudakis[4], Wim A. Wuyts[5], Athol Wells[6], Paola Rottoli[7], Hiliaro Nunes[8], Elyse E. Lower[9], Marc A. Judson[9], Dominique Israel-Biet[10], Jan C. Grutters[11,12], Marjolein Drent[11,13,14], Daniel A. Culver[15], Francesco Bonella[16], Katerina Antoniou[17], Filippo Martone[18], Bernd Quadder[19], Gisela Spitzer[20], Blin Nagavci[21], Thomy Tonia[22], David Rigau[23] and Daniel R. Ouellette[24]

- Systematic review
- Meta-analysis where appropriate
- GRADE methodology
- 10 Questions
- MDT Review
- **DIAGNOSIS ONLY**

- GRADE Methodology
- 8 PICO questions
- **TREATMENT ONLY**

Due to time – will skip over recommendations that aren't surprising!!



Question 1: Should Lymph Node Sampling Be Performed in a Patient Presenting with Asymptomatic Bilateral Hilar Lymphadenopathy?

2,106 papers
75 reviewed
16 studies in stage 1 disease

- **High Clinical Suspicion of sarcoidosis**
- Lofgrens, Lupus Pernio, Heerfordt syndrome
- **No need to biopsy**
- But close clinical follow up
- Conditional recommendation
- Very low quality

- **Asymptomatic bihilar lymphadenopathy**
- **No recommendation re LNS**
- Case by Case basis
- Consider regional prevalence of TB, patient risk factors for malignancy, Patients risks of complications; patient preference

16 Studies	**556 patients**	**Stage 1 disease**	**85% Sarcoidosis** **1.9% Alternative Diagnosis (38% TB; 25% Lymphoma)** **11% Non Diagnostic**

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Question 2: Should Patients with Suspected Sarcoidosis and Mediastinal and/or Hilar Lymphadenopathy, for Whom It Has Been Determined That Tissue Sampling Is Necessary, Undergo EBUS-guided Lymph Node Sampling or Mediastinoscopy as the Initial Mediastinal and/or Hilar Lymph Node Sampling Procedure?

703 papers
64 reviewed
29 studies
No head to head comparison

EBUS	**87% Diagnostic Yield** (98% Sarcoid and 2% Alternative)	<0.1% Complication
Mediastinoscopy	**98% Diagnostic Yield** (91% sarcoid 9% Reactive)	Only severe complications recorded

- Systematic review of 9 studies and 960 patients
- EBUS versus mediastinoscopy for lung cancer stagi
- Higher complications for mediastinoscopy
- Higher costs

Recommendation.

1. For patients with suspected sarcoidosis and mediastinal and/or hilar lymphadenopathy for whom it has been determined that tissue sampling is necessary, we suggest EBUS-guided lymph node sampling, rather than mediastinoscopy, as the initial mediastinal and/or hilar lymph node sampling procedure (conditional recommendation, very low-quality evidence).

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Question 3: Should Patients with Sarcoidosis Who Do Not Have Ocular Symptoms Undergo Screening for Ocular Sarcoidosis by Routine Eye Examination?

582 papers
25 reviewed
18 studies
None compared eye exam vs no eye exam

- Eye exam identified ocular sarcoid in 26% (95% CI 23-29%) of cases (53% Ant Uveitis)
- Higher than expected – related to studies in patients with ocular symptoms
- 78% with abnormalities had ocular symptoms and required topical or oral steroids – severe.
- In Japanese >50%
- Sight threatening problems
- Treatment could reduce harm
- Eye exam is neither harmful nor burdensome

Recommendation.

1. For patients with sarcoidosis who do not have ocular symptoms, we suggest a baseline eye examination to screen for ocular sarcoidosis (conditional recommendation, very low-quality evidence).

Question 4: Should Patients with Sarcoidosis Who Do Not Have Renal Symptoms Undergo Screening for Renal Sarcoidosis by Routine Serum Creatinine Testing?

- Meta-analysis : abnormal renal function in 7% (95% CI 3-11%)
- 6 of 8 studies reported kidney biopsies – 1-63% granulomas; 0-50% nephrocalcinosis
- Often asymptomatic
- Associated with poor outcomes
- Renal function testing not harmful
- Good response to therapy
- Acknowledged that we don't know whether to do Creatinine or 24hr urine collection but much cheaper to do!
- Annual testing if normal

Recommendation.

1. For patients with sarcoidosis who have neither renal symptoms nor established renal sarcoidosis, we suggest baseline serum creatinine testing to screen for renal sarcoidosis (conditional recommendation, very low-quality evidence).

Question 5: Should Patients with Sarcoidosis Who Do Not Have Hepatic Symptoms Undergo Screening for Hepatic Sarcoidosis by Routine Transaminase and Alkaline Phosphatase Testing?

- Meta-analysis: LFTS abnormal in 12% (95% CI 6-19%)
- Those that had a biopsy granulomas found in 96% - selection bias
- Steroid treatment in 25-95%
- But implications for treatment unclear as cirrhosis and liver failure very rare
- Annual ALP if normal
- No recommendation for transaminases
- Helps avoid hepatotoxic drugs and monitor for symptoms

Recommendations.

1. For patients with sarcoidosis who have neither hepatic symptoms nor established hepatic sarcoidosis, we suggest baseline serum alkaline phosphatase testing to screen for hepatic sarcoidosis (conditional recommendation, very low-quality evidence).
2. For patients with sarcoidosis who have neither hepatic symptoms nor established hepatic sarcoidosis, we make no recommendation for or against baseline serum transaminase testing.

Question 6: Should Patients with Sarcoidosis Who Do Not Have Symptoms or Signs of Hypercalcemia Undergo Screening for Abnormal Calcium Metabolism by Routine Serum Calcium and Vitamin D Testing?

- Hypercalcaemia detected in 6% (95% CI 4-8%)
- Renal failure developing in 42% of untreated patients

Recommendations.

1. For patients with sarcoidosis who do not have symptoms or signs of hypercalcemia, we recommend baseline serum calcium testing to screen for abnormal calcium metabolism (strong recommendation, very low-quality evidence).
2. If assessment of vitamin D metabolism is deemed necessary in a patient with sarcoidosis, such as to determine if vitamin D replacement is indicated, we suggest measuring both 25- and 1,25-OH vitamin D levels before vitamin D replacement (conditional recommendation, very low-quality evidence).

Question 7: Should Patients with Sarcoidosis Undergo Screening for Hematological Abnormalities by Routine Complete Blood Cell Count Testing?

- Anaemia in 22% (95% CI 14-30%) – 38% (95% CI 13-64%) had bone marrow granulomas – common and may contribute to fatigue and SOB
- Leukopenia of <4000 cells/mm in 4% (95% CI 1-7%)
- Leukopenia of <5000 cells/mm in 30% (95% CI 26-34%)
- Lymphopenia varies 27%- 55%
- One study no difference in FBC between healthy versus sarcoid
- Abnormalities often transient

Recommendation.

1. We suggest that patients with sarcoidosis undergo baseline complete blood cell count testing to screen for hematological abnormalities (conditional recommendation, very low-quality evidence).

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Question 8: Should Patients with Sarcoidosis Who Do Not Have Cardiac Symptoms or Signs Undergo Routine Screening for Cardiac Sarcoidosis Using ECG, TTE, or 24-Hour Ambulatory ECG Monitoring?

1212 papers
13 (ECG) 30 (TTE)6 (Holter) reviewed
4 (ECG) 2 (TTE) 2 (Holter) studies
No comparison of testing
Versus no testing

- Cardiac sarcoid unrecognized and could present with sudden death
- Early detection important
- Should ask about palpitations, light headedness, chest pain, syncope
- Only one study assessed ECG, TTE and Holter in one population

- No one test is sensitive enough
- ECG and TTE 32% sensitivity
- TTE and Holter 62% sensitivity

Recommendations.

1. For patients with extracardiac sarcoidosis who do not have cardiac symptoms or signs, we suggest performing baseline ECG to screen for possible cardiac involvement (conditional recommendation, very low-quality evidence).
2. For patients with extracardiac sarcoidosis who *do not have cardiac symptoms or signs*, we suggest NOT performing routine baseline TTE or 24-hour continuous ambulatory ECG (Holter monitor) to screen for possible cardiac involvement (conditional recommendation, very low-quality evidence). *Remarks:* The panel recognizes the low risks attendant to the use of TTE or 24-hour continuous ambulatory ECG (Holter monitor) to screen for cardiac sarcoidosis. Thus, these tests should be considered on a case-by-case basis.

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Question 9: Should Patients Who Are Suspected of Having Cardiac Sarcoidosis Undergo Cardiac MRI, TTE, or PET as an Initial Imaging Test?

2152 papers
45 (CMR) 34 (cPET) 30 (TTE) reviewed
11 (CMR) 6 (cPET) 2 (TTE) studies
No study with all 3

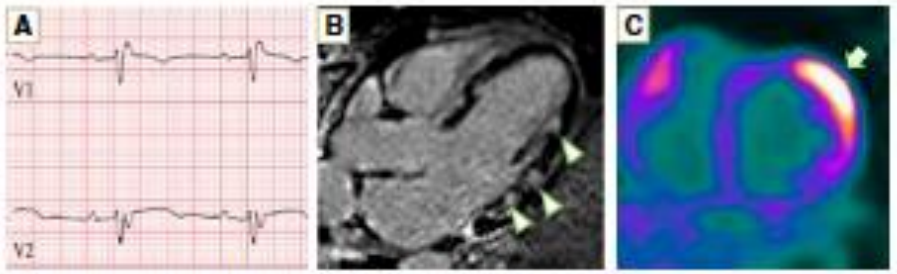


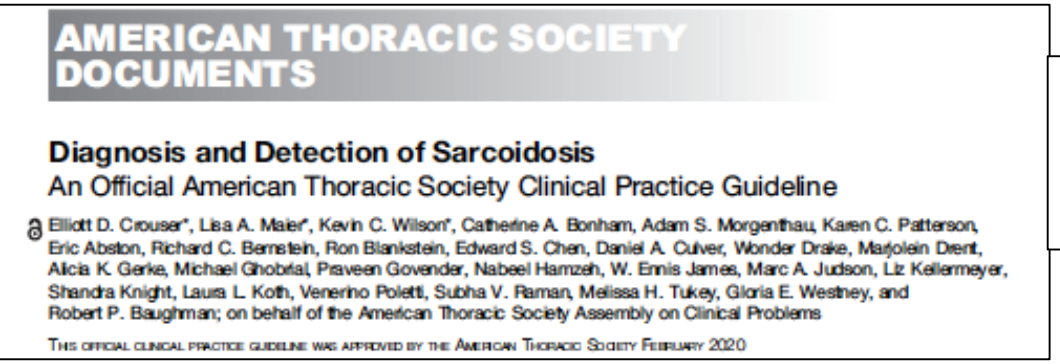
Figure 2. Typical ECG and radiographic features of cardiac sarcoidosis. (A) ECG demonstrates first-degree A-V block (P-R interval, 200 ms) and right bundle branch block. (B) Cardiac magnetic resonance showing multifocal abnormal late gadolinium enhancement involving the mid- to epicardial lateral ventricular wall (arrowheads). (C) Cardiac positron emission tomography demonstrates intense hypermetabolic uptake of ^{18}F-fluorodeoxyglucose in the lateral left ventricular wall (arrow).

- Based on those with symptoms

Mode	Finding	Freq % (95% CI)	RR all cause mortality (95 CI)
CMR	Late Gadolinium enhancement (LGE)	27 % (23-31)	9.9 vs 4.7% RR 2.54 (0.38-17.16)
cPET	Variety of definitions	52% (43-60)	HR 1.33 (0.68-2.26)
TTE	Reduced EF or wall motion abnormalities	11% (5-17)	

Recommendations.

1. For patients with extracardiac sarcoidosis and suspected cardiac involvement, we suggest cardiac MRI, rather than cPET or TTE, to obtain both diagnostic and prognostic information (conditional recommendation, very low-quality evidence).
2. For patients with extracardiac sarcoidosis and suspected cardiac involvement who are being managed in a setting in which cardiac MRI is not available, or when CMR results are inconclusive, we suggest dedicated cPET, rather than a TTE, to obtain diagnostic and prognostic information (conditional recommendation, very low-quality evidence).

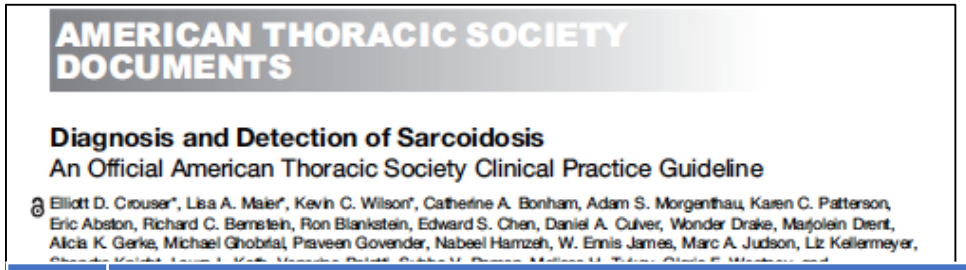


Question 10: Should Patients with Sarcoidosis Who Are Suspected of Having PH Undergo TTE?

137 papers
13 reviewed
9 studies
No comparison of testing
Versus no testing

- Sarcoidosis associated PH (SAPH)
- 5-20%
- Independent risk factor for mortality
- TTE suggestive of PH in 29% (95% CI 20-39)
- 78% (95% CI 67-86)confirmed on RHC

- Persistent breathlessness
- Exertional chest pain
- Syncope
- Prominent P2 or S4
- Reduced 6MWT
- Desaturation on exercise
- Reduced DLCO
- Increased PA size vs Aorta on CT
- Raised BNP
- Unreliable markers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	QUESTION	OUTCOME
1	Should lymph node sampling be performed in **asymptomatic** bilateral hilar lymphadenopathy	Case by Case
2	EBUS versus Mediastinoscopy?	EBUS
3	Should you screen for ocular sarcoid with Eye exam? **Asymptomatic**	YES Baseline Eye Exam
4	Should you screen for renal sarcoid? **Asymptomatic**	YES Baseline Creatinine
5	Should you screen for hepatic sarcoid? **Asymptomatic**	YES Baseline ALP
6	Should you screen for abnormal calcium metabolism? **Asymptomatic**	YES Baseline Calcium
7	Should you screen for hematological abnormality? **Asymptomatic**	YES Baseline FBC
8	Should you screen for cardiac sarcoid? **Asymptomatic**	Perform Baseline ECG NOT ECHO, Amb monitor
9	Suspicion of cardiac sarcoid Cardiac MRI vs PET? **Symptomatic**	Cardiac MRI
10	Suspected PH Should you do an ECHO?	ECHO then RHC

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PICO 1: In patients with pulmonary sarcoidosis, should glucocorticoid treatment be used versus no immunosuppressive treatment?

Recommendation

For untreated patients with major involvement from pulmonary sarcoidosis believed to be at higher risk of future mortality or permanent disability from sarcoidosis, we recommend the introduction of glucocorticoid treatment to improve and/or preserve FVC and QoL. *(Strong recommendation, low quality of evidence.)*

- High risk of future mortality or
- Permanent disability
- GC good symptomatic and radiological response

PICO 2: In patients with pulmonary sarcoidosis, should one add immunosuppressive treatment or remain on glucocorticoid treatment alone?

Recommendations

Recommendation 1: For patients with symptomatic pulmonary sarcoidosis believed to be at higher risk of future mortality or permanent disability from sarcoidosis who have been treated with glucocorticoids and have continued disease or unacceptable side-effects from glucocorticoids, we suggest the addition of methotrexate to improve and/or preserve FVC and QoL. *(Conditional recommendation, very low quality of evidence.)*

Recommendation 2: For patients with symptomatic pulmonary sarcoidosis believed to be at higher risk of future mortality or permanent disability from sarcoidosis who have been treated with glucocorticoids or other immunosuppressive agents and have continued disease, we suggest the addition of infliximab to improve and/or preserve FVC and QoL. *(Conditional recommendation, low quality of evidence.)*

1747 papers. 1319 papers
36 reviewed 41 43 viewed
19 studies 6 studies

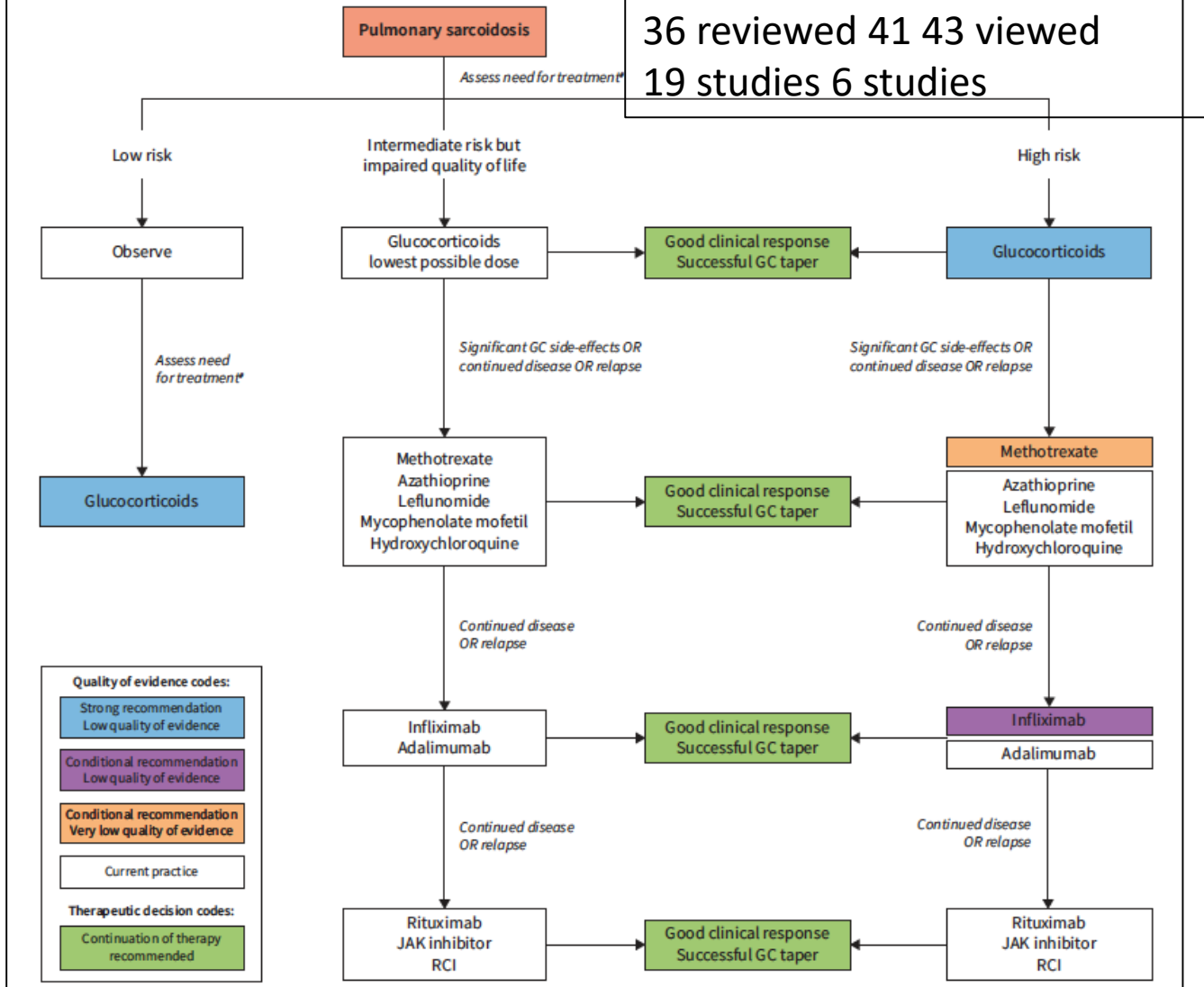

FIGURE 1 Approach for pulmonary sarcoidosis. Use of rituximab, JAK inhibitor and repository corticotropin injection (RCI) should be on a case-by-case basis. This figure is a combination of the recommendations made in this guideline and a description of Task Force members' current practice in situations where there was not enough evidence to warrant a recommendation or for questions for which a systematic review of the literature was not undertaken. Note that the information depicted as current practice (in white boxes) is not intended as a recommendation for clinical practice. *: assess need for treatment based on low risk, intermediate risk but impaired quality of life or high risk as discussed in text. GC: glucocorticoid.

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SKIN

1032 papers 980
33 reviewed 91
7 studies 5

- Cutaneous : up to 30%
- Treat cosmetically important lesions
- No RCTS 6 retrospective observational
- Consider steroid sparing in chronic lesions eg Lupus Pernio

PICO 3: In patients with cutaneous sarcoidosis, should glucocorticoid treatment be used versus no immunosuppressive treatment?

Recommendation

For patients with cutaneous sarcoidosis and cosmetically important active skin lesions which cannot be controlled by local treatment, we suggest oral glucocorticoids be considered to reduce skin lesions. *(Conditional recommendation, very low quality of evidence.)*

PICO 4: In patients with cutaneous sarcoidosis, should one add other immunosuppressive treatment when treatment with glucocorticoids has not been effective?

Recommendation

For patients with cutaneous sarcoidosis who have been treated with glucocorticoids and/or other immunosuppressive agents and have continued cosmetically important active skin disease, we suggest the addition of infliximab compared to no additional treatment to reduce skin lesions. *(Conditional recommendation, low quality of evidence.)*

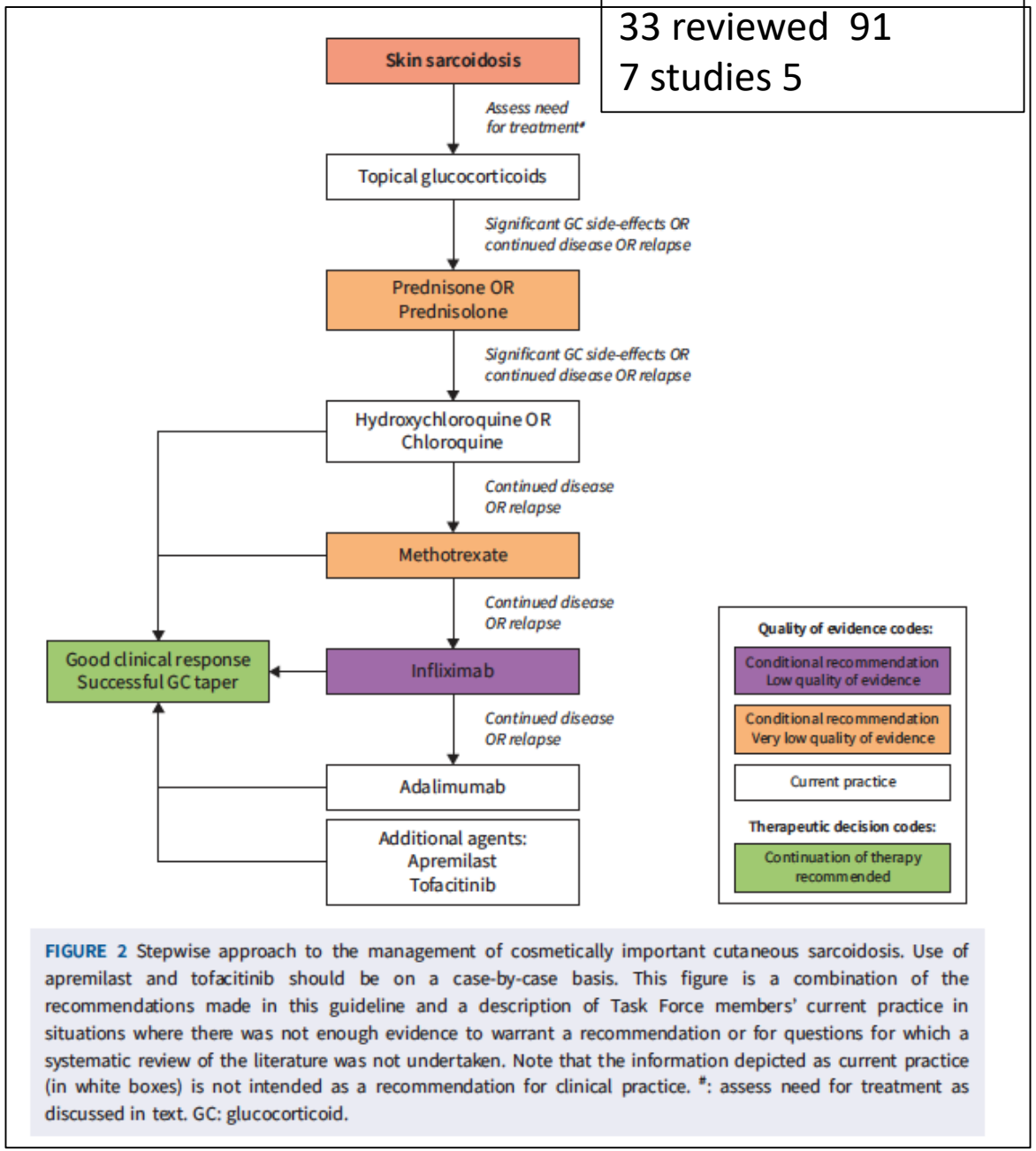

FIGURE 2 Stepwise approach to the management of cosmetically important cutaneous sarcoidosis. Use of apremilast and tofacitinib should be on a case-by-case basis. This figure is a combination of the recommendations made in this guideline and a description of Task Force members' current practice in situations where there was not enough evidence to warrant a recommendation or for questions for which a systematic review of the literature was not undertaken. Note that the information depicted as current practice (in white boxes) is not intended as a recommendation for clinical practice. #: assess need for treatment as discussed in text. GC: glucocorticoid.

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CARDIAC

996 papers
33 reviewed
17 studies

- 2-5% in unselected patients
- Maybe as high as 25-30% (autopsy)

TABLE 4 Prognostic variables that may influence treatment decisions for cardiac sarcoidosis

- Age >50 years
- Left ventricular ejection fraction <40%
- New York Heart Association Functional Class III or IV
- Increased left ventricular end-diastolic diameter
- Late gadolinium enhancement on cardiac magnetic resonance imaging
- Ventricular tachycardia
- Cardiac inflammation identified by fluorodeoxyglucose positron emission tomography scan
- Echocardiographic evidence of abnormal global longitudinal strain
- Interventricular septal thinning
- Elevated troponin or brain natriuretic peptide

Features found to be associated with increased risk for morbidity or mortality from cardiac sarcoidosis [150–159].

- Retrospective studies – high bias

PICO 5: In patients with clinically relevant cardiac sarcoidosis, should glucocorticoids with or without other immunosuppressives versus no immunosuppression be used?

Recommendation

For patients with evidence of functional cardiac abnormalities, including heart block, dysrhythmias or cardiomyopathy, we recommend the use of glucocorticoids (with or without other immunosuppressives). *(Strong recommendation, very low quality of evidence.)*

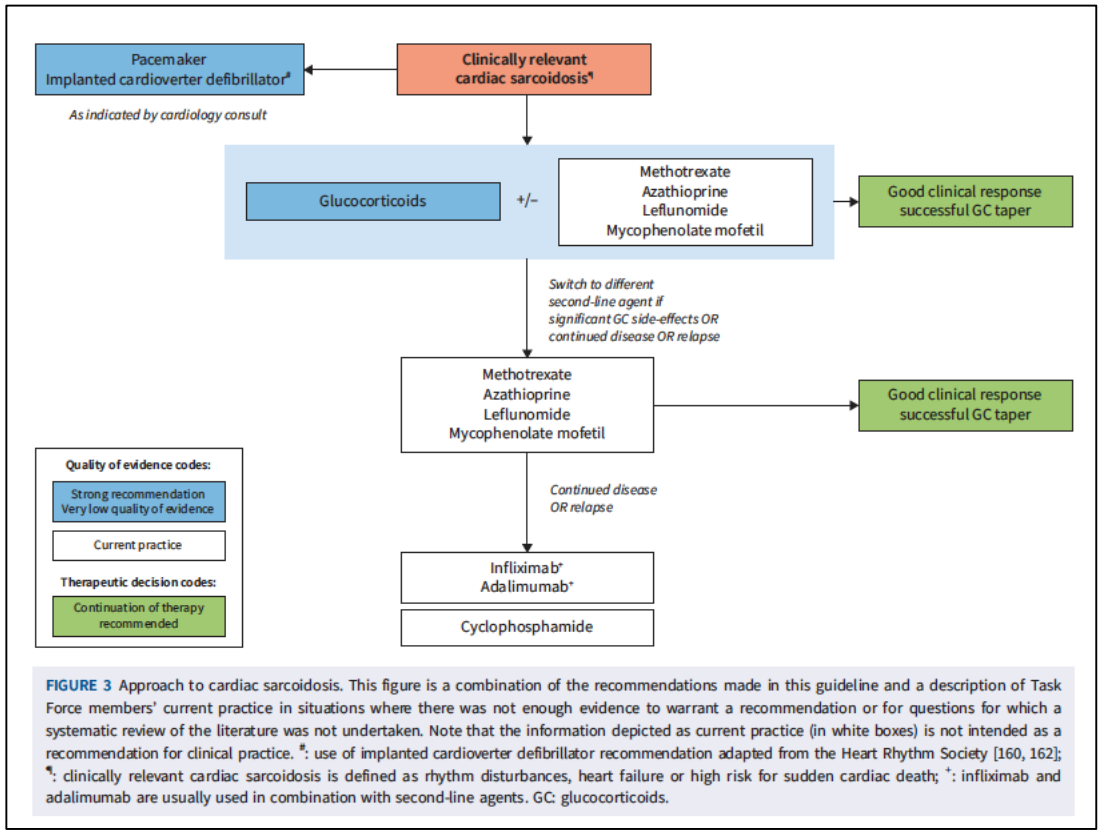

FIGURE 3 Approach to cardiac sarcoidosis. This figure is a combination of the recommendations made in this guideline and a description of Task Force members' current practice in situations where there was not enough evidence to warrant a recommendation or for questions for which a systematic review of the literature was not undertaken. Note that the information depicted as current practice (in white boxes) is not intended as a recommendation for clinical practice. #: use of implanted cardioverter defibrillator recommendation adapted from the Heart Rhythm Society [160, 162]; ¶: clinically relevant cardiac sarcoidosis is defined as rhythm disturbances, heart failure or high risk for sudden cardiac death; +: infliximab and adalimumab are usually used in combination with second-line agents. GC: glucocorticoids.

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Robert P. Baughman[1], Dominique Valeyre[2], Peter Korsten[3], Alexander G. Mathioudakis[4], Wim A. Wuyts[5], Athol Wells[6], Paola Rottoli[7], Hiliaro Nunes[8], Elyse E. Lower[1], Marc A. Judson[9], Dominique Israel-Biet[10], Jan C. Grutters[11,12], Marjolein Drent[11,13,14], Daniel A. Culver[15], Francesco Bonella[16], Katerina Antoniou[17], Filippo Martone[18], Bernd Quadder[19], Ginger Spitzer[20], Blin Nagavci[21], Thomy Tonia[22], David Rigau[23] and Daniel R. Ouellette[24]

NEURO

1305 papers
56 reviewed
4 studies

- 5-20%
- Significant Q of L impact

PICO 6: In patients with neurosarcoidosis, should immunosuppressive treatment be used versus no immunosuppressive treatment?

Recommendations

Recommendation 1: For patients with clinically significant neurosarcoidosis, we recommend treatment with glucocorticoids. *(Strong recommendation, very low quality of evidence.)*

Recommendation 2: For patients with neurosarcoidosis that have been treated with glucocorticoids and have continued disease, we suggest the addition of methotrexate. *(Conditional recommendation, very low quality of evidence.)*

Recommendation 3: For patients with neurosarcoidosis that have been treated with glucocorticoids and a second-line agent (methotrexate, azathioprine, mycophenolate mofetil) and have continued disease, we suggest the addition of infliximab. *(Conditional recommendation, very low quality of evidence.)*

- 81% GC First line
- 71% favorable outcomes
- Reduced relapse rate with MTX in one study HR 0.47 and HCQ HR 0.37 not AZA or MMF

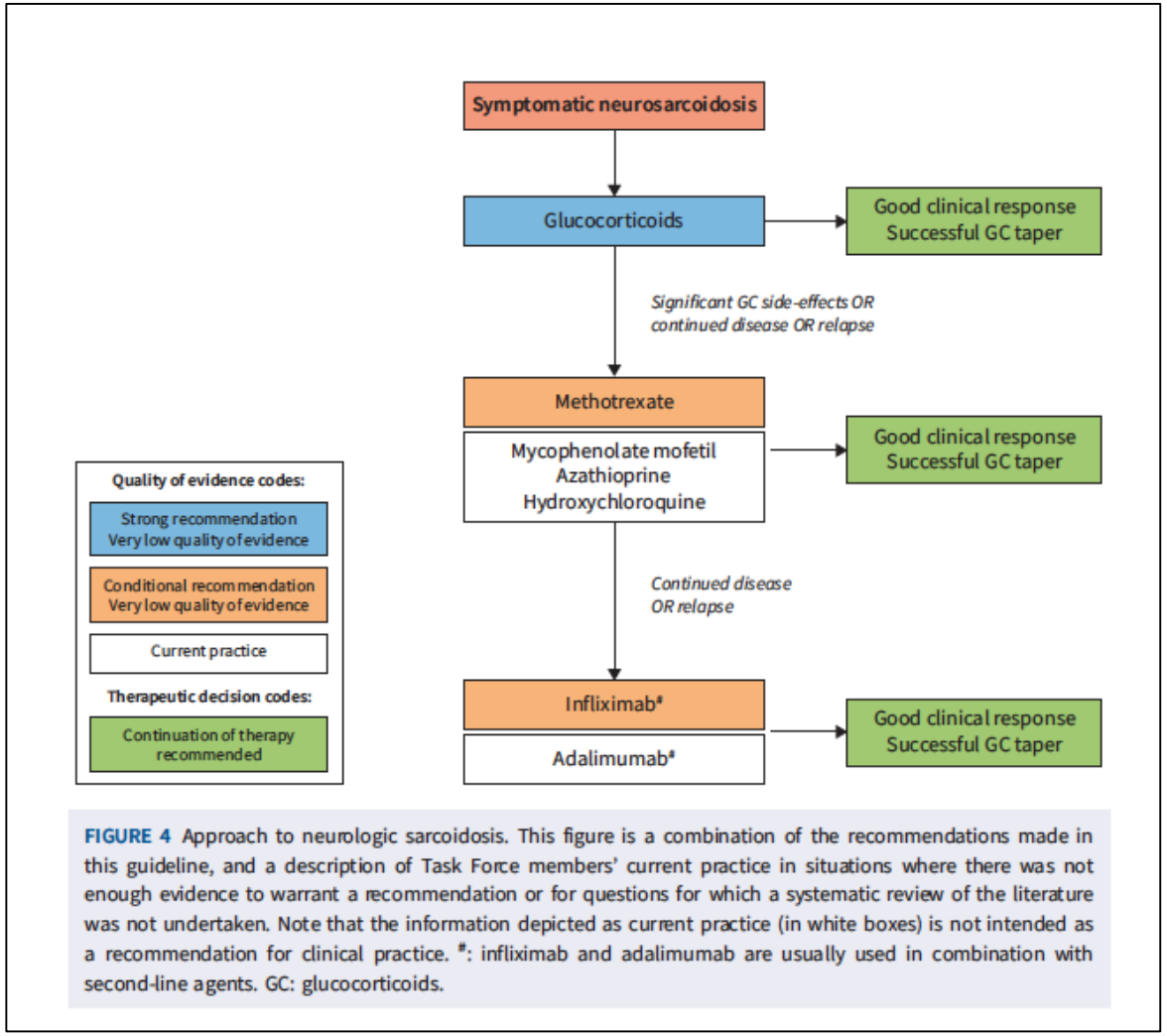

FIGURE 4 Approach to neurologic sarcoidosis. This figure is a combination of the recommendations made in this guideline, and a description of Task Force members' current practice in situations where there was not enough evidence to warrant a recommendation or for questions for which a systematic review of the literature was not undertaken. Note that the information depicted as current practice (in white boxes) is not intended as a recommendation for clinical practice. #: infliximab and adalimumab are usually used in combination with second-line agents. GC: glucocorticoids.

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FATIGUE

165 papers
27 reviewed
5 studies

- Up to 90%
- Low Q of L\May not be related to organ involvement
- Need to exclude other causes eg Diabetes, Thyroid, Vit D def, Depression, OSA, SFN

- 2 RCTs with physio intervention
- 2 RCTs of pharmacological therapies

PICO 7: In patients with sarcoidosis-associated fatigue, should immunosuppressants, neurostimulants, exercise or other treatments be used versus no treatment for fatigue?

Recommendations

Recommendation 1: In patients with sarcoidosis who have troublesome fatigue, we suggest a pulmonary rehabilitation programme and/or inspiratory muscle strength training for 6–12 weeks to improve fatigue. *(Conditional recommendation, low quality of evidence.)*

Recommendation 2: In patients with sarcoidosis who have troublesome fatigue that is not related to disease activity, and after consideration of a pulmonary exercise or rehabilitation programme, we suggest the use of D-methylphenidate or armodafinil for 8 weeks to test its effect on fatigue and tolerability. *(Conditional recommendation, low quality of evidence.)*

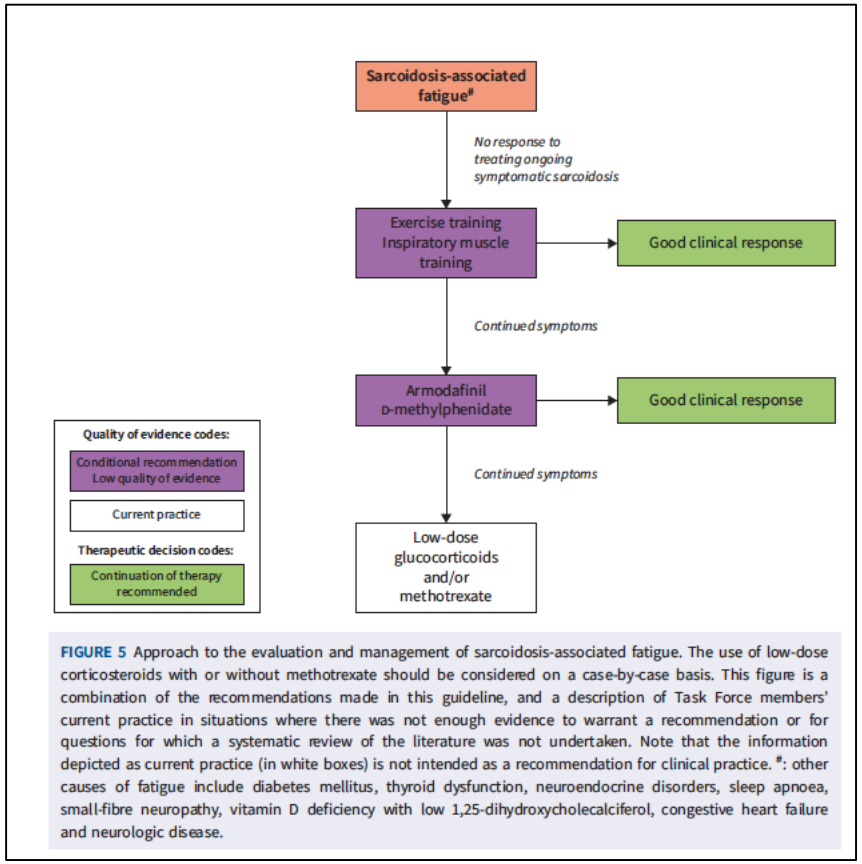

FIGURE 5 Approach to the evaluation and management of sarcoidosis-associated fatigue. The use of low-dose corticosteroids with or without methotrexate should be considered on a case-by-case basis. This figure is a combination of the recommendations made in this guideline, and a description of Task Force members' current practice in situations where there was not enough evidence to warrant a recommendation or for questions for which a systematic review of the literature was not undertaken. Note that the information depicted as current practice (in white boxes) is not intended as a recommendation for clinical practice. #: other causes of fatigue include diabetes mellitus, thyroid dysfunction, neuroendocrine disorders, sleep apnoea, small-fibre neuropathy, vitamin D deficiency with low 1,25-dihydroxycholecalciferol, congestive heart failure and neurologic disease.

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SMALL FIBRE NEUROPATHY

427 papers
9 reviewed
4 studies

- Neuropathic symptoms and dysautonomia
- Loss of thinly myelinated and unmyelinated fibres
- 40-60% Females and Caucasians
- Paraesthesia, allodynia – sensitive to touch, numbness, pain syndromes, GI dysmotility, diaphoresis – excessive sweating, orthostasis, palpitations
- No diagnostic tool
- SFN screening list – 21 item validated
- Exclude large fibre involvement
- Can do skin biopsy for intraepidermal nerve fibre density, nerve fibre density assessed by corneal confocal microscopy

PICO 8: In sarcoidosis patients with small-fibre neuropathy, should immunosuppressants or intravenous immunoglobulin be prescribed versus no treatment?
No recommendations were made for this PICO question due to a lack of sufficient evidence.

- Under reported and under recognized
- Studies us IVIg, anti TNF or Cibinetide

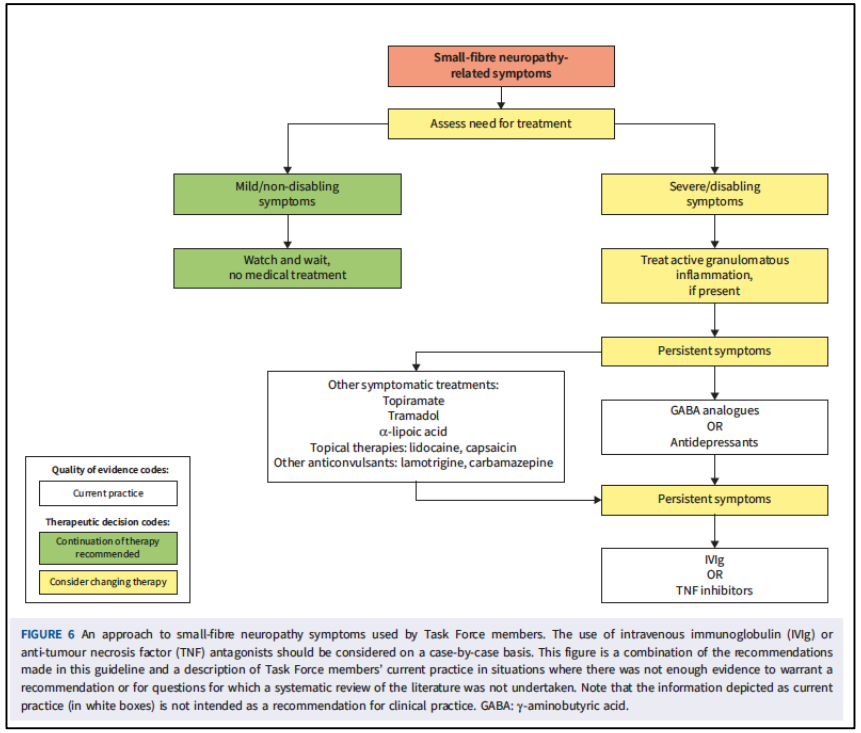
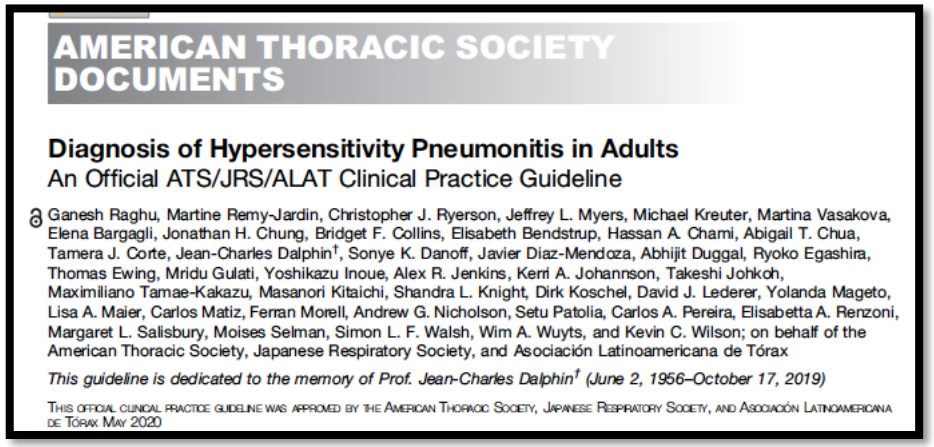


FIGURE 6 An approach to small-fibre neuropathy symptoms used by Task Force members. The use of intravenous immunoglobulin (IVIg) or anti-tumour necrosis factor (TNF) antagonists should be considered on a case-by-case basis. This figure is a combination of the recommendations made in this guideline and a description of Task Force members' current practice in situations where there was not enough evidence to warrant a recommendation or for questions for which a systematic review of the literature was not undertaken. Note that the information depicted as current practice (in white boxes) is not intended as a recommendation for clinical practice. GABA: γ-aminobutyric acid.

Hypersensitivity Pneumonitis



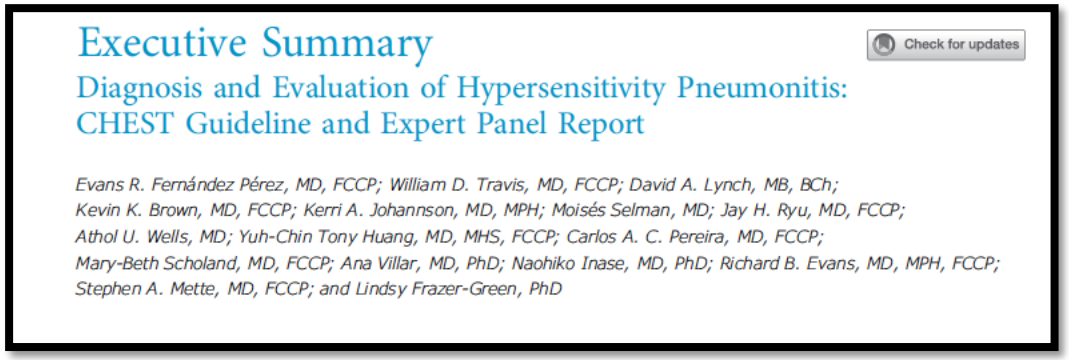
AMERICAN THORACIC SOCIETY DOCUMENTS

Diagnosis of Hypersensitivity Pneumonitis in Adults
An Official ATS/JRS/ALAT Clinical Practice Guideline

Ganesh Raghu, Martine Remy-Jardin, Christopher J. Ryerson, Jeffrey L. Myers, Michael Kreuter, Martina Vasakova, Elena Bargagli, Jonathan H. Chung, Bridget F. Collins, Elisabeth Bendstrup, Hassan A. Chami, Abigail T. Chua, Tamera J. Corte, Jean-Charles Dalphin†, Sonye K. Danoff, Javier Diaz-Mendoza, Abhijit Duggal, Ryoko Egashira, Thomas Ewing, Mridu Gulati, Yoshikazu Inoue, Alex R. Jenkins, Kerri A. Johannson, Takeshi Johkoh, Maximiliano Tamae-Kakazu, Masanori Kitaichi, Shandra L. Knight, Dirk Koschel, David J. Lederer, Yolanda Mageto, Lisa A. Maier, Carlos Matiz, Ferran Morell, Andrew G. Nicholson, Setu Patolia, Carlos A. Pereira, Elisabetta A. Renzoni, Margaret L. Salisbury, Moises Selman, Simon L. F. Walsh, Wim A. Wuyts, and Kevin C. Wilson; on behalf of the American Thoracic Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax

This guideline is dedicated to the memory of Prof. Jean-Charles Dalphin† (June 2, 1956–October 17, 2019)

This official clinical practice guideline was approved by the American Thoracic Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax May 2020



Executive Summary

Check for updates

Diagnosis and Evaluation of Hypersensitivity Pneumonitis: CHEST Guideline and Expert Panel Report

Evans R. Fernández Pérez, MD, FCCP; William D. Travis, MD, FCCP; David A. Lynch, MB, BCh; Kevin K. Brown, MD, FCCP; Kerri A. Johannson, MD, MPH; Moisés Selman, MD; Jay H. Ryu, MD, FCCP; Athol U. Wells, MD; Yuh-Chin Tony Huang, MD, MHS, FCCP; Carlos A. C. Pereira, MD, FCCP; Mary-Beth Scholand, MD, FCCP; Ana Villar, MD, PhD; Naohiko Inase, MD, PhD; Richard B. Evans, MD, MPH, FCCP; Stephen A. Mette, MD, FCCP; and Lindsy Frazer-Green, PhD

- Systematic review
- 6 questions
- MDT experts formulate recommendations based on GRADE

- 14 PICO questions
- GRADE recommendations
- All evidence very low quality

ATS/JRS/ALAT vs Chest

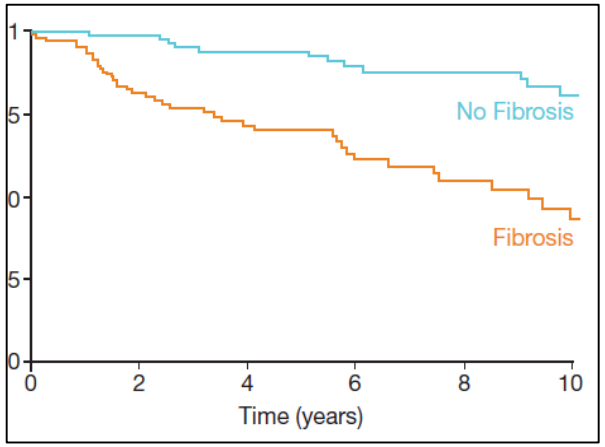
ATS

- Thorough history of exposures important
- Need to develop and validate questionnaires No recommendation

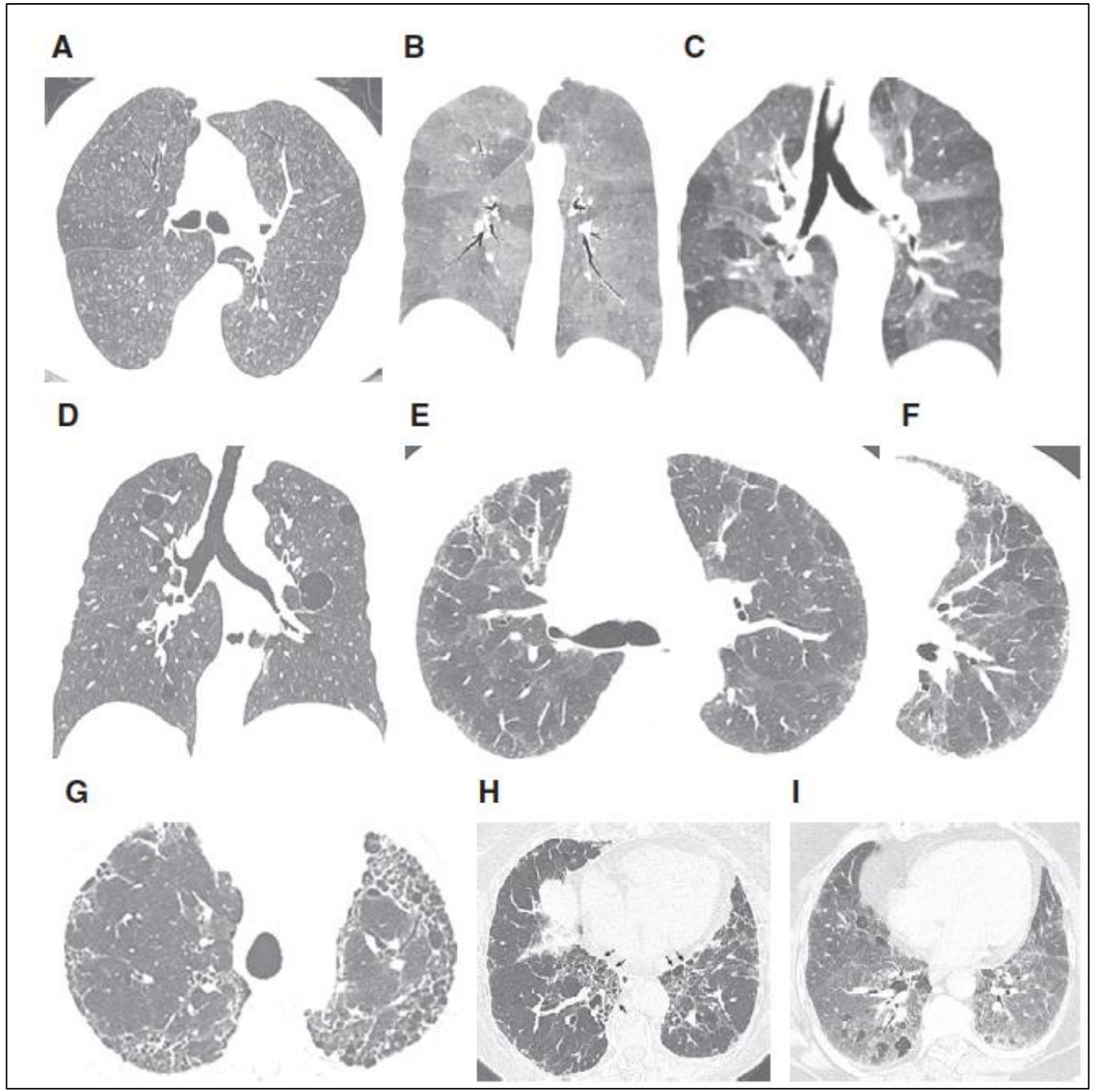
- Fibrotic (mixed inflammatory plus fibrotic or purely fibrotic
- Non-Fibrotic (Inflammatory)

Chest

- Thorough history of exposures important
- Use a questionnaire! (Ungraded Consensus statement)
- If felt to be occupational include an occupational medicine specialist and environmental hygeinist ! (Ungraded Consensus statement)
- Agree!



Ulster University



ATS/JRS/ALAT vs Chest

ATS

- Suggests performing Serum IgG that target specific antigens (very low confidence)
- Suggests performing BAL in all HSP

Chest

- Dont rely solely on IgG to confirm or rule out a diagnosis of HSP (Weak recommendation, very low quality)
- Don’t perform antigen challenges or antigen specific proliferation assay as not validated and standardization
- If CT classical and exposure history Don’t perform BAL (Weak recommendation, very low quality)

ATS/JRS/ALAT vs Chest

ATS

	Non fibrotic	Fibrotic
TBBx	Recommends	No Recommendation
Cryobiopsy	No Recommendation	Recommends
Lung biopsy	Recommends	Recommends

- Suggests performing BAL in all HSP

Chest

- Not addressed
- Not addressed
- Agrees if diagnostic uncertainty

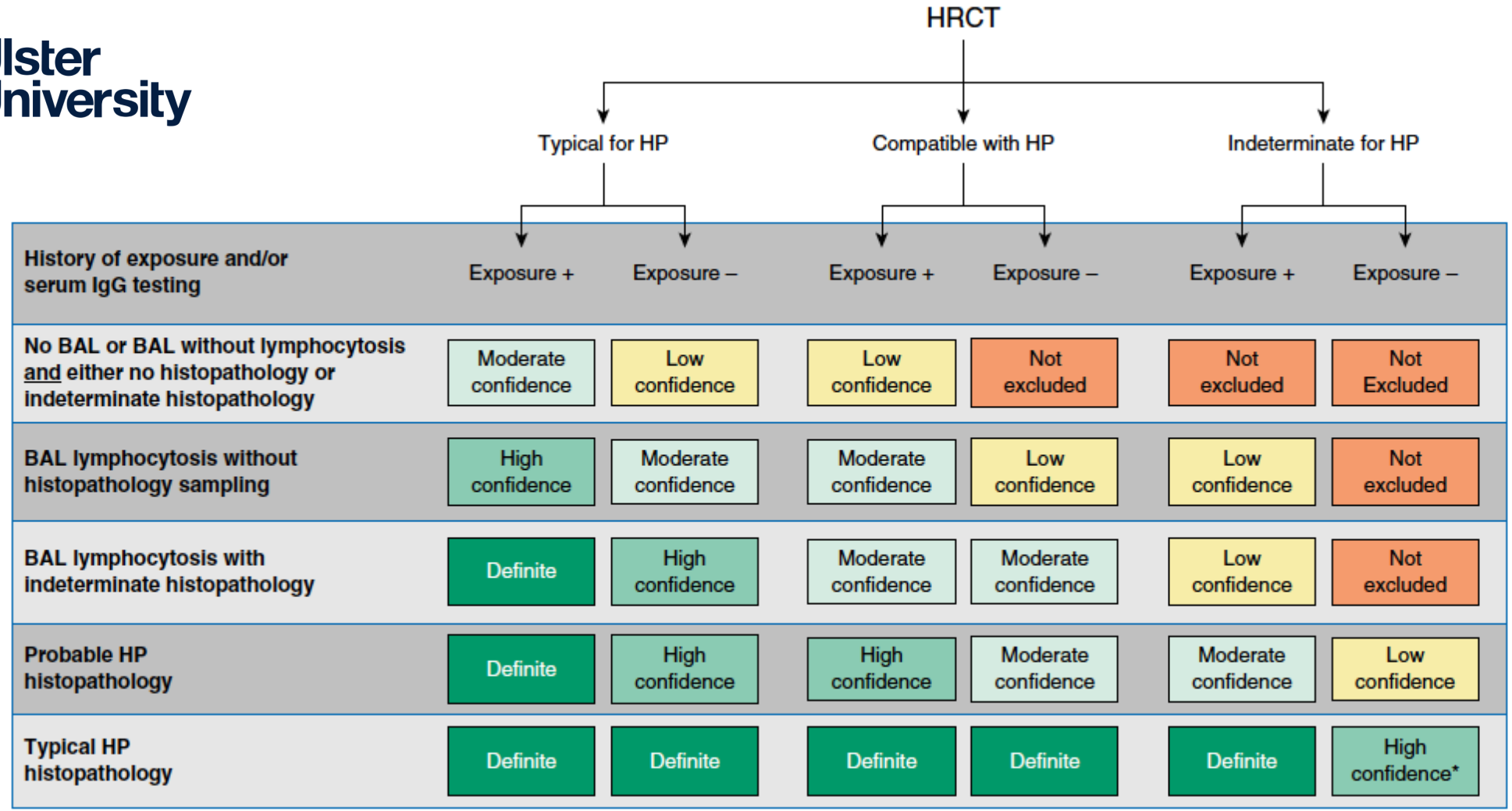


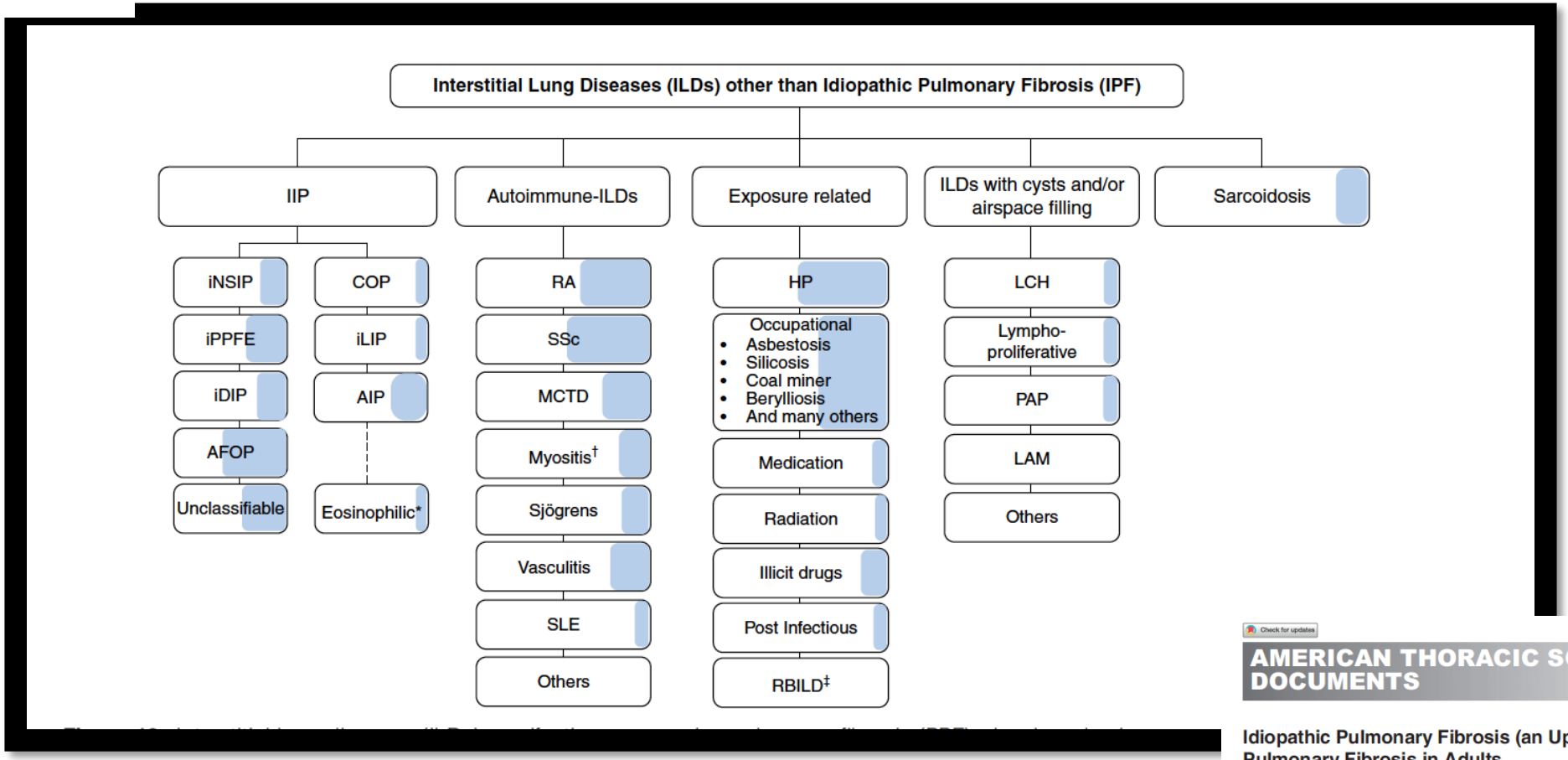
Figure 6. Hypersensitivity pneumonitis diagnosis based on incorporation of imaging, exposure assessment, BAL lymphocytosis, and histopathological findings. All confidence levels are subject to multidisciplinary discussion. *Confidence may increase to "definite" if the pathologist's conclusion persists after reevaluation in the context of additional clinical information or an expert second opinion on histopathology. HP = hypersensitivity pneumonitis; HRCT = high-resolution computed tomography.

Ulster University

CLINICAL TRIALS TRIAL ON A PAGE

Trial	Drug	Disease
INBUILD	Nintedanib	PF-ILD
RELIEF	Pirfenidone	PF-ILD
TRAIL	Pirfenidone	RA-ILD
SENSCIS	Nintedanib	Sys Scl ILD
FocuSSed	Tocilizumab	Sys Scl ILD
RECITAL	Cycloph vs Rituximab	CTD-ILD
INCREASE	Treprostinil	PH ILD
	Nalbuphine	IPF Cough

ILDs have varying progression



Check for updates

AMERICAN THORACIC SOCIETY DOCUMENTS

Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults

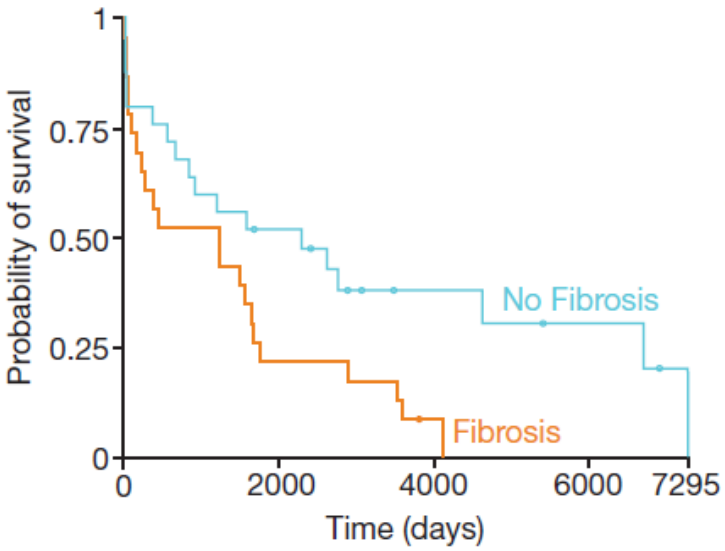
An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

Ganesh Raghu, Martine Remy-Jardin, Luca Richeldi, Carey C. Thomson, Yoshikazu Inoue, Takeshi Johkoh, Michael Kreuter, David A. Lynch, Toby M. Maher, Fernando J. Martinez, Maria Molina-Molina, Jeffrey L. Myers, Andrew G. Nicholson, Christopher J. Ryerson, Mary E. Strek, Lauren K. Troy, Marlies Wijsenbeek, Manoj J. Mammen, Tanzib Hossain, Brittany D. Bissell, Derrick D. Herman, Stephanie M. Hon, Fayez Kheir, Yet H. Khor, Madalina Macrea, Katerina M. Antoniou, Demosthenes Bouros, Ivette Buendia-Roldan, Fabian Caro, Bruno Crestani, Lawrence Ho, Julie Morisset, Amy L. Olson, Anna Podolanczuk, Venerino Poletti, Moisés Selman, Thomas Ewing, Stephen Jones, Shandra L. Knight, Marya Ghazipura, and Kevin C. Wilson; on behalf of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax

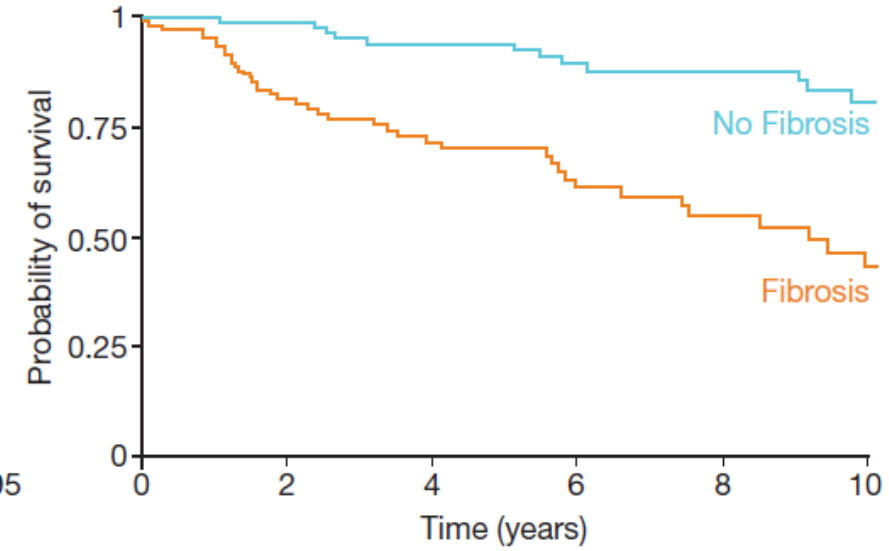
This official clinical practice guideline was approved by the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax February 2022

Presence of fibrosis = worse survival

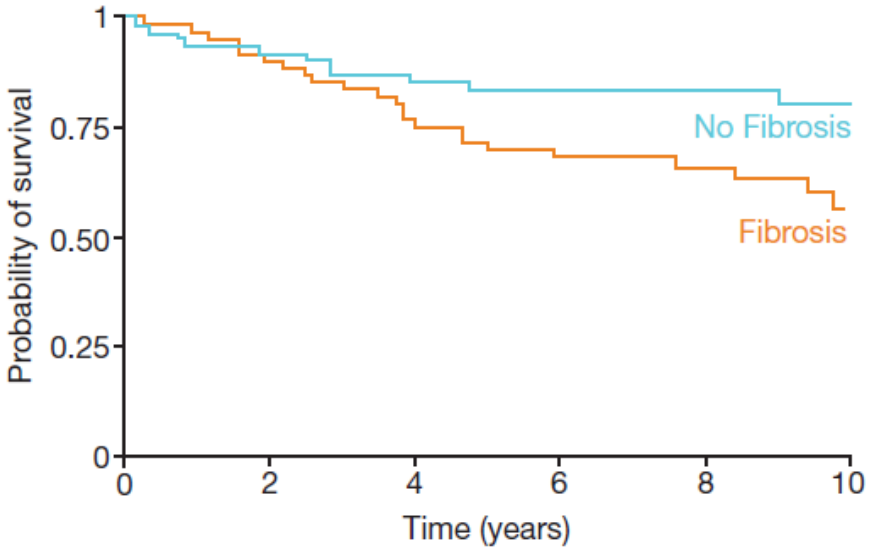
RA-ILD[1]



Chronic hypersensitivity pneumonitis[2]



Systemic sclerosis[3]



1. Solomon JJ et al. Respir Med 2013;107:1247-1252; 2. De Sadeleer LJ et al. J Clin Med 2018;8:14; 3. Hoffmann-Vold AM et al. Am J Respir Crit Care Med 2019;200:1258-1266.

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Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults

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Progressive Pulmonary Fibrosis: Should the Timelines Be Taken Out of the Definition?

To the Editor:

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Table 4. Definition of Progressive Pulmonary Fibrosis

Definition of PPF

In a patient with ILD of known or unknown etiology other than IPF who has radiological evidence of pulmonary fibrosis, PPF is defined as at least two of the following three criteria occurring within the past year with no alternative explanation*:

1 Worsening respiratory symptoms

2 Physiological evidence of disease progression (either of the following):
- a. Absolute decline in FVC ⩾5% predicted within 1 yr of follow-up
- b. Absolute decline in D_{LCO} (corrected for Hb) ⩾10% predicted within 1 yr of follow-up

3 Radiological evidence of disease progression (one or more of the following):
- a. Increased extent or severity of traction bronchiectasis and bronchiolectasis
- b. New ground-glass opacity with traction bronchiectasis
- c. New fine reticulation
- d. Increased extent or increased coarseness of reticular abnormality
- e. New or increased honeycombing
- f. Increased lobar volume loss

Definition of abbreviations: ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; PPF = progressive pulmonary fibrosis.
*Although it is critical to exclude alternative explanations of worsening features for all patients with suspected progression, this is particularly important in patients with worsening respiratory symptoms and/or decline in D_{LCO} given the lower specificity of these features for PPF compared with FVC and chest computed tomography.

1. Raghu G. et al. Idiopathic Pulmonary Fibrosis (an update) and Progressive Pulmonary Fibrosis in adults. An official ATS/ERS/JRS/ALAT Clinical Practice Guideline. American Journal of Resp and Crit Car Med. 2022; 205:18

How to define disease progression: case study

Ulster University

Worsening Cough and Breathlessness
Reduced walk distance
Fatigue
Worsening quality of life

Clinical assessment

A 55-year-old patient with seropositive RA and a 1-year history of progressive shortness of breath and/or cough

Reduction in exercise tolerance from 500 to 100 yards

Treated with prednisolone, methotrexate, rituximab

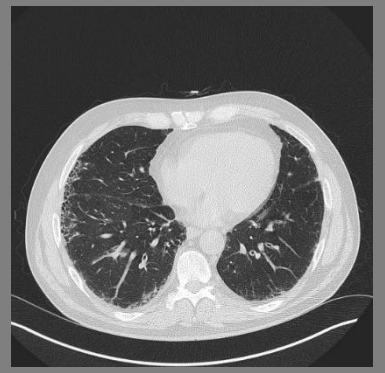
Lung function

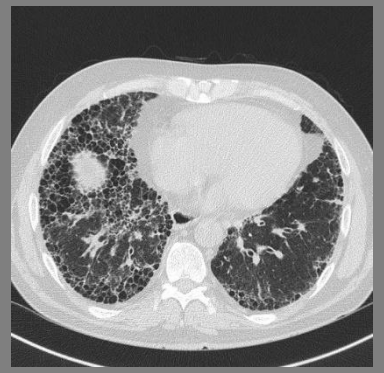
Decline in FVC and DL_{CO} over time

Date	FVC	DL_{CO}
April 2019	78%	65%
Aug 2019	69%	57%
Dec 2019	57%	50%

Imaging

HRCT features of progression:
increased area involved the development of traction bronchiectasis
or honeycombing





DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography; RA, rheumatoid arthritis.

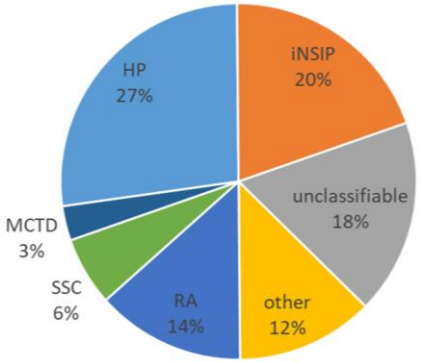
TM-GB-100033 | August 2020

Images courtesy of Dr Nazia Chaudhuri

INBUILD – Progressive Fibrotic ILD (PF-ILD)

Criteria

- Fibrosing ILD
- >10% fibrosis on CT
- 2/3 UIP pattern on CT
- Progression despite 24 months of 'treatment'
- FVC ≥45% pred
- DLco ≥30%–<80% pred



Progression in 2 yrs

- Relative FVC decline ≥ 10%
- Worsening symptoms AND Progression on HRCT
- Relative FVC decline 5-10% AND Worsening symptoms AND/OR Progression on HRCT

663 randomised

Age 65
UIP 62%
FVC 69% pred
DLco 46% pred

331 placebo → -188 mls

49 (15%) stopped

332 nintedanib → -81 mls

80 (24%) stopped

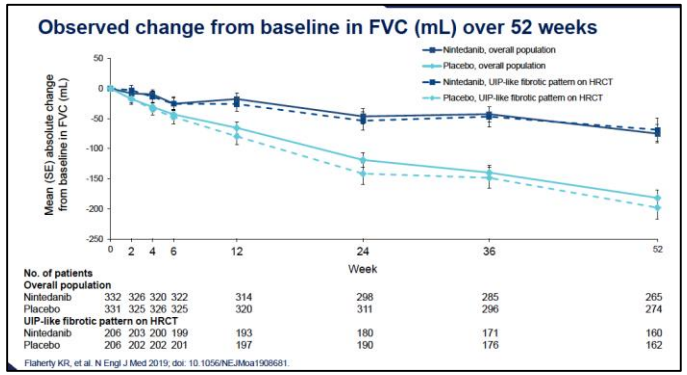
Primary endpoint
FVC change at 1 yr

- K-BILD ns
- AE ns
- Death ns
- AE or death – favoured nintedanib

Adverse events

Diarrhoea	67 vs 24%
Nausea	29 vs 9%
Vomiting	18 vs 5%
Anorexia	15 vs 5%
ALT↑	13 vs 4%
Wt loss	12 vs 3%
Abdo pain	10 vs 2%

AE stopped 20 vs 10%
AE dose red 33 vs 4%



Flaherty KR, et al. N Engl J Med 2019; doi: 10.1056/NEJMoa1908681

The burden of progressive fibrotic interstitial lung disease across the UK

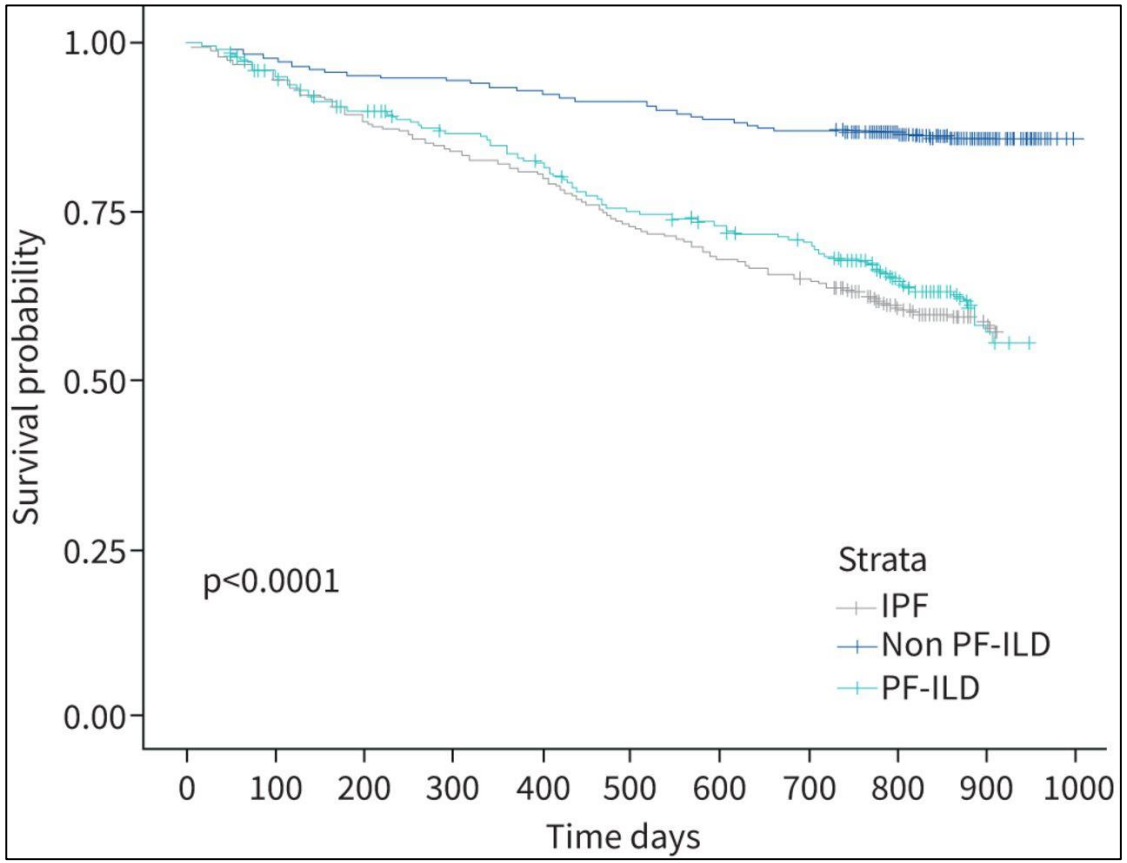
Simpson, T., Barratt, S. L., Beirne, P., Chaudhuri, N., Crawshaw, A., Crowley, L. E., Fletcher, S., Gibbons, M. A., Hallchurch, P., Horgan, L., Jakaityte, I., Lewis, T., McLellan, T., Myall, K. J., Miller, R., Smith, D. J. F., Stanel, S., Thillai, M., Thompson, F., Wallis, T., & 3 others, 31 Jul 2021, In: Eur Respir J. 58, 1, p. 1-4 4 p., 58.

Research output: Contribution to journal › Letter › peer-review

Open Access File

9 Citations (Scopus)

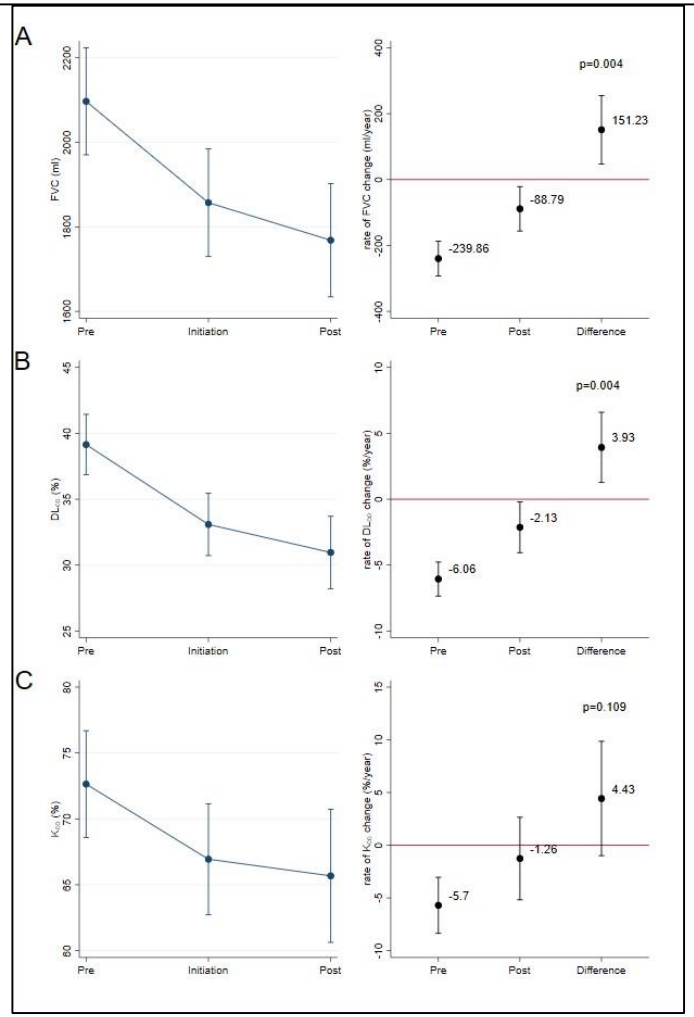
3 Downloads (Pure)



Nintedanib for non-IPF progressive pulmonary fibrosis: 12-month outcome data from a real-world mulHcentre observaHonal study

Raman, Lavanya; Stewart, Iain; BarraN, Shaney; Chua, Felix; Chaudhuri, Nazia; Crawshaw, Anjali; Gibbons, Michael; Hogben, CharloNe; Hoyles, Rachel; Kouranos, Vasileios; MarHnovic, Jennifer; Mulholland, Sarah; Myall, Katherine; Navqi, Marium; Renzoni, ElisabeNa; Saunders, Peter; Steward, MaNhew; Suresh, Dharmic; Thillai, Muhunthan; Wells, Athol; West, Alex; Mitchell, Jane; George, Peter

ERJ Open Research Accepted 2022



RELIEF – Pirfenidone in PF-ILD

Criteria

CTD-ILD, Fib NSIP, Ch HSP or asbestosis

FVC 40-90%

DLCO 25-75 (10-90)

FVC decline 5% based on 3 measurements over 6-24 months

randomised

63 placebo

64 Pirfenidone

Age 63 yrs
Female 49 vs 33%
MMF 10%
AZA 18%
FVC 62.5% pred
DLco 38% pred
Ch HSP 45%;
CTD-ILD 29%
F NSIP 21% asb 5%

Primary endpoint
Absolute change of % pred FVC 48 weeks

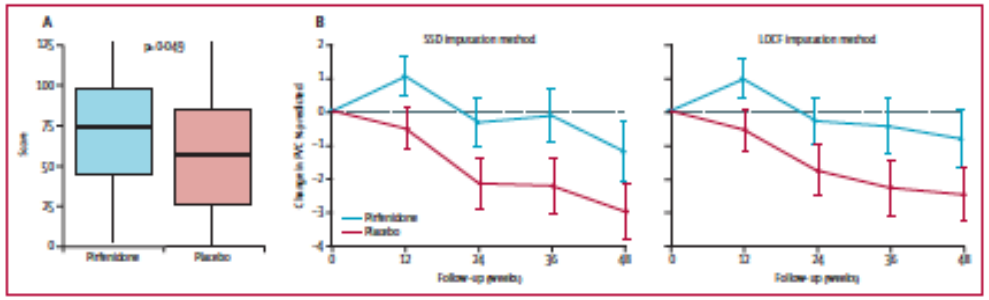
Diff 1.69%
P=0.049

Categorical FVC change -114 vs 36.6 ml ns

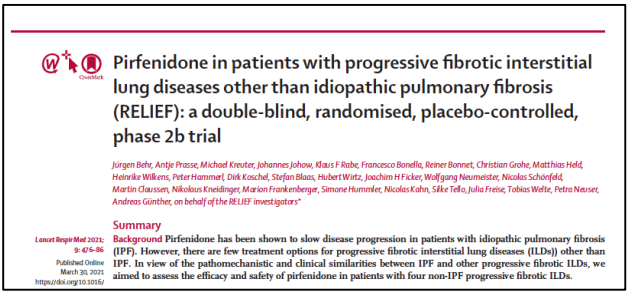
- PFS ns

Trial stopped due to poor recruitment and Futility after 34% of sample size enrolled.
Data for 47% patients imputted

Absolute change in percentage of predicted FVC and time course for mean change in percentage of predicted FVC from baseline to week 48:



Pirfenidone is indicated in adults for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF).



Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial

Jürgen Behr, Antje Prasse, Michael Kreuter, Johannes Johow, Klaus F Rabe, Francesco Bonella, Reiner Bonnet, Christian Grohe, Matthias Held, Heinrike Wilkens, Peter Hammerl, Dirk Koschel, Stefan Blaas, Hubert Wirtz, Joachim H Ficker, Wolfgang Neumeister, Nicolas Schönfeld, Martin Claussen, Nikolaus Kneidinger, Marion Frankenberger, Simone Hummler, Nicolas Kahn, Silke Tello, Julia Freise, Tobias Welte, Petra Neuser, Andreas Günther, on behalf of the RELIEF investigators*

Summary

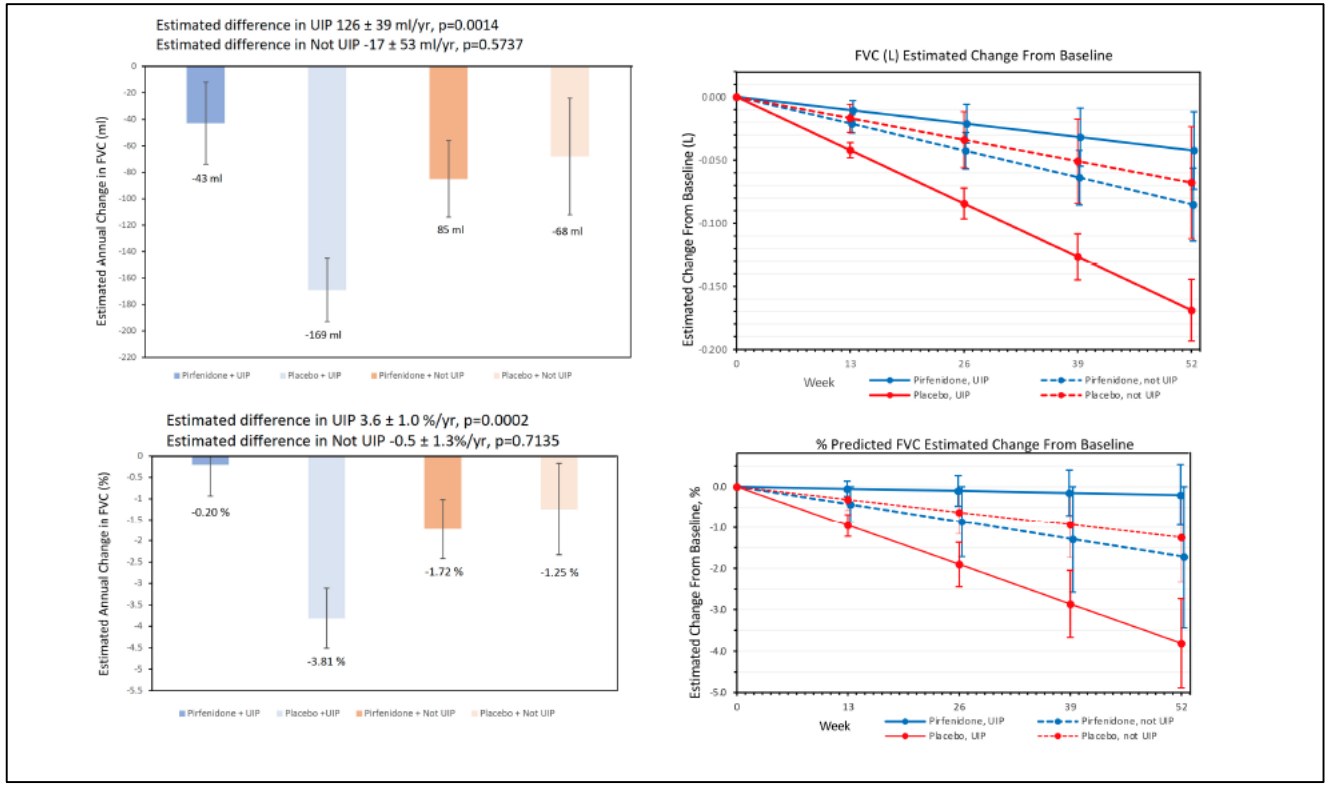
Lancet Respir Med 2021; 9: 476–86 Published Online March 20, 2021 https://doi.org/10.1016/

Background Pirfenidone has been shown to slow disease progression in patients with idiopathic pulmonary fibrosis (IPF). However, there are few treatment options for progressive fibrotic interstitial lung diseases (ILDs)) other than IPF. In view of the pathomechanistic and clinical similarities between IPF and other progressive fibrotic ILDs, we aimed to assess the efficacy and safety of pirfenidone in patients with four non-IPF progressive fibrotic ILDs.

1. Behr J et al. Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial. *Lancet Respir Med* 2021;9:476-486

TRAIL– Pirfenidone in RA-ILD

Pirfenidone vs placebo
Prim: FVC decline or PFS
ILD>10%
FVC >45
DLCO>30%
Stable RA treatment
33 sites
Struggled to recruit due to Covid
Recruited 123/231



A Randomized, Double-Blinded, Placebo-Controlled, Phase 2 Study of Safety, Tolerability and Efficacy of Pirfenidone in Patients with Rheumatoid Arthritis Interstitial Lung Disease

Solomon, JJ., Danoff, S., Woodhead, F., Hurwitz, S., Maurer, R., Glaspole, I., Dellaripa, PF., Gooptu, B., Vassallo, R., Cox, PG., Flaherty, KR., Adamali, HI., Gibbons, MA., Chaudhuri, N. & Investigators, T. TRAIL. N., 22 Oct 2021.

Research output: Contribution to conference › Abstract › peer-review

Pirfenidone | Interstitial Lung Diseases | Vital Capacity | Rheumatoid Arthritis | Placebos

SENSCIS – SSC-ILD

Criteria

- SSC
- Disease onset <7 years
- ILD with CT fibrosis ≥10%
- FVC ≥40% pred
- DLco 30-89% pred
- Pred ≤10mg/d
- Stable Rx with MTX or MMF for ≥6 mo

randomised

288 placebo

Age 54 yrs
Female 75%
Diffuse 52%
Scl-70+ 61%
MMF 48%
FVC 73% pred
DLco 53% pred

288 nintedanib

31 (11%) stopped

56 (19%) stopped

Primary endpoint
FVC change at 1 yr

-93.3 mls

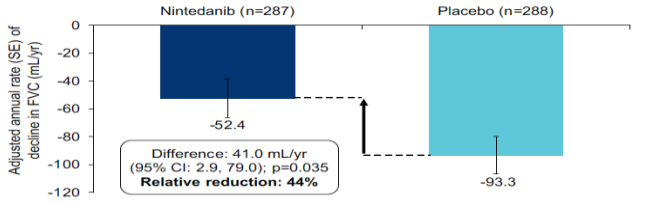
-52.4 mls

- mRSS ns
- SGRQ ns

Adverse events

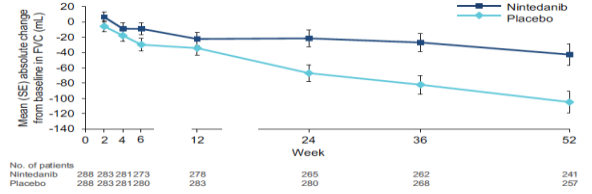
Diarrhoea	76 vs 32%
Nausea	32 vs 14%
Vomiting	25 vs 10%
Anorexia	9 vs 4%
Wt loss	12 vs 4%
Abdo pain	12 vs 7%
ALT↑	7 vs 1%
AE stopped	16 vs 9%

Annual rate of decline in FVC (mL/yr) over 52 weeks



- The adjusted annual rate of decline in FVC was significantly lower in the nintedanib group than in the placebo group (-52.4 vs -93.3 mL/year).

Change from baseline in FVC (mL) over 52 weeks



Distler O, et al. N Engl J Med 2019; doi:10.1056/NEJMoa1903076

focuSSed Tocilizumab – SSC-ILD

Criteria

SSC - Diffuse

Disease onset < 5 years

mRSS 10-35

Elevated acute phase reactant CRP>6 or ESR.28 or Platelets>330

Active disease: Disease duration<18m or mRSS increase by 3 or mRSS inc 2 and new body area

Primary endpoint
mRSS change at 48w

randomised

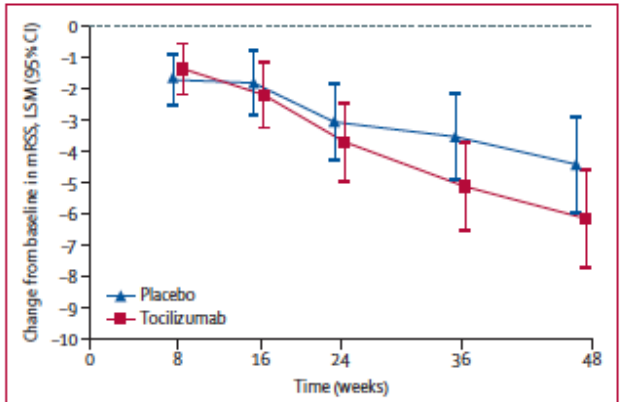
106 placebo → -4.4

104 Tocilizumab sc → -6.1

P=0.1

Age 48.2 yrs
Female 81%
Duration mean 23m
mRSS 20.4
MMF 48%
FVC 84/80% pred
DLco 77/74% pred
65% ILD on HRCT

- % pred FVC
- SGRQ ns



	Placebo n=106	Tocilizumab n=104	
LSM change from baseline at week 48 (primary outcome)	−4·4	−6·1	−1·7 (95% CI −3·8 to 0·3); p=0·10
LSM change from baseline at week 24 (exploratory outcome)	−3·1	−3·7	−0·6 (95% CI −2·3 to 1·0); nominal p=0·45

Figure 2: **Mean change from baseline in mRSS (ITT population)**
Mixed-model repeated measures analysis included the fixed categorical effects of treatment, visit, IL-6 stratification (<10 or ≥10 pg/mL at screening), IL-6 level at screening-by-visit interaction, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction. IL-6=interleukin-6. ITT=intention-to-treat. LSM=least squares mean. mRSS=modified Rodnan skin score.

Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial

Dinesh Khanna, Celia J F Lin, Daniel E Furst, Jonathan Goldin, Grace Kim, Masataka Kuwana, Yannick Allanore, Marco Matucci-Cerinic, Oliver Distler, Yoshihito Shima, Jacob M van Laar, Helen Spotswood, Bridget Wagner, Jeffrey Siegel, Angelika Jahreis, Christopher P Denton*, for the focuSSced investigators†*

Summary
Background A phase 2 trial of tocilizumab showed preliminary evidence of efficacy in systemic sclerosis. We assessed skin fibrosis and systemic sclerosis-associated interstitial lung disease (SSc-ILD) in a phase 3 trial to investigate the safety and efficacy of tocilizumab, an anti-interleukin-6 receptor antibody, in the treatment of systemic sclerosis.

Lancet Respir Med 2020; 8: 963-74
Published Online August 28, 2020

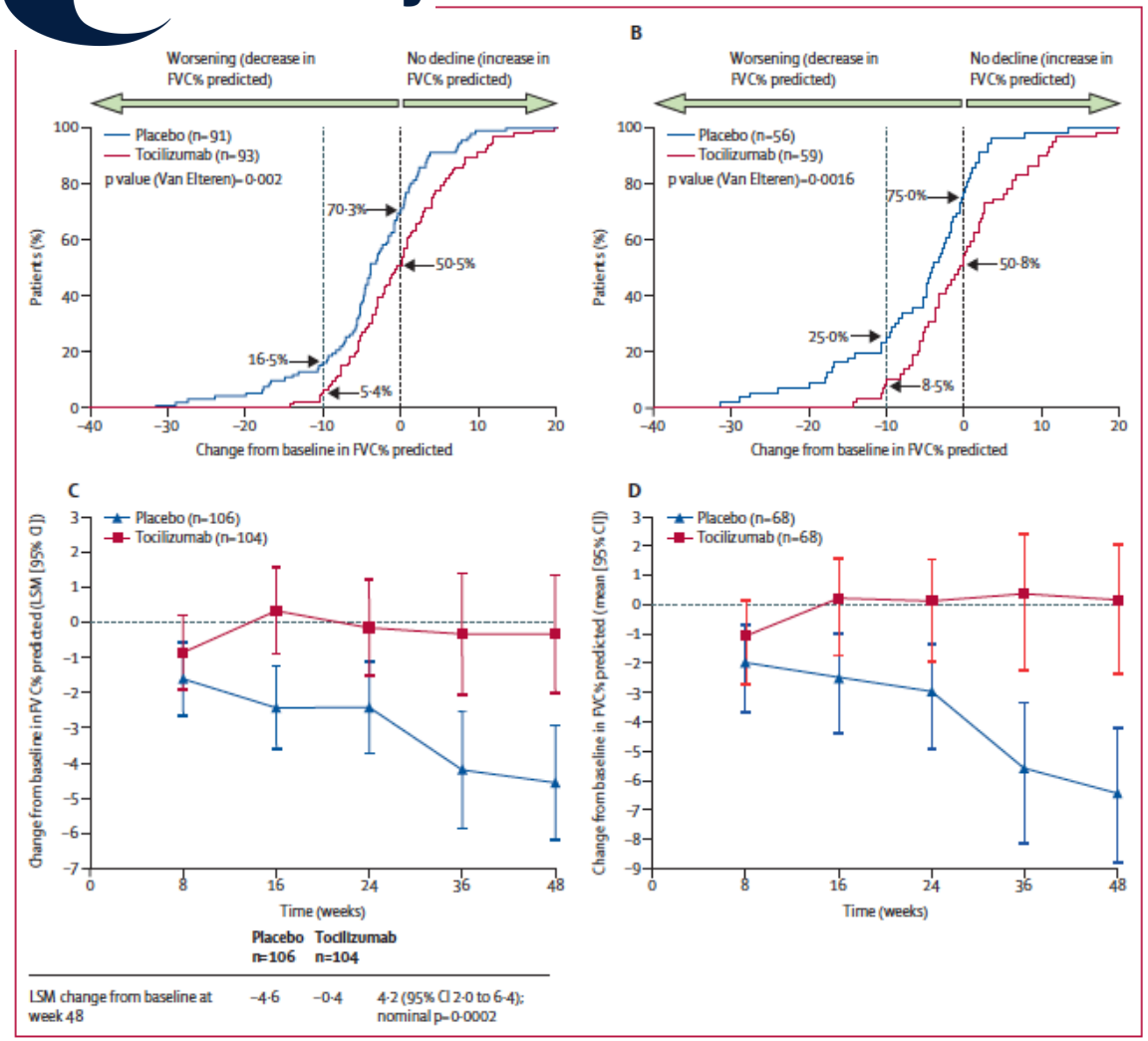


Figure 3: **Cumulative distribution (A, B) and mean change from baseline (C, D) for FVC% predicted at week 48**
Data are shown (A, C) for all participants and (B, D) for participants with systemic sclerosis-interstitial lung disease at baseline. FVC=forced vital capacity. LSM=least squares mean.

Rescue immunosuppression:
21% placebo
vs 9% tocilizumab
Selected for moderate skin scores and inflammation based on ESR/CRP
Mild early ILD

	Placebo group (n=106)	Tocilizumab group (n=104)
Participants with ≥1 adverse event	82 (77%)	89 (86%)
Participants with ≥1 infectious adverse event	53 (50%)	54 (52%)
Participants with injection site reactions	3 (3%)	8 (8%)
Participants with ≥1 serious adverse event	18 (17%)	13 (13%)
Participants with ≥1 infectious serious adverse event	7 (7%)	2 (2%)
Participants with ≥1 non-infectious serious adverse event	11 (10%)	11 (11%)
Withdrawal because of adverse event	4 (4%)	3 (3%)
Deaths	3 (3%)	1 (1%)
Most frequent serious adverse events by system organ class*		
Infections and infestations	8	3
Pneumonia	3 (3%)	0
Infected skin ulcer	1 (1%)	0
Osteomyelitis	0	1 (1%)
Pelvic inflammatory disease	0	1 (1%)
Chronic pyelonephritis	1 (1%)	0
Respiratory tract infection	1 (1%)	0
Sepsis	1 (1%)	0
Soft tissue infection	1 (1%)	0
Wound infection	0	1 (1%)
Cardiac disorders	7†	2
Acute myocardial infarction	1 (1%)	0
Angina pectoris	0	1 (1%)
Atrial fibrillation	2 (2%)	0
Cardiac failure	0	1 (1%)
Chronic cardiac failure	1 (1%)	0
Microvascular coronary artery disease	1 (1%)	0
Myocardial infarction	1 (1%)	0
Myocarditis	1 (1%)	0

Data are n (%) or n. *At least 5% of participants in either treatment arm.
†Six patients had seven events (one patient had two events of atrial fibrillation).

Table 4: **Safety (safety population)**

Ulster University

The RECITAL trial compared cyclophosphamide and rituximab in CTD-ILD

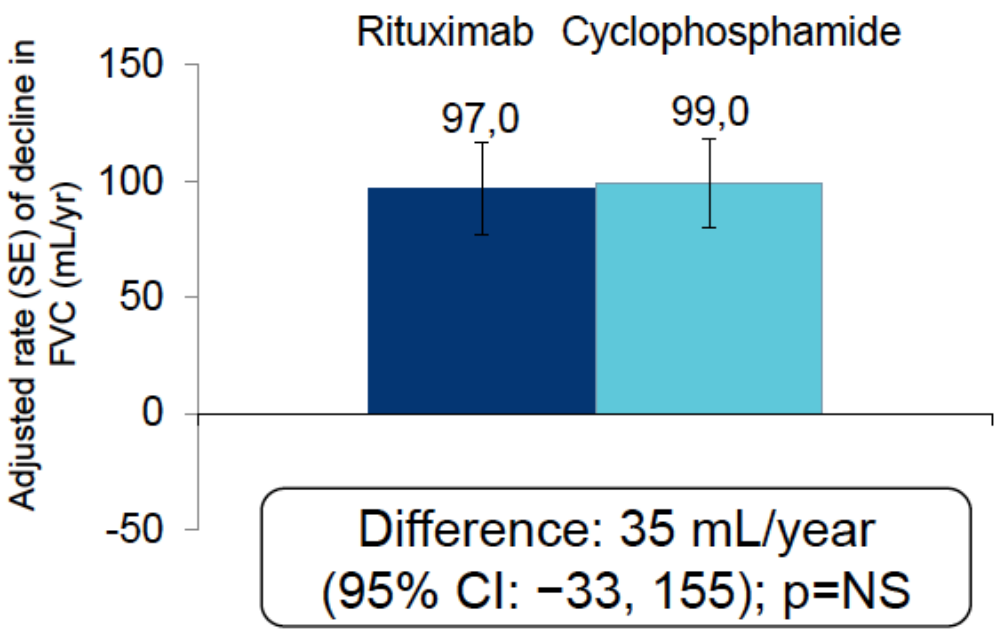
Factor	Cyclophosphamide	Rituximab
N	50	51
Age (years), median (IQR)	57.5 (50.0, 66.0)	58.0 (51.0, 64.0)
Sex		
Female	37 (74%)	33 (65%)
Male	13 (26%)	18 (35%)
Connective tissue disease type		
Myositis	23 (46%)	22 (43%)
Mixed Connective Tissue Disease (MCTD)	8 (16%)	9 (18%)
Systemic sclerosis	19 (38%)	20 (39%)
Time since onset of CTD (years), median (IQR)	1.5 (0.7, 8.1)	2.3 (1.1, 4.6)

Maher et al. Lancet Respir Med. 2022 Nov 11:S2213-2600(22)00359-9

Ulster University

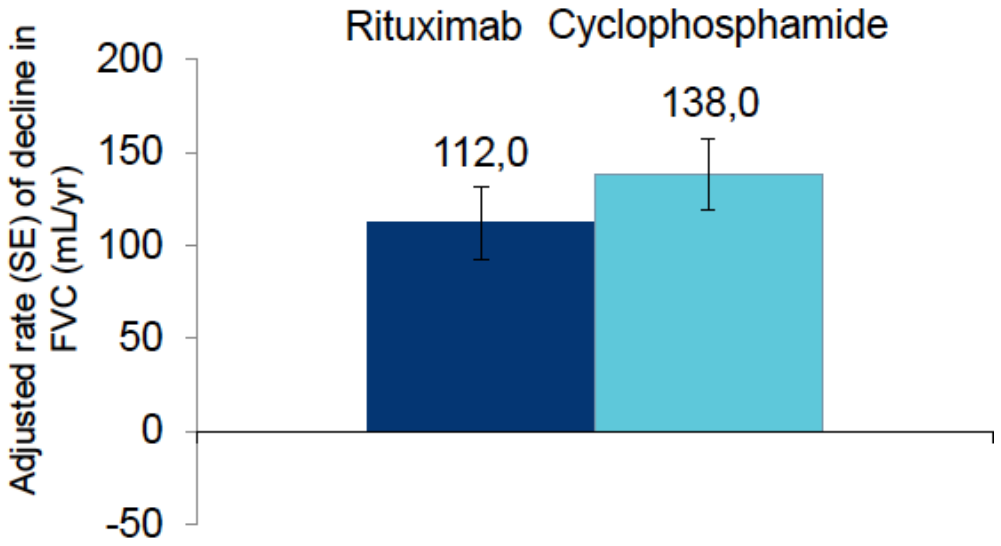
Similar improvement of FVC with both drugs was shown

Prim. endpoint: Δ FC week 24



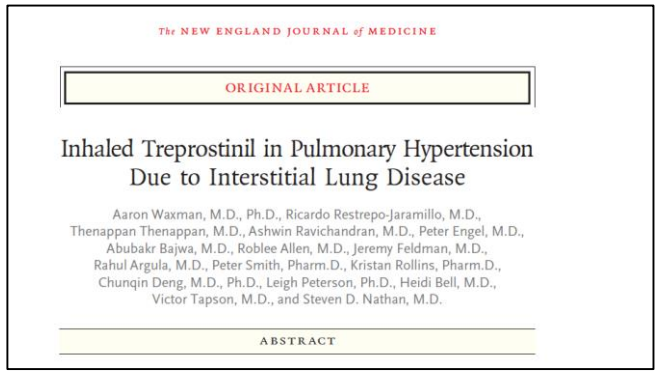
Difference: 35 mL/year
(95% CI: −33, 155); p=NS

Sec. endpoint: Δ FVC week 48



But less toxicity with Rituximab

Maher et al. Lancet Respir Med. 2022 Nov 11:S2213-2600(22)00359-9



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease

Aaron Waxman, M.D., Ph.D., Ricardo Restrepo-Jaramillo, M.D., Thenappan Thenappan, M.D., Ashwin Ravichandran, M.D., Peter Engel, M.D., Abubakr Bajwa, M.D., Roblee Allen, M.D., Jeremy Feldman, M.D., Rahul Argula, M.D., Peter Smith, Pharm.D., Kristan Rollins, Pharm.D., Chunqin Deng, M.D., Ph.D., Leigh Peterson, Ph.D., Heidi Bell, M.D., Victor Tapson, M.D., and Steven D. Nathan, M.D.

ABSTRACT

INCREASE Treprostinil – PH-ILD

Occurrence of clinical worsening — no. (%)			0.61 (0.4 to 0.92)**	0.04
Any event	37 (22.7)	54 (33.1)		
Hospitalization for cardiopulmonary indication	18 (11.0)	24 (14.7)		
Decrease in 6-minute walk distance of >15% from baseline	13 (8.0)	26 (16.0)		
Death from any cause	4 (2.5)	4 (2.5)		
Lung transplantation	2 (1.2)	0		

Criteria

ILD

WHO gp 3 PH on RHC within a year

CTD-ILD FVC<70%

randomised

163 placebo

163 Treprostinil Neb qds

Age 66.5 yrs
Female 46.9%
IIP 44.8% (IPF28.2%)
CPFE 25.2%; CTD 22.1% chHSP 5.8%
m6MWD 259.6m
mPVR 6.2 WU
mNT-proBNP 1832.9
Pirfenidone 13% Nint 9.2% None 77.3

Primary endpoint
Change in 6MWD at 16 w

-10.04m

21.08m

P<0.001

- Change NT-proBNP p<0.001
- -396 vs 1453
- SGRQ ns

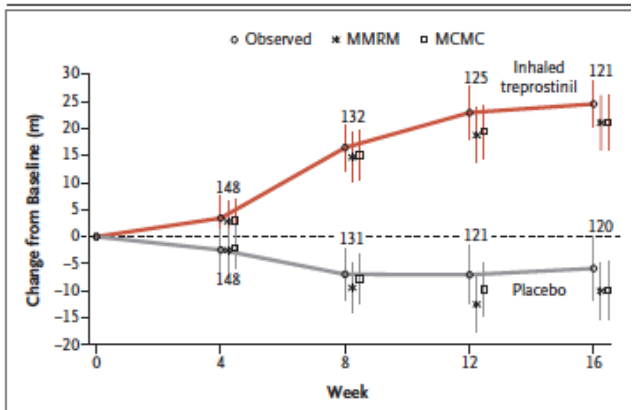


Figure 2. Mean Change from Baseline in Peak 6-Minute Walk Distance through Week 16.

Short duration
21% discontinuation
Effect size same as MCID

Ulster University

NEJM Evidence
Published May 22, 2023
DOI: 10.1056/EVIDoa2300083

ORIGINAL ARTICLE

Nalbuphine Tablets for Cough in Patients with Idiopathic Pulmonary Fibrosis

Toby M. Maher, M.D., Ph.D.,[1,2] Cristina Avram, M.D.,[3] Enoch Bortey, Ph.D.,[4] Simon P. Hart, M.D., Ph.D.,[5] Nikhil Hirani, M.D., Ph.D.,[6] Philip L. Molyneux, M.D., Ph.D.,[2] Joanna C. Porter, M.D., Ph.D.,[2] Jaclyn A. Smith, M.D., Ph.D.,[7] and Thomas Sciascia, M.D.[8]

- 22 day treatment Cross over trial
- 41 patients enrolled

Table 1. Baseline Characteristics.

No. of patients	38
Mean age — yr	74
Male — no. (%)	32 (84.2)
Antifibrotic usage — no. (%)	18 (47.4)
Proton pump inhibitors — no. (%)*	28 (68.3)
Daytime cough frequency (coughs/hour)	
Mean	28.0
Median	20.0
Minimum–maximum	3.2–92.4
24-hour cough frequency (coughs/hour)	
Mean	21.2
Median	16.0
Minimum–maximum	3.1–66.4

* These data are collected from the safety analysis set (n=41). All other data are from the full analysis set (patients completed one or more treatment periods).

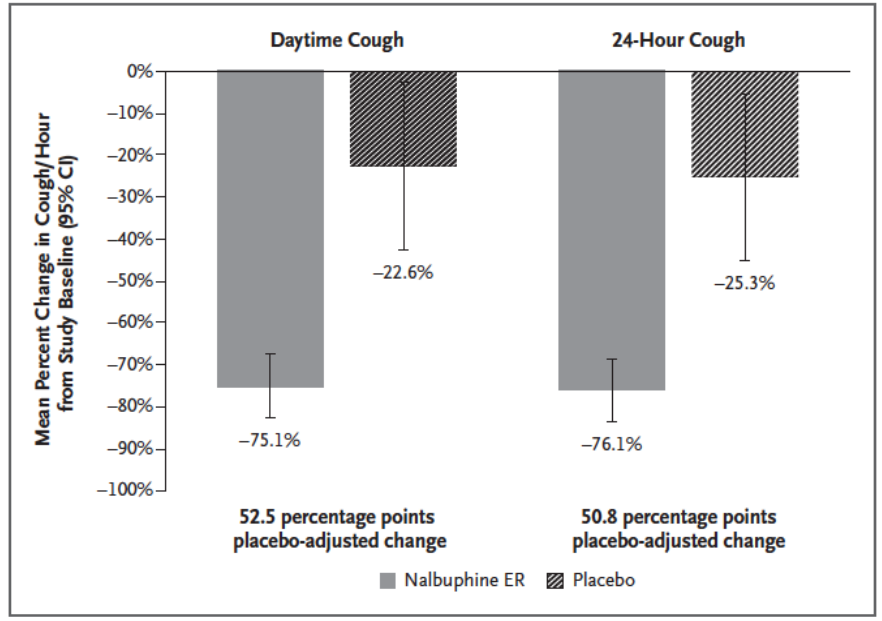


Figure 2. Geometric Mean Percent Change from Study Baseline in Coughs per Hour (n=38).
Daytime was defined as the period between the time the patient reported being awake and the time the patient went to bed. CI denotes confidence interval; and ER, extended release.

ABPI recommendations for clinical research in UK

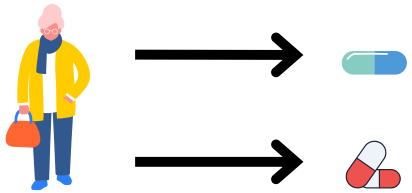
Slides courtesy of Prof Jenkins

1. Embedding Clinical Research in Healthcare
2. Reforming and streamlining approvals and set up
3. Increasing and diversifying patient recruitment into clinical trials
4. Adopting innovative clinical trial design and delivery approaches
5. Improving how the UK reports on clinical research performance

https://www.abpi.org.uk/r-d-manufacturing/clinical-research/an-opportunity-for-growth-clinical-research-in-the-uk/

REMAP Trials

Slides courtesy of Prof Jenkins

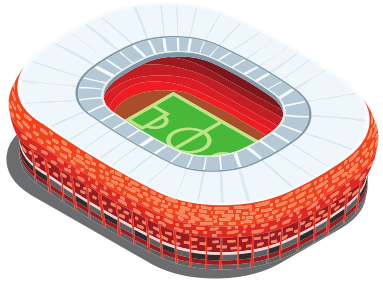


Randomised

Embedded

Multifactorial

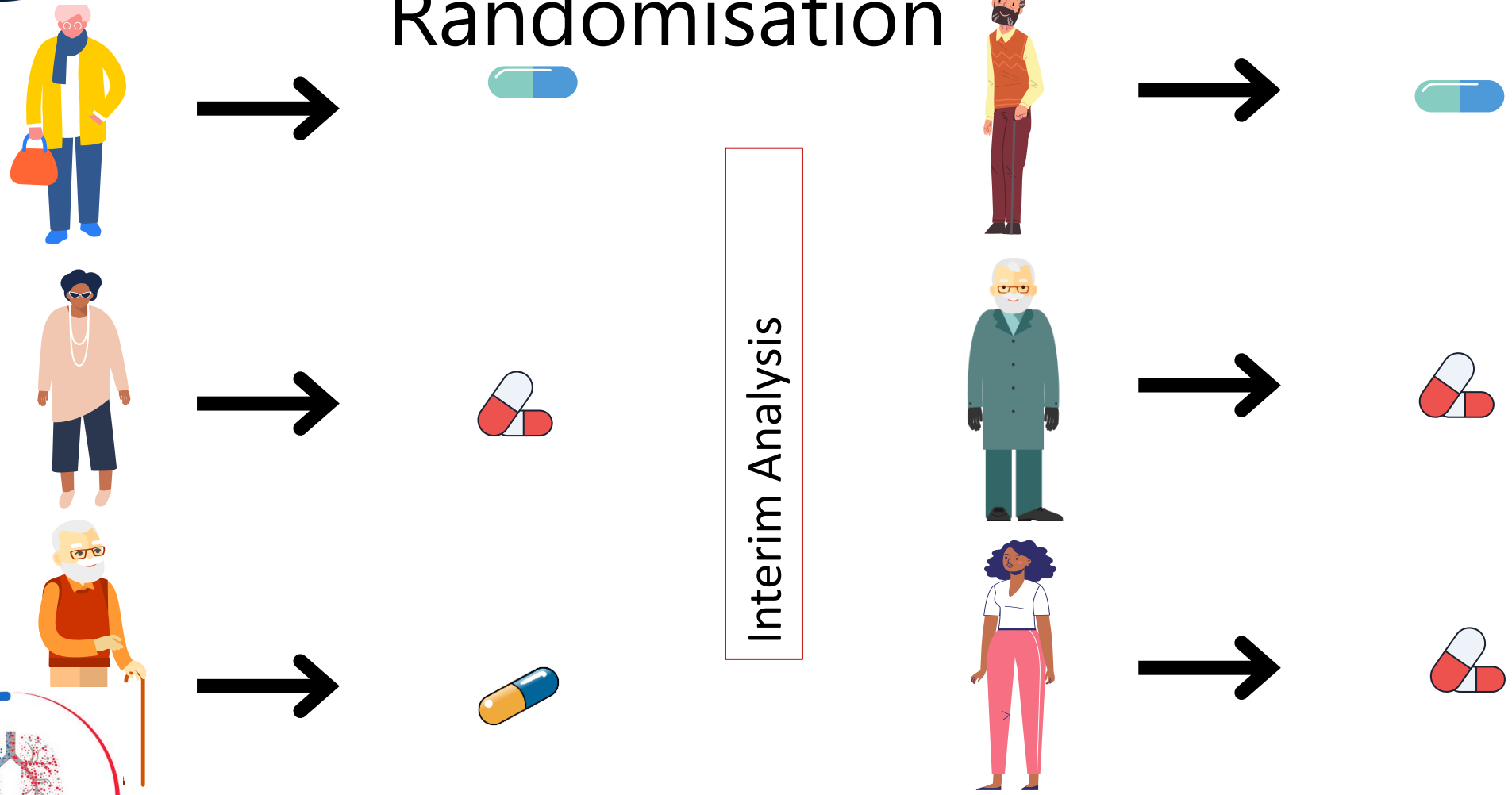
Adaptive



Platform

Thanks to Derek C. Angus, MD, MPH, University of Pittsburgh Medical Center, for "REMAP"

Response Adaptive Randomisation



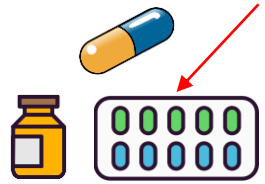
Embedded

- Improves patient care
- Improves patient recruitment
- Improves patient retention
- Reduces costs

Multifactorial

DOMAINS

Factor



Anti-fibrotic

Pulmonary Rehab

Immunomodulatory

REGIMEN

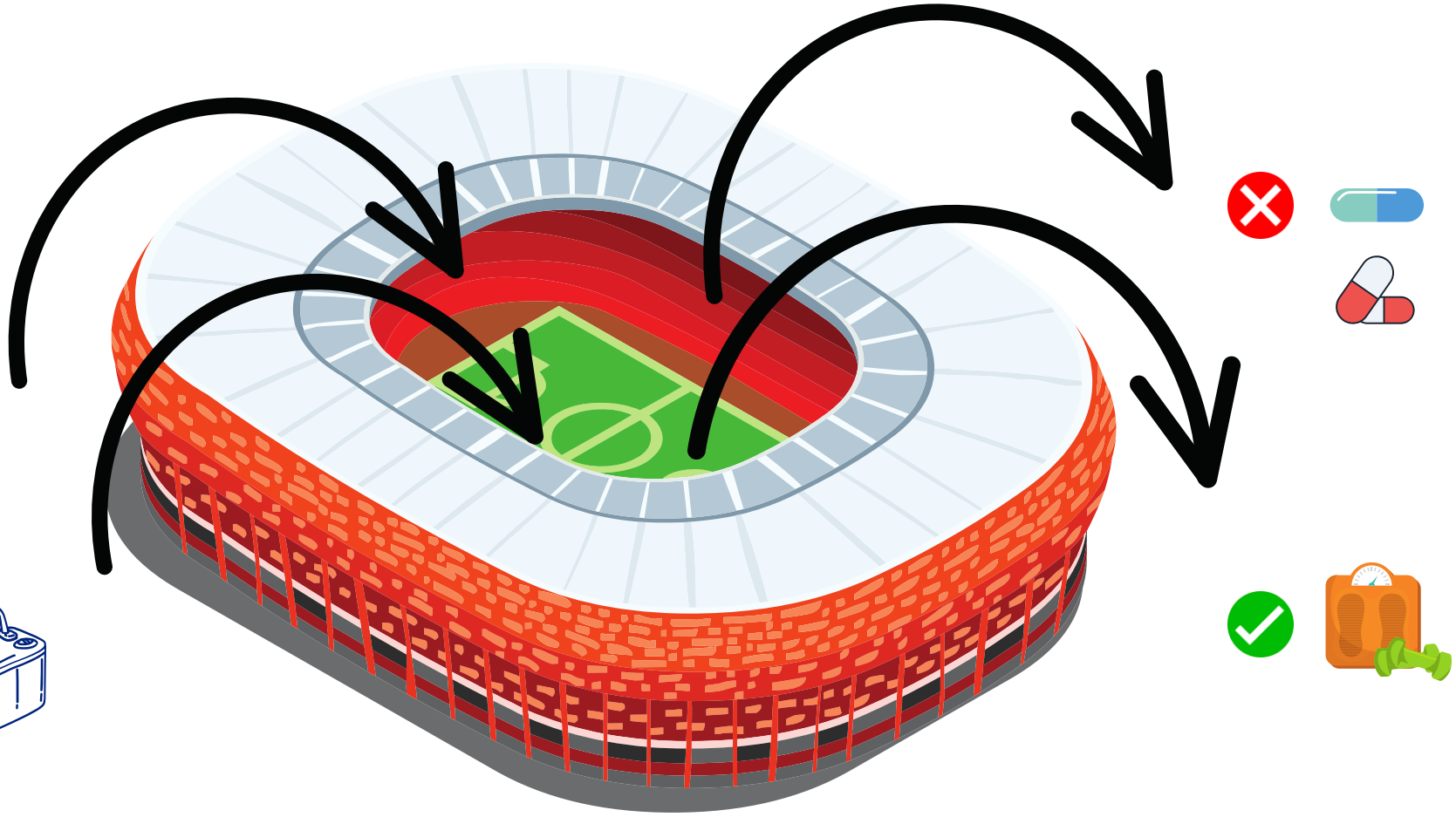
REMAP-ILD

Adaptive

- Frequent interim analyses at which adaptations are possible
- Explicit decision rules based on Bayesian predictive probabilities at each interim analysis
  - Early stopping for success
  - Early stopping for futility
- IMPs, randomization & SoC change as data evolve
- Enrichment of study population

Courtesy Berry Consultants Statistical Innovation

Platform



NIHR Accelerator Award

Develop global modular adaptive platform trial to maximise trial enrolment and participation for patients with Fibrotic ILD (FILD) aiming to achieve equitable trial access.

Our specific aims are to:

- Develop a statistical design for REMAP-ILD
- Refine the protocol for REMAP-ILD
- Engage key stakeholders to ensure successful delivery of REMAP-ILD

NIHR | National Institute for Health and Care Research

To summarise:

- Summary of Guidelines
- Lots of ongoing clinical trials