Meso-ORIGINS feasibility study results, final design and main study update

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Background

- Mesothelioma presaged by an apparent episode of Benign Pleurisy (aka Benign Asbestos Pleural Effusion (BAPE)) in some patients (Davies *et al*, EJCThS 2010 12% (95%CI 5-24%))
- True nature uncertain (?false negative sampling in some) but window of opportunity to study Benign-MPM evolution
- Focus of the CRUK Accelerator Project PREDICT-Meso
- Within PREDICT-Meso, Meso-ORIGINS will recruit and follow up patients with **benign initial biopsies**, generating matched **Benign-MPM tissue pairs**
- The current MESO-ORIGINS feasibility study addresses areas of uncertainty in study design, including sample size and surveillance protocol

Uncertainties prior to Feasibility Study

PREDICT-Meso

1. Sample size, based on a more precise estimate of evolution rate (benign biopsy with subsequent Mesothelioma ≤2 years)?
   - Target = 63 pairs needed for downstream 'omic pipeline
   - Pre-feasibility sample size = 590 (Based on 12% (5-24%) Evolution[1] & 10% loss to FU)

2. Recruitment Feasibility
   - Can sufficient numbers be recruited over 3.5 yr using the proposed eligibility criteria?
   - Assumption that 25 UK sites will be opened.
   - Target = 27 patients in 12 months from 4 UK sites (2.25 patients/month)

3. What form of surveillance and repeat pleural biopsy would be:
   a) Acceptable to participants
   b) Technically possible, particular repeat Thoracoscopy

1. Davies *et al*, EJCTS 2010

Methods

- Multi-centre feasibility study with retrospective and prospective elements
- 4 UK Pleural Disease centres

Inclusion Criteria

- History of asbestos exposure or compatible imaging, e.g. plaques
- Initial histological diagnosis (LAT/image guided) of Benign Fibrinous Pleurisy, Non-specific Pleuritis, Atypical Mesothelial Proliferation (radiological diagnosis of BAPE permitted for prospective study)

Exclusion Criteria

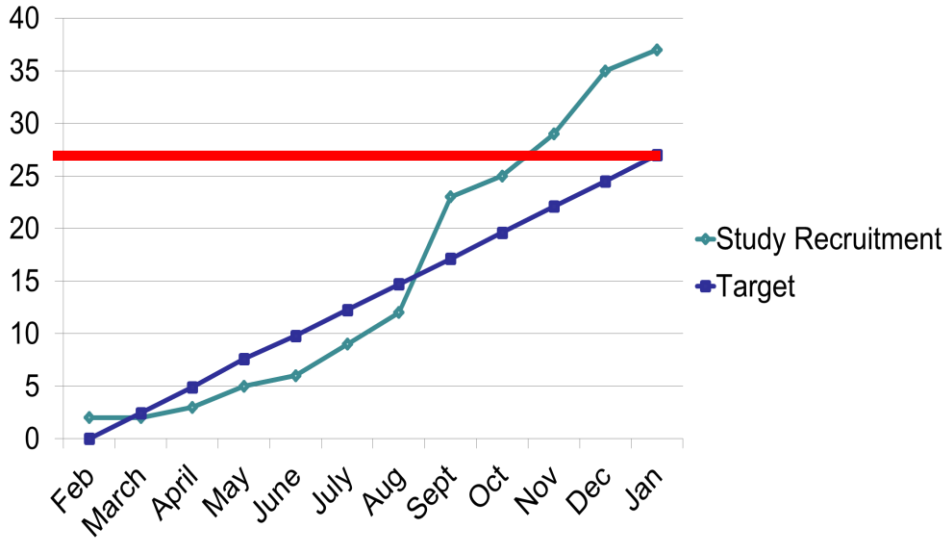
- MPM or any secondary pleural malignancy
- Pleural infection, empyema or granulomatous pleuritis

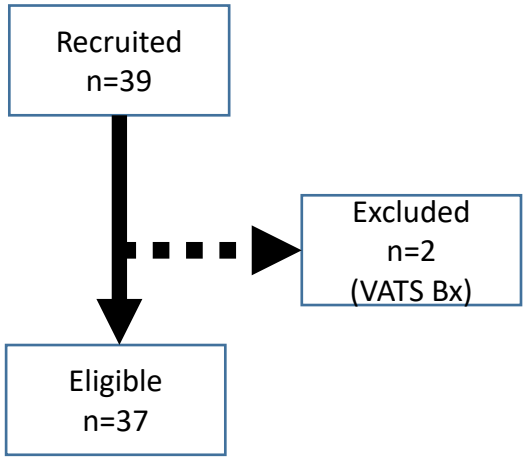
<u>PLUS</u> for retrospective study – VATS biopsy cases permitted and two years follow up data required

Objectives and Endpoints

	Study Objective	Associated End-point
Prospective Study	**Primary**: Feasibility of recruitment based on proposed surveillance protocol (including LAT)	Recruitment rate
	Secondary: To explore reasons for declining consent to surveillance and the acceptability	Patient acceptability questionnaire results
Retrospective Study	**Primary**: To determine the rate of MPM evolution in patients with initial benign biopsies	Proportion of eligible patients in whom MPM is diagnosed within 2 years of biopsy
	Secondary: identify baseline predictors of MPM transition	Logistic regression model for MPM evolution using baseline data

Results - Prospective Study



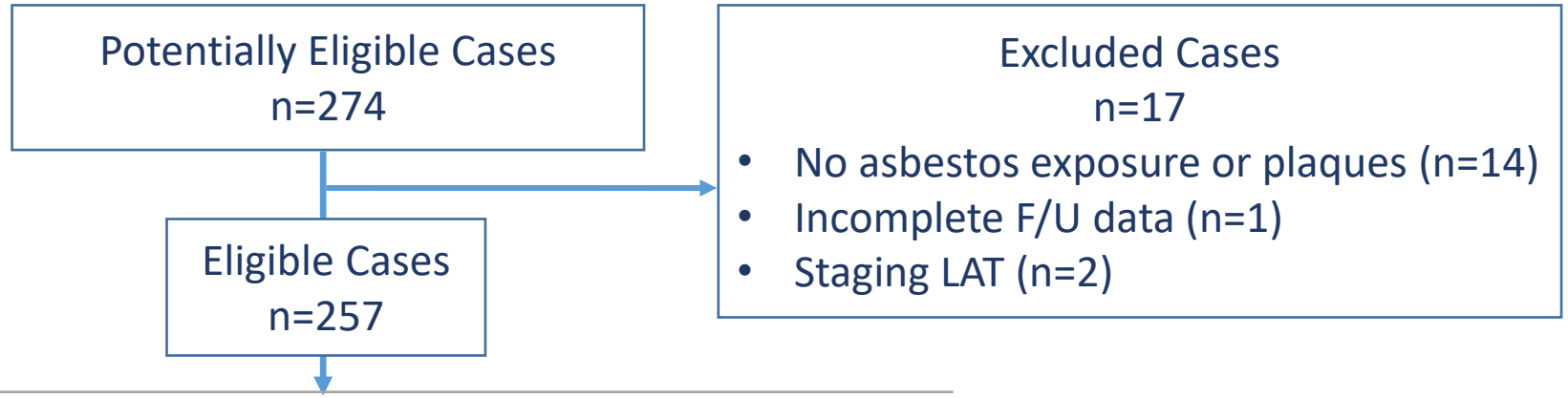


Baseline Characteristics	n=37
Age, median (range)	73 (52-88)
Male, No. (%)	37 (100%)
Effusion left sided, No. (%)	19 (51%)
Effusion unilateral, No. (%)	35 (95%)
Effusion <50% thorax, No. (%)	32 (86%)
Pleural Plaques on CT, No. (%)	29 (78%)
Benign CT according to report, No. (%)	32 (86%)

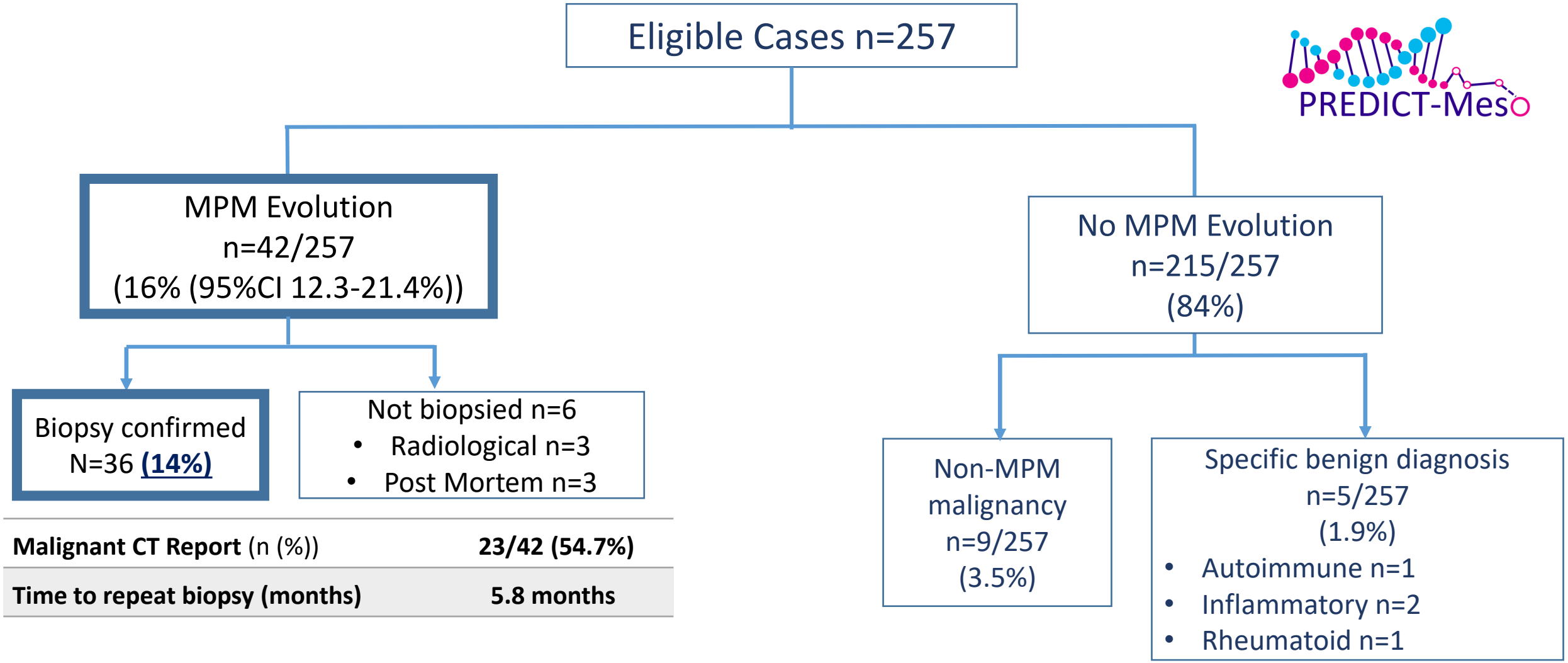
- 27 completed face-to-face LAT assessment (9 unable due to COVID restrictions and 1 death)
- LAT was technically feasible in 13/27 (48%) patients who had US assessment BUT 5/13 would refuse repeat LAT – **LAT is both feasible and acceptable in 8/27 (29.6%)**
- US guided biopsy was feasible in 3/27 (11%)
- Rate of BAPE to MPM progression – 4/37 (10.8%)

Patient acceptability Questionnaire Results	Number of patients (hypothetically) consenting (%) n=35
Blood test	35 (100%)
Breath test	34 (97%)
CT scan	34 (97%)
MRI scan	35 (100%)
Pleural fluid aspirate	28 (80%)
LAT	23 (66%)

Results - Retrospective Study



Age (Mean (SD))	72 (9) years
Male gender (n (%))	243 (95%)
Asbestos exposure history (n (%))	236 (92%)
Effusion: **Right sided** (n (%))	126 (49%)
Unilateral (n (%))	236 (92%)
<50% Hemithorax (n (%))	201 (78%)
Pleural plaques on CT (n (%))	167 (65%)
Malignant CT Report (n (%))	68 (26%)



Malignant CT Report (n (%))	**23/42 (54.7%)**
Time to repeat biopsy (months)	**5.8 months**

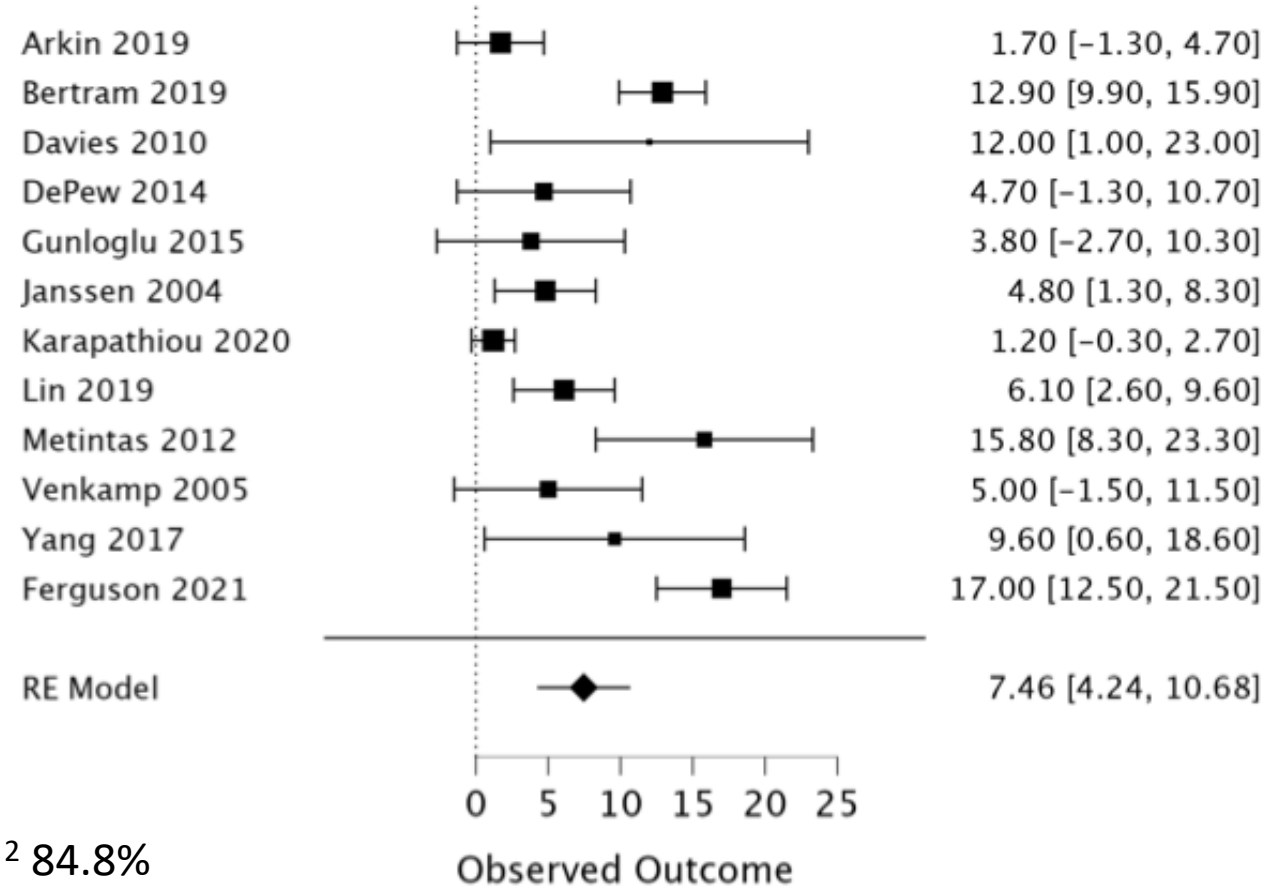
Regression model:

- Univariate analysis: age (OR 1.06, (95% CI 1.02-1.11), p=0.0055) and malignant CT report (O.R 4.41, (95% CI 2.22-8.9), p <0.0001) were the only variables associated with MPM evolution
- Multivariate analysis: age (OR 1.06, (95% CI 1.02-1.12), P<0.0001) and malignant CT (OR 4.78, (95% CI 2.36-9.86), p<0.0001) retained independent predictive value for MPM evolution

Results in Context

	Benign Pleuritis Cases (n)	MPM Evolutions (n)	Evolution Rate (%)	Entry Criteria: VATS/LAT/Other	Exposure/Plaques	Median F/U (months)	Country and Region	Prospective or Retrospective
Arkin 2019	119	2	1.7	VATS	N/R	29	Turkey, Istanbul	Retrospective
Bertram 2019	658	85	12.9	VATS	N/R	36	Denmark	Retrospective
Davies 2010	42	5	12	LAT	22	21	UK, Oxford	Retrospective
DePew 2014	64	3	4.7	VATS & Open	N/R	60	USA, Minnesota	Retrospective
Gunloglu 2015	53	2	3.8	VATS	N/R	24	Turkey	Retrospective
Janssen 2004	208	10	4.8	LAT	N/R	9	Netherlands	Retrospective
Karapathiou 2020	259	3	1.2	VATS & LAT	N/R	47	France	Retrospective
Lin 2019	213	13	6.1	LAT	N/R	40	UK, Cambridge	Retrospective
Metintas 2012	101	16	15.8	LAT	N/R	24	Turkey	Prospective
Venkamp 2005	60	3	5	LAT	22.9	33	Belgium	Retrospective
Yang 2017	52	5	9.6	LAT	N/R	35	China	Retrospective
Ferguson 2021	257	42	17	LAT, VATS, image guided Bx	100	24	UK	Retrospective
TOTAL	**2086**	**189**						

Results: Random Effects Metanalysis

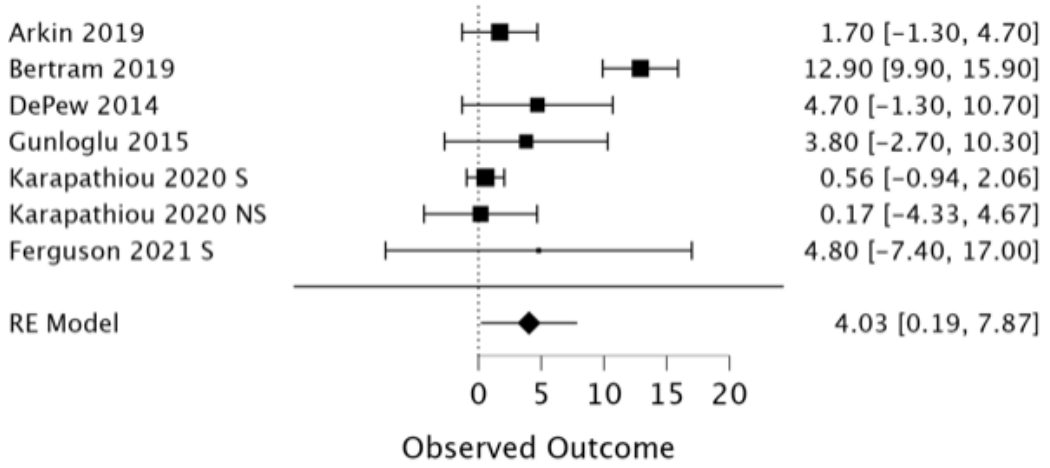


I^2 84.8%
p<0.001

Study Characteristic	Residual I^2	P-value
Surgical v Non-surgical Biopsy	81.9%	0.223
Age of Study (Pre-/Post-2010)	81.14	0.461
Median F/U	75.596	0.077
Regional MPM Incidence	Not Computed	
Asbestos Exposure	Not Computed	

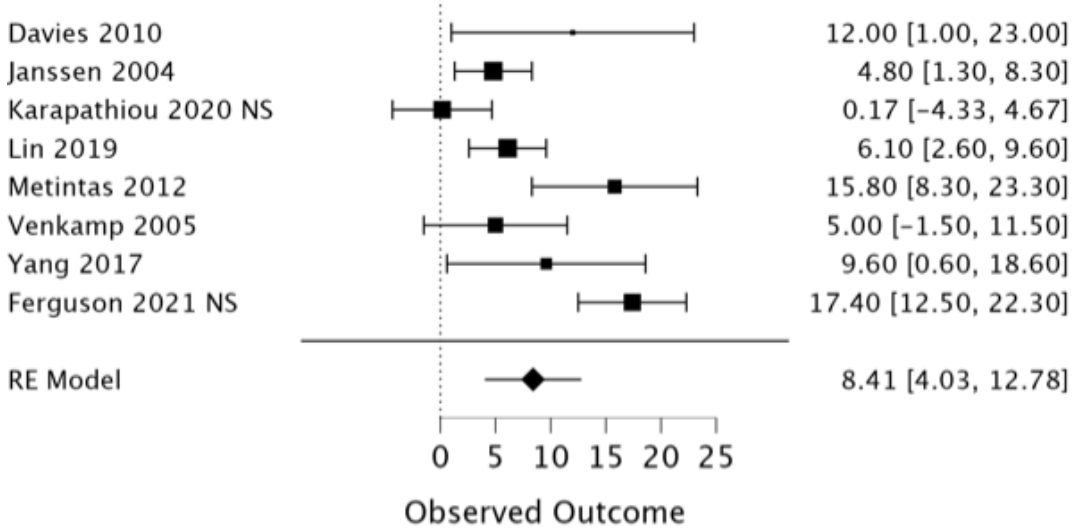
Results: Surgical v Non-surgical Sampling

Surgical: VATS or Open Biopsy



I^2 86.1%
p<0.001

Non-Surgical: LAT or Image guided Biopsy



I^2 80.7%
p<0.001

Summary and Final Design

1. Based on biopsy confirmed evolution rate of 14%, the original sample size estimate (n=590) will generate > 63 Benign-MPM tissue pairs
   - Sample size therefore reduced to n=500 (assuming 10% loss to FU)

2. Recruitment of sufficient numbers using current eligibility criteria is feasible
   - When upscaled over 25 sites, this should deliver 500 participants
   - Frequency of Malignant CT features in Evolution cases in retrospective arm suggests initial false negatives are common - these cases will not be excluded

3. Surveillance and repeat biopsies are generally but not universally acceptable. Repeat LAT may only be technically feasible in half of patients
   - Range of repeat biopsy techniques (LAT/VATS/image-guided) required

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Questions or Comments

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Glasgow Pleural Disease Unit