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Application of a model based longitudinal network meta-analysis of FEV1 in COPD trials in clinical drug development

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Background

Clinical background

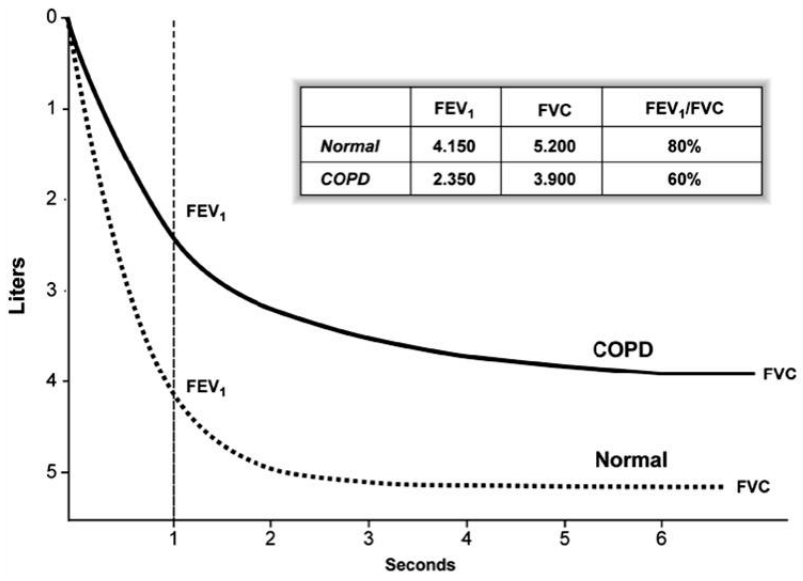
COPD = Chronic obstructive pulmonary disease:

- Projected to become 3rd leading cause of death worldwide
- Slow developing, progressive disease
- Airway obstruction & inflammation
- Maintenance treatment classes:

Direct bronchodilators (BD)	Anti-inflammatory (AI)
Long-acting β_2-agonists (**LABA**)	Inhaled corticosteroids (**ICS**)
Long-acting anticholinergics (**LAAC**)	Phosphodiesterase4 inhibitors (**PDE4i**)
	Neutrophil elastase inhibitors (**NEi**)
	P38 MAP kinase inhibitors (**P38i**)

Clinical background

Forced expiratory volume in 1 sec (FEV1):



	FEV_1	FVC	FEV_1/FVC
Normal	4.150	5.200	80%
COPD	2.350	3.900	60%

= greatest volume that can be exhaled in 1 sec after taking a deep breath

⇨ Measure for airway obstruction

- Diagnosis & assessment of COPD
- Biomarker for dose selection in *Phase 2b studies*

http://www.hse.ie/eng/health/hl/living/copd/clinical/Spirometry_Graph.html

Clinical background

Exacerbations:

= acute worsening of the COPD symptoms beyond normal day-to-day variations that lead to a change in medication

Severity class	Requires…
Moderate	Antibiotics and / or systemic corticosteroids
Severe	Visit to emergency room or hospitalization

- Annual **exacerbation rate** (**ER**) used as primary endpoint in *Phase 3 studies* and pharmacoeconomic analyses

Cazzola *et al.* Eur Respir J 2008; 31: 416–468

Clinical drug development

Decision making during clinical drug development:

Go / No-go

Should the development proceed into the next phase?

- Clinical trials are expensive and time-consuming:
  - Study design should ensure best possible outcome
  - Early prediciton of study outcomes desirable
- COPD: effect size on ER small, long studies required
  - Annual ER cannot be used as Phase 2 endpoint
  - Bridging predictions across endpoints desirable

Clinical drug development

Decision making during clinical drug development:

Comparative effectiveness

How does a new compound compare with the existing treatment options?

- Clinical trials are expensive and time-consuming
  - Conducting head-to-head trials with all available competitors is most often unfeasible
- Comparisons of observed treatment effects across studies confounded by differences in study setup

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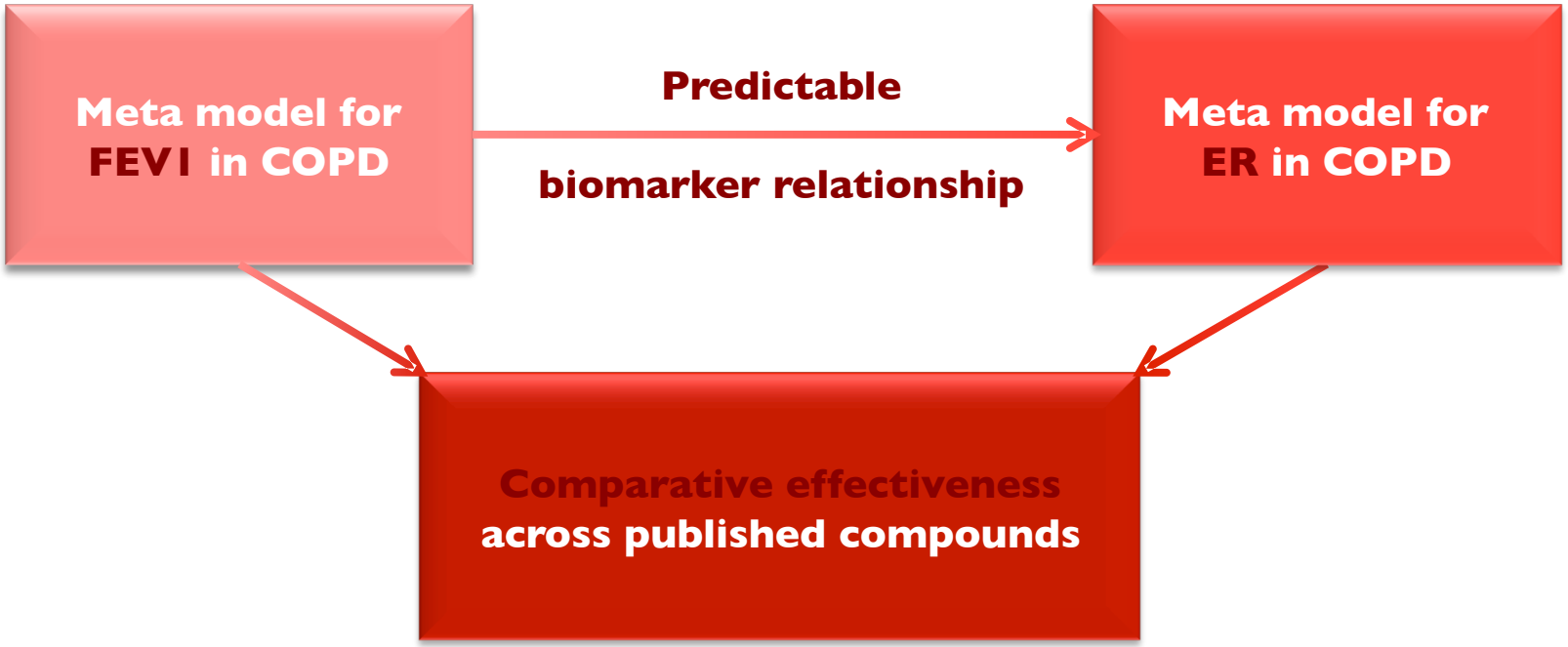
Aim

To illustrate how a model based longitudinal network meta-analysis can facilitate decision making in clinical drug development



Model based meta-analysis

Characteristics:

- *Model based* (**parametric**) analysis of *mean response* across individuals (**aggregate data**) in each study arm at *all available time points* (**longitudinal**)
- Simultaneous modelling of effects of *all available / published treatments* (**network** meta-analysis)
- Quantification of *inter-study* (ISV), *inter-arm* (IAV) and *residual unexplained variability* (RUV) possible
  - ⇨ Equivalent to population approach / mixed effects analysis (study = individual)

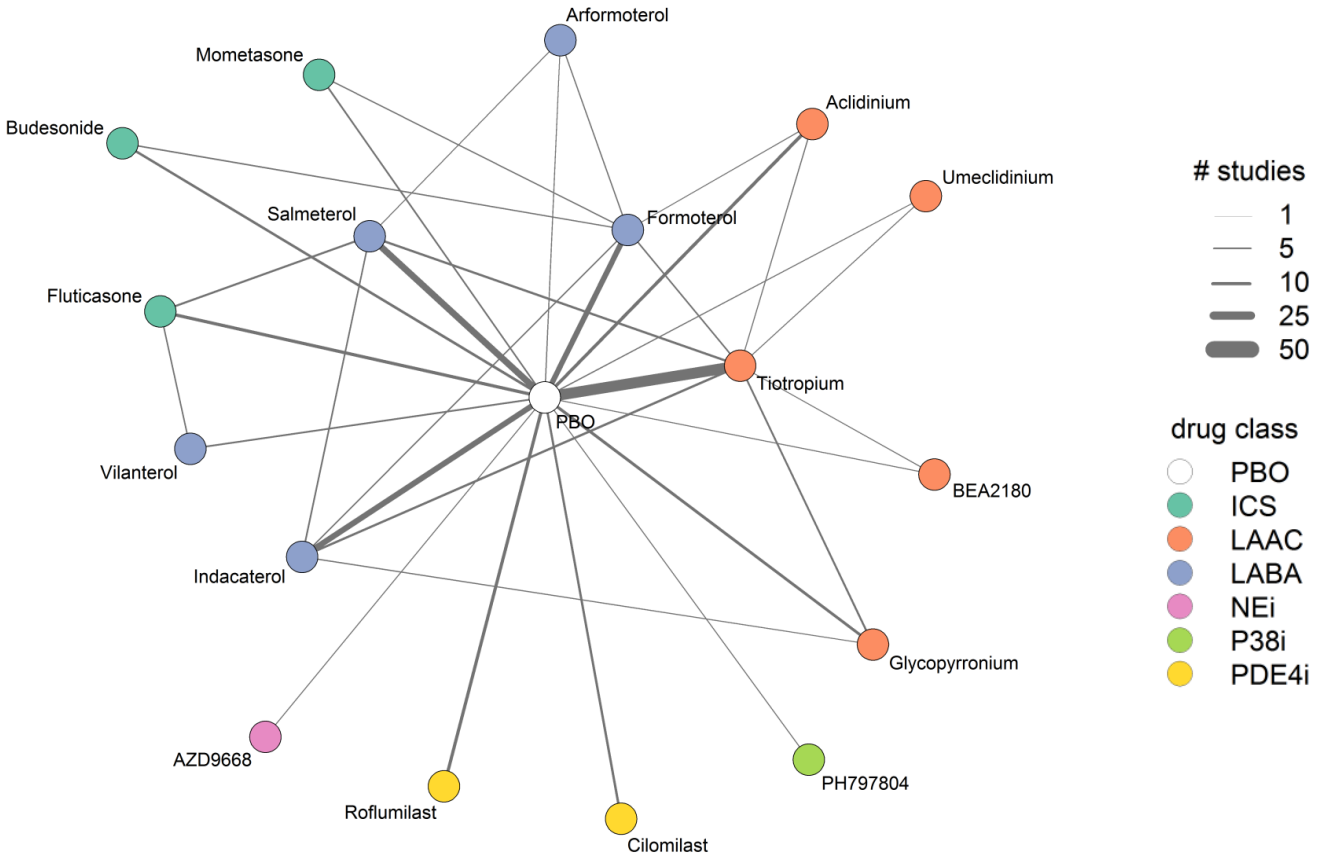
Model based meta-analysis

Benefits of conducting a model based meta-analysis:

- More efficient use of available data
- Allows more precise characterisation of:
  - Time course of on- & offset of effect
  - Placebo effect & Disease progression
  - Covariate effects
  - Random effects: ISV, IAV & RUV
- Predictions across compounds & treatment combinations and differences in study setup possible
- Comparative effectiveness can be assessed, *even in absence of direct head-to-head trials*

Literature data on FEV1 in COPD

Published head-to-head comparisons for FEV1 endpoint in COPD



Only showing studies on mono treatments

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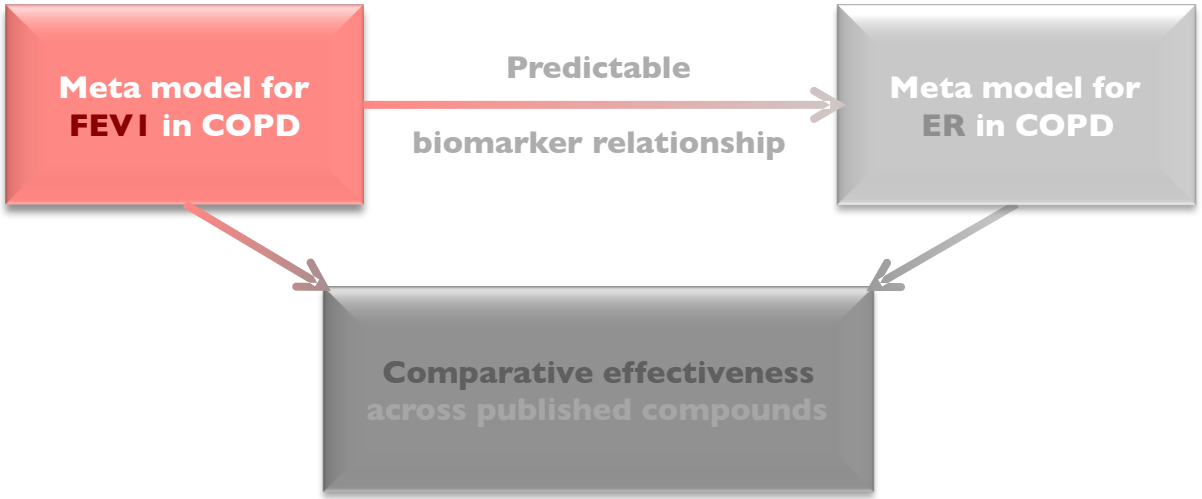
FEV1 meta model in COPD



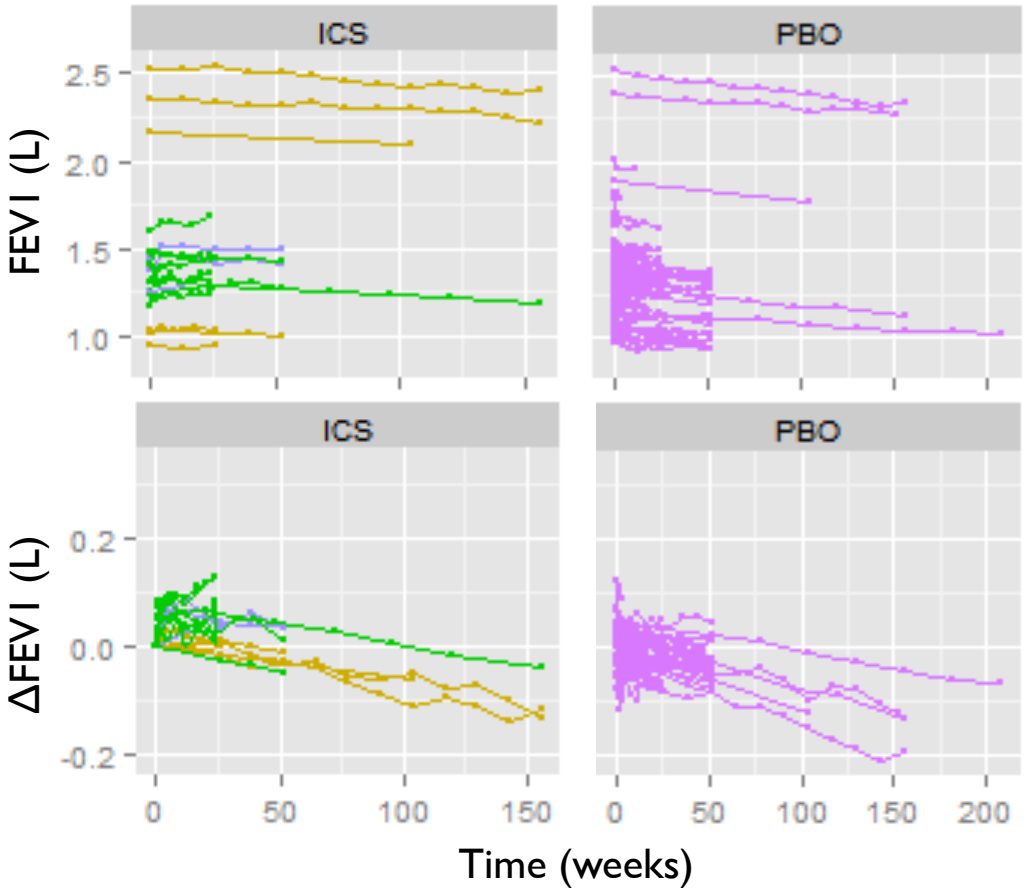
Based on Ribbing *et al.* PAGE 2012 Abstr 2530

Longitudinal FEV1 literature data

Updated Database	
until July 2013	
references	133
studies	141
arms	419
compounds	19
drug classes	6
combinations	105
observations	1982
subjects	106,422

Randomised, controlled, blinded trials
(except Spiriva® Tiotropium)

Absolute & change from baseline (Δ) FEV1 response illustrated for ICS and placebo (PBO) study treatments:



Model characteristics

Components in the updated FEV1 meta model:

- Baseline (B) with disease severity & age as covariates, ISV & IAV
- Disease progression (DP) with ISV
- Placebo effect (E_{PBO}) with additive ISV to allow for nocebo effect
- Effect of background treatment (E_{back}) with ISV
- Effect of study drug treatment (E_{drug}) with ISV

$$FEV1(t) = B - DP(t) + E_{PBO}(t) + E_{back}(t) + E_{drug}(t)$$

⇨ Not entirely additive due to:

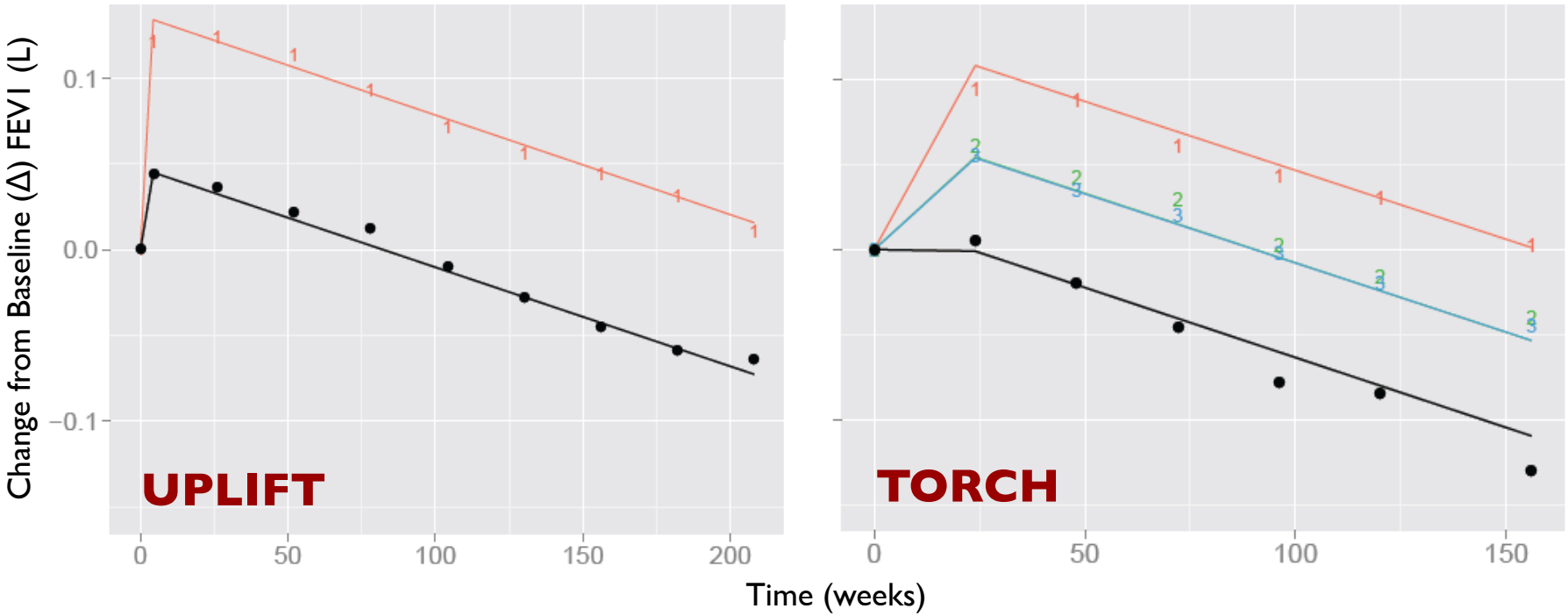
- Baseline is correlated with DP, E_{back} & E_{drug}
- Drug - drug interactions

ISV = inter-study variability
IAV = inter-arm variability
RUV dropped from equation

Based on Ribbing *et al.* PAGE 2012 Abstr 2530

Model predictions

Individual model fits for two selected studies:



Tiotropium (LAAC)
Placebo

N = 5993

Fluticasone + Salmeterol (ICS+LABA)
Fluticasone (ICS) Salmeterol (LABA)
Placebo

N = 6112

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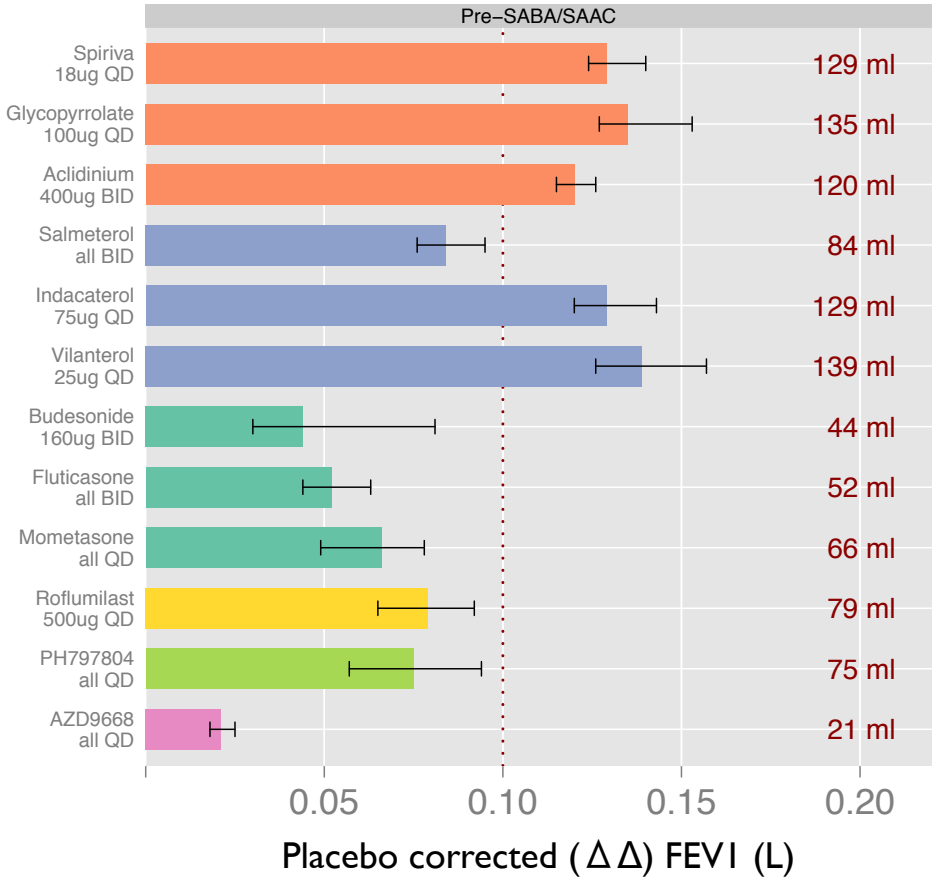
FEV1 meta model: Results

Model predictions

Predicted treatment effects in **moderate COPD** (baseline FEV1 1.2 L)



Long-acting bronchodilators (*LABD*):

Long-acting anti-cholinergics (LAAC)

Long-acting beta2-agonists (LABA)

Anti-inflammatory treatments (*AI*):

Inhaled corticosteroids (ICS)

Phosphodiesterase4 inhibitor (PDE4i)

P38 MAP kinease inhibitor (P38i)

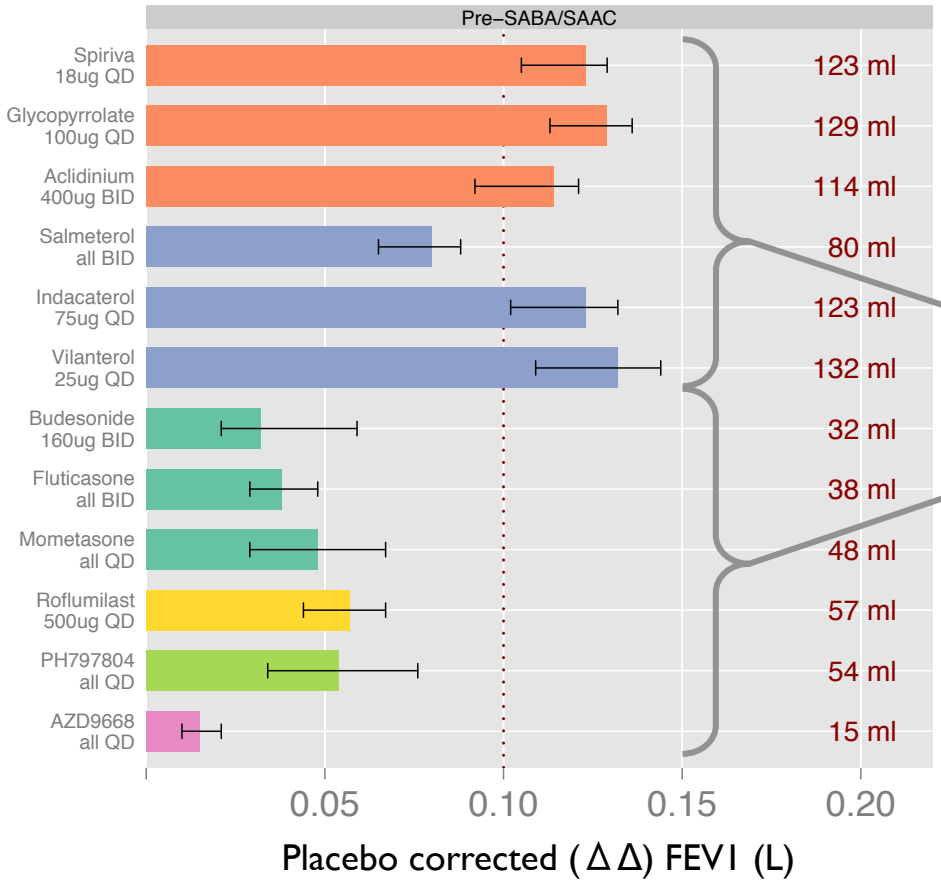
Neutrophil elastatse inhibitor (NEi)

Parameter uncertainty assessed using *sampling-importance resampling* (**SIR**) to allow for asymmetry in the 95% confidence intervals.

Dosne *et al.* PAGE 2013 Abstract 2907

Model predictions

Predicted treatment effects in **more severe COPD** (baseline FEV1 1.0 L)



Effect of lower baseline (<1.2L) on treatment effects:

Treatment	Reduction
LABD	– 4.7%
AI	– 27.8%

May explain disappointing results in published studies on roflumilast:

Reported efficacy ~50 ml

Parameter uncertainty assessed using *sampling-importance resampling* (**SIR**) to allow for asymmetry in the 95% confidence intervals.

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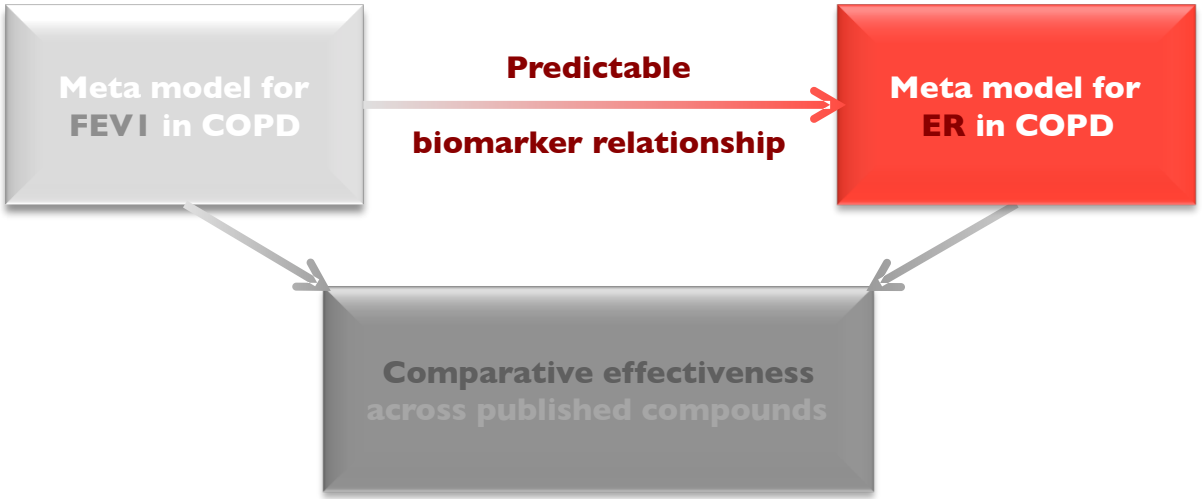
FEV1 - Exacerbation rate model



Linking FEV1 with ER

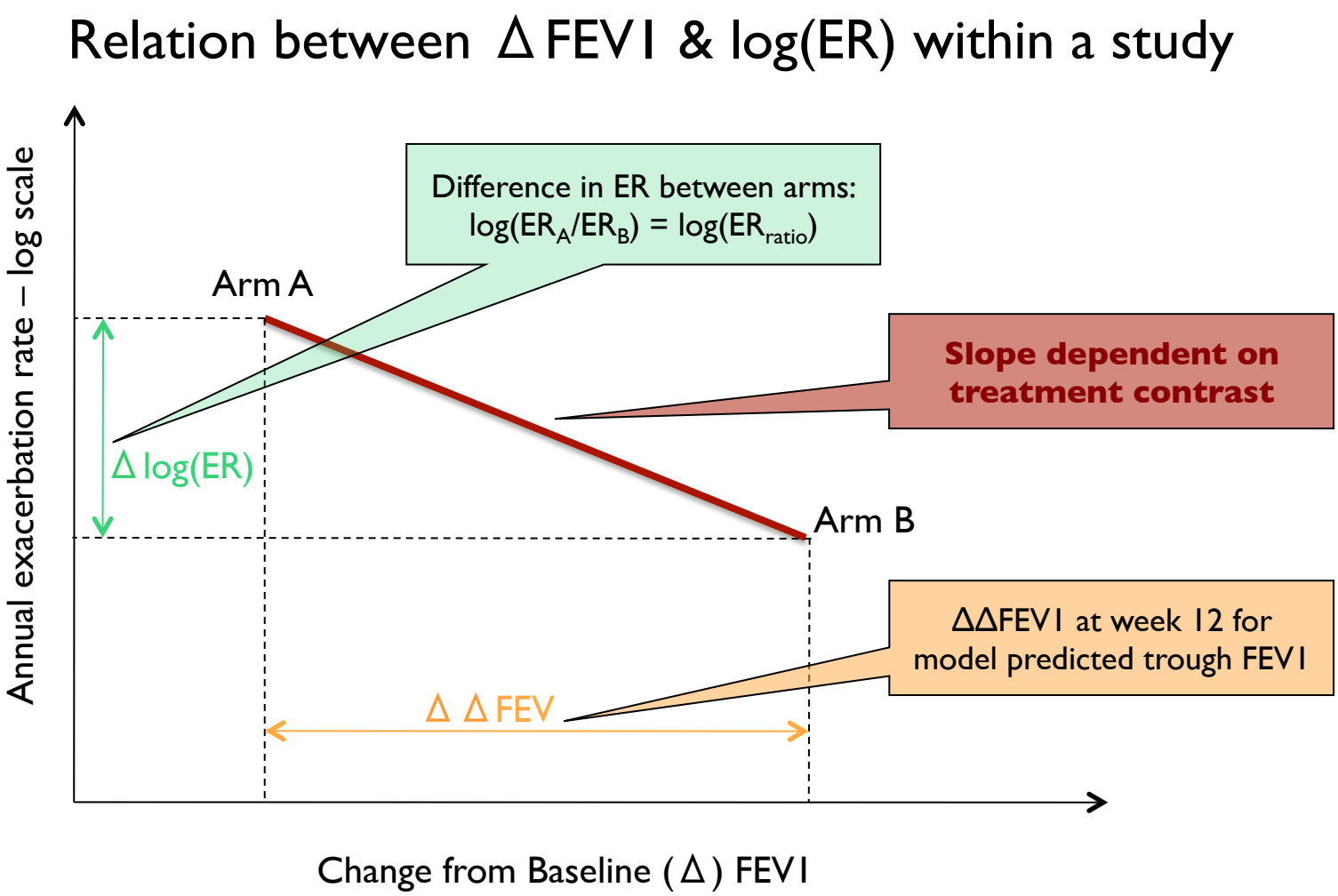
Study inclusion criteria for FEV1 - ER meta model:

- ≥ 500 subjects & ≥ 24 weeks
- Mean annual rate of *moderate or severe exacerbations* per patient per year as outcome measure

Individual FEV1 model predictions for each study arm at week 12 used as main predictor of annual ER

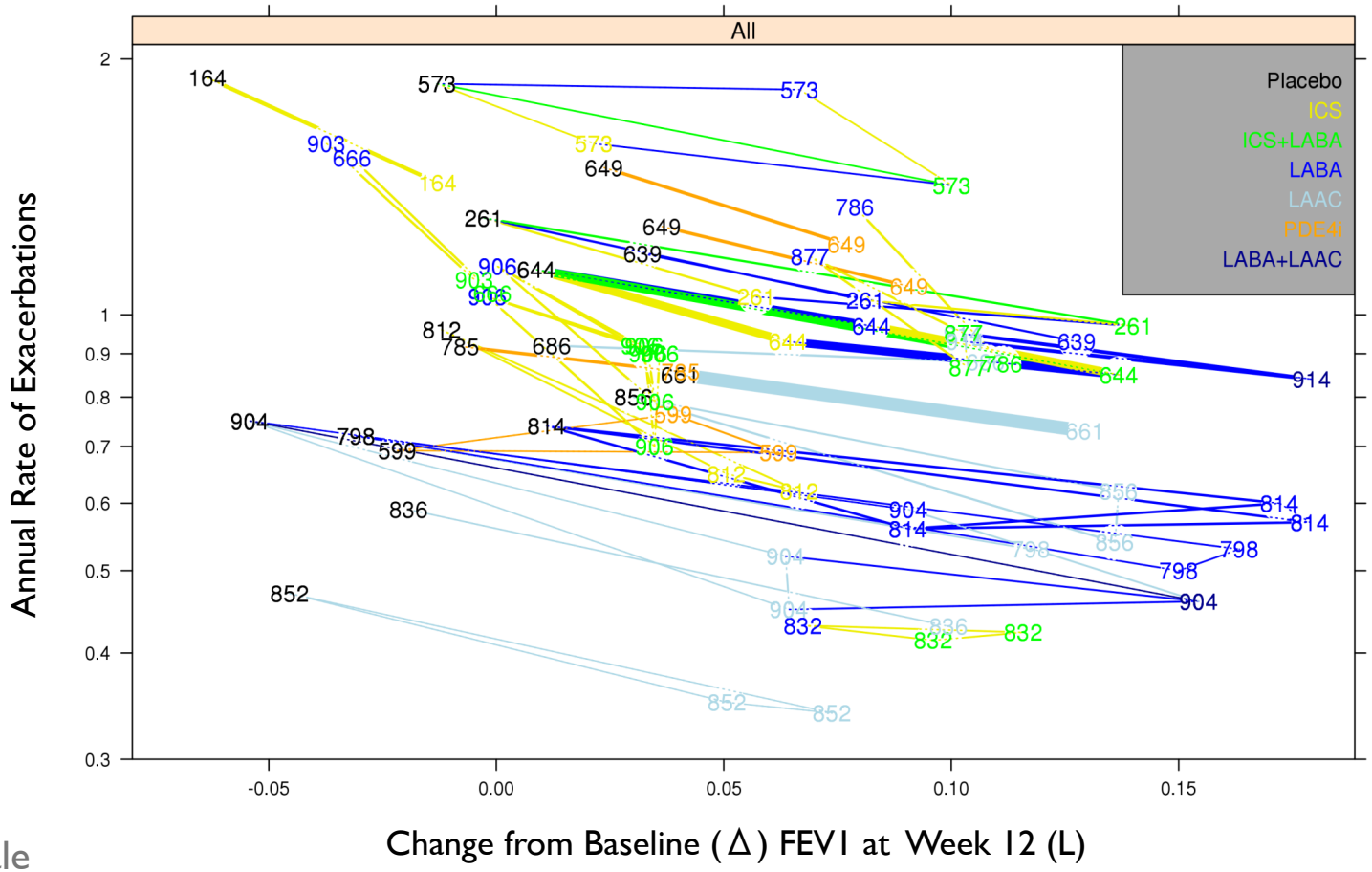
- Uncertainty in FEV1 predictions propagated (SIR)

Hypothesized FEV1 – ER relation



The data

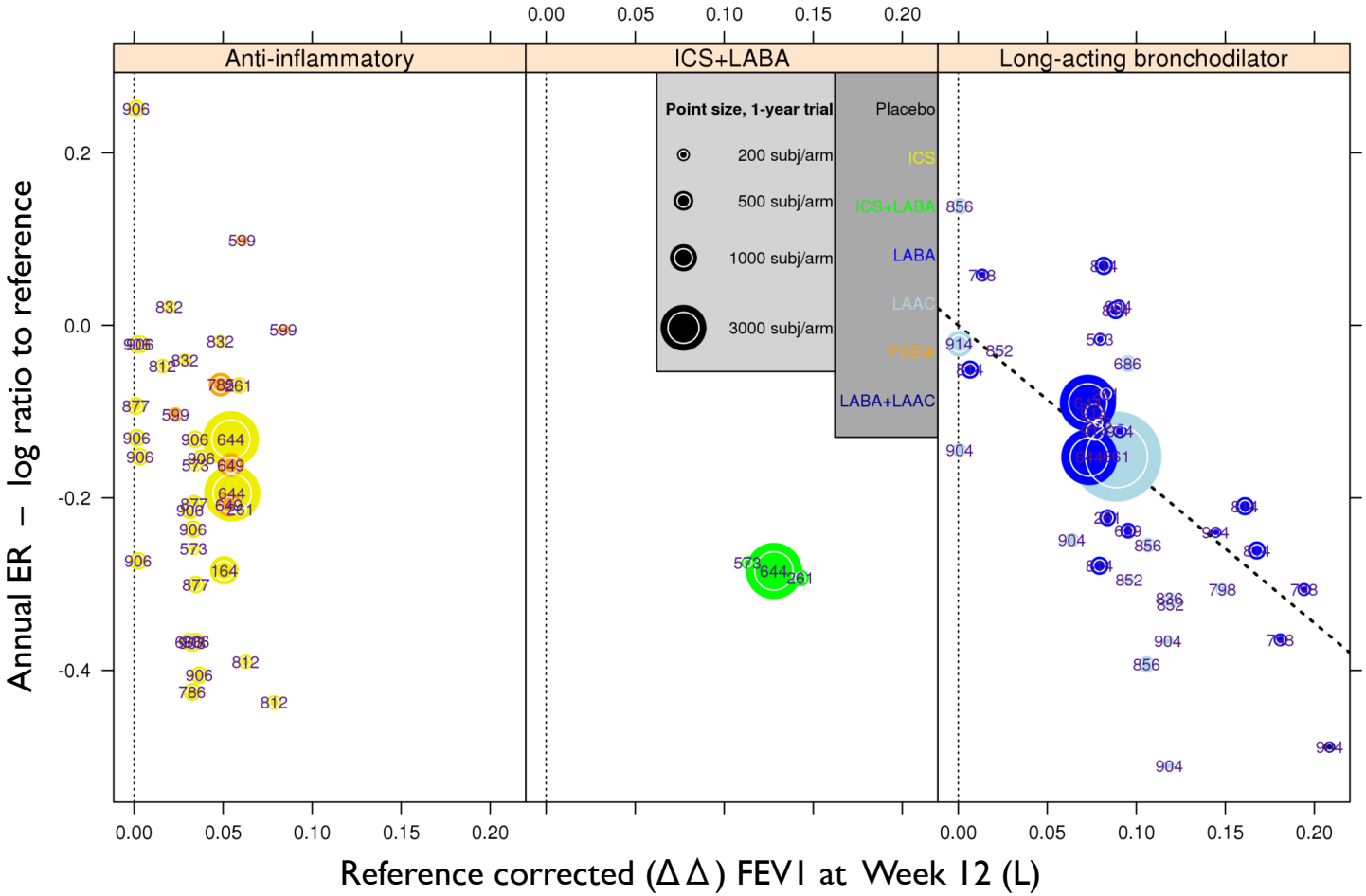
Observed ER vs. predicted Δ FEV1 at week 12



y-axis on log scale

The data

Observed $\log(ER_{ratio})$ vs. predicted $\Delta\Delta$FEV1



Model characteristics

$$ER_{obs} = ER_{PBO} \cdot exp(slp_{BD} \cdot \Delta FEV1_{BD} + slp_{AI} \cdot \Delta FEV1_{AI})$$

Additional components:

- Effect for fraction of ICS experienced subjects
- Effect for washing out ICS prior to randomization
- ISV on ER_{PBO}

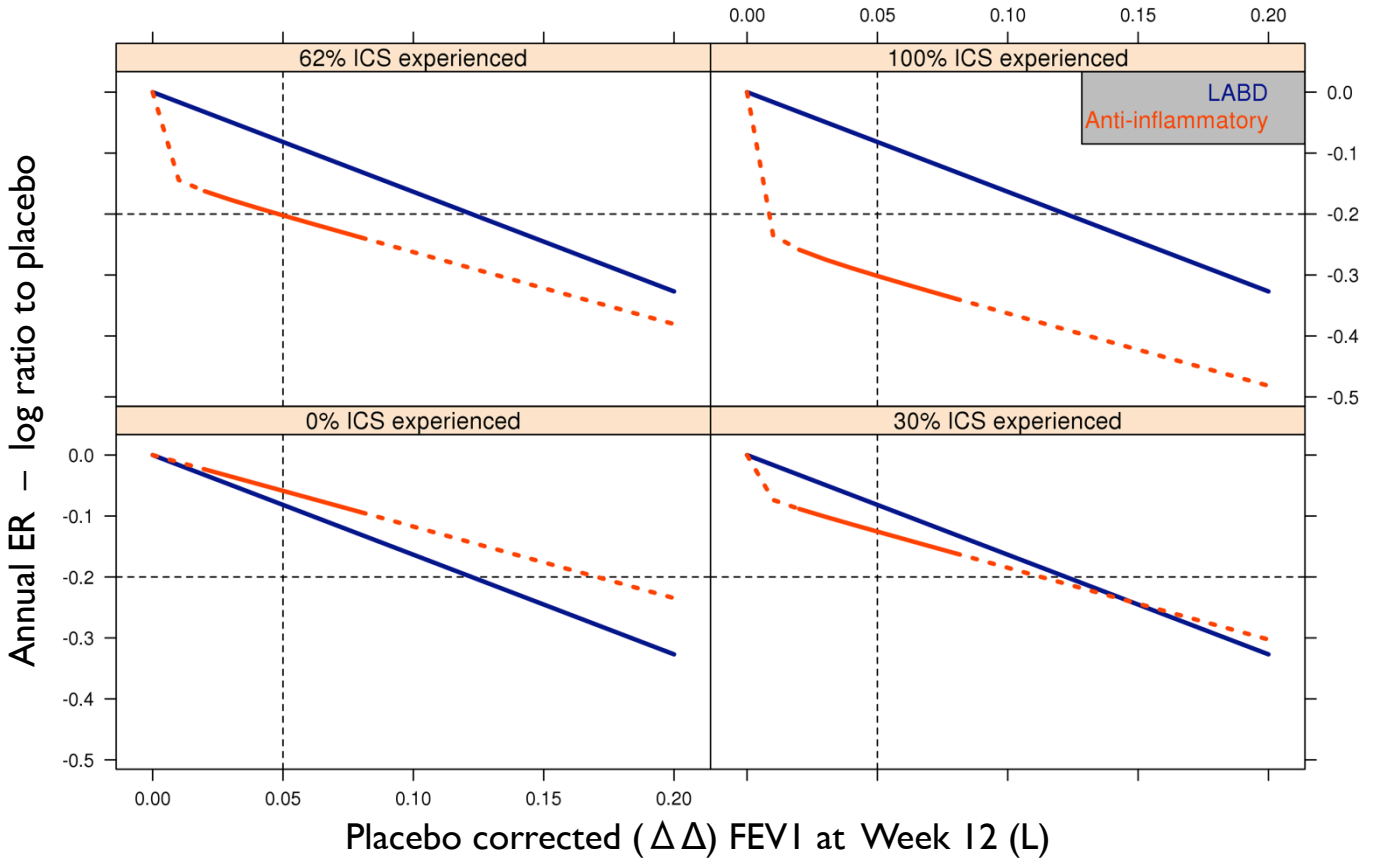
RUV dropped from equations
AI = anti-inflammatory

Estimated parameters
BD = direct bronchodilator

slp = slope
PBO = placebo

Model predictions

Effect of ICS experienced subjects in study population where ICS are washed out prior to randomization



----- extrapolation beyond available data range

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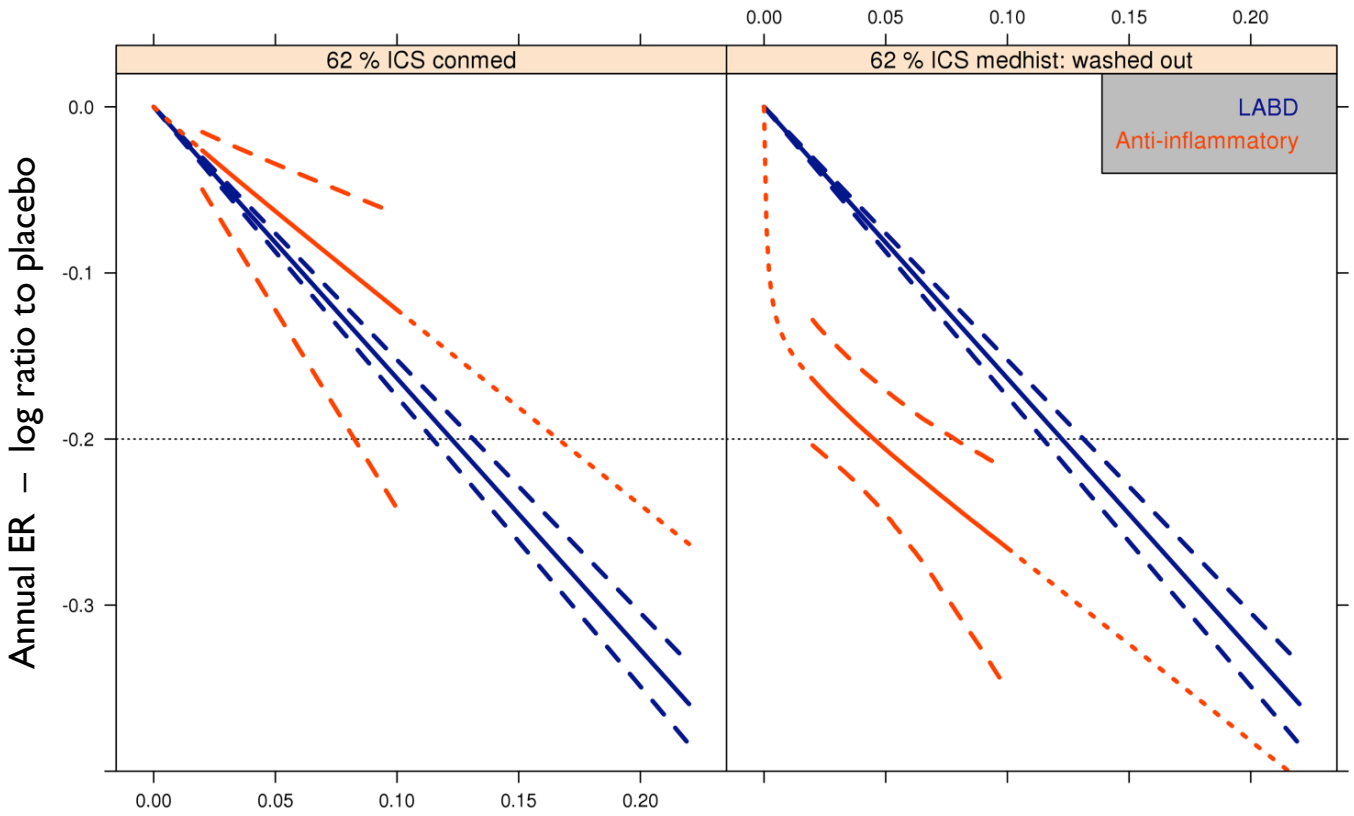
ER meta model: Results

Model predictions

Effect of washing out ICS in experienced subjects prior to randomization



––– 95% confidence interval

----- extrapolation beyond available data range

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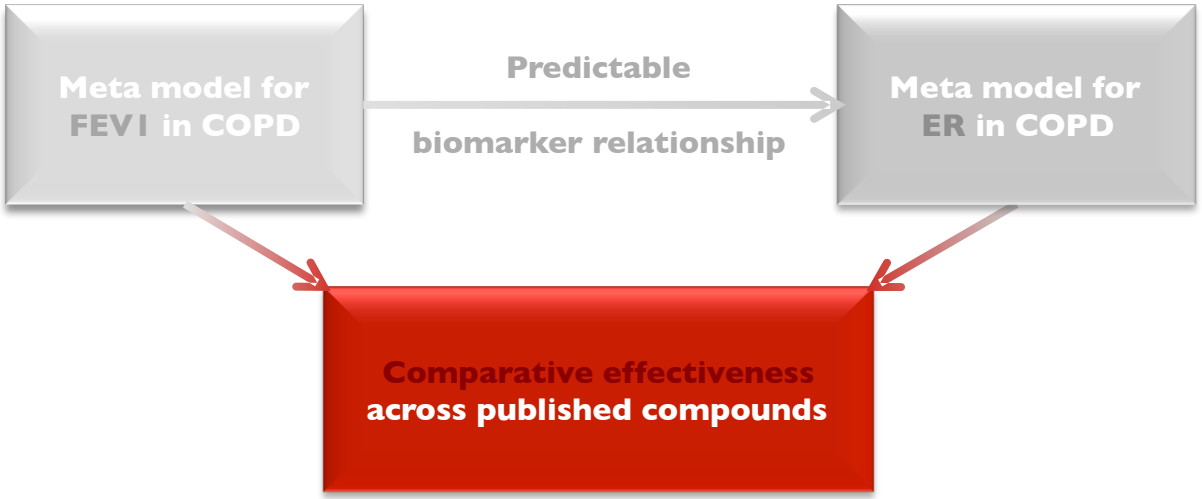
Comparative effectiveness



Comparative effectiveness for FEV1

Drug effects re-parameterized as relative effects of Drug 1 vs. Drug 2 for all comparisons of interest:

$$\text{relative effect} \quad r = \frac{E_{Drug1}}{E_{Drug2}}$$

- Uncertainty in r assessed using log-likelihood profiling:
  - Drug 1 is superior to Drug 2 if $r > 1$
  - Drug 1 is inferior to Drug 2 if $r < 1$
  - Superiority / inferiority cannot be established if the 95% confidence interval for r includes 1

⇨ Comparison of true treatment effect sizes

Comparative effectiveness for FEV1

Anti-inflammatory treatments (ICS / PDE4i)

Drug 1 / Drug 2	Beclo.	Bude.	Fluti.	Mome.	Cilo.	Roflu.
Beclomethasone (bid)	1	1.45 0.51 – **Inf**	1.73 0.72 – **Inf**	1.81 0.67 – **Inf**	1.52 0.58 – **Inf**	2.61 1.09 – **Inf**
Budesonide (160ug bid)	0.69 **0** – 1.95	1	1.19 0.78 – 2.42	1.24 0.66 – 2.65	1.04 0.58 – 2.15	1.80 1.17 – 3.48
Fluticasone (bid)	0.58 **0** – 1.38	0.84 0.43 – 1.27	1	1.05 0.62 – 1.72	0.87 0.55 – 1.33	1.51 1.14 – 2.03
Mometasone (bid)	0.55 **0** – 1.49	0.80 0.37 – 1.52	0.96 0.58 – 1.62	1	0.83 0.46 – 1.53	1.44 0.86 – 2.47
Cilomilast (bid)	0.66 **0** – 1 .71	0.96 0.46 – 1.71	0.15 0.75 – 1.80	1.20 0.65 – 2.18	1	1.73 1.12 – 2.75
Roflumilast (500ug qd)	0.38 **0** – 0.92	0.56 0.28 – 0.86	0.66 0.49 – 0.88	0.69 0.40 – 1.16	0.58 0.36 – 0.90	1

Drug 1 is superior • Drug 1 is inferior • Not established

Point estimates and 95% confidence intervals for $r = E_{Drug1} / E_{Drug2}$

Comparative effectiveness for FEV1

Direct long-acting bronchodilators (LABA / LAAC)

Drug 1 / Drug 2	Form.	Salm.	Ind.	Vil.	Tio. Sp.	Glyco.	Acli.	Ume.
Formoterol (9ug bid)	1	1.19 1.00 – 1.45	1.82 1.50 – 2.24	1.96 1.60 – 2.42	1.83 1.55 – 2.17	1.91 1.52 – 2.44	1.79 1.33 – 2.46	1.70 1.25 – 2.27
Salmeterol (bid)	0.84 0.69 – 1.00	1	1.53 1.30 – 1.79	1.65 1.38 – 1.94	1.53 1.36 – 1.73	1.60 1.31 – 1.98	1.43 1.07 – 1.87	1.50 1.13 – 2.03
Indacaterol (75ug qd)	0.55 0.44 – 0.67	0.65 0.55 – 0.77	1	1.08 0.89 – 1.31	1.00 0.87 – 1.16	1.05 0.85 – 1.31	0.93 0.69 – 1.24	0.98 0.74 – 1.34
Vilanterol (25ug qd)	0.51 0.41 – 0.63	0.61 0.51 – 0.73	0.93 0.76 – 1.13	1	0.93 0.79 – 1.10	0.97 0.78 – 1.23	0.87 0.64 – 1.15	0.91 0.68 – 1.25
Tiotropium Spiriva (18ug qd)	0.55 0.46 – 0.65	0.65 0.58 – 0.74	1.00 0.86 – 1.15	1.07 0.90 – 1.26	1	1.05 0.87 – 1.28	0.93 0.70 – 1.21	0.98 0.75 – 1.32
Glycopyrronium (100ug qd)	0.53 0.41 – 0.66	0.62 0.50 – 0.76	0.95 0.76 – 1.17	1.03 0.81 – 1.29	0.96 0.78 – 1.15	1	0.89 0.64 – 1.20	0.94 0.68 – 1.30
Aclidinium (400ug bid)	0.59 0.44 – 0.80	0.70 0.53 – 0.93	1.07 0.81 – 1.44	1.15 0.87 – 1.56	1.07 0.83 – 1.41	1.12 0.83- 1.55	1	1.05 0.74 – 1.54
Umeclidinium (bid & qd)	0.56 0.40 – 0.76	0.67 0.49 – 0.88	1.02 0.75 – 1.35	1.10 0.80 – 1.47	1.02 0.76 – 1.34	1.07 0.77 – 1.46	0.95 0.64 – 1.36	1

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Comparative effectiveness $\log(ER_{ratio})$

Drug 1 / Drug 2	Salm.	Ind.	Tio.	Glyco.	Bude.	Fluti.	Roflu.
Placebo	-0.13 -0.17 – -0.08	-0.20 -0.26 – -0.12	-0.20 -0.26 – -0.13	-0.21 -0.27 – -0.14	-0.18 -0.26 – -0.13	-0.17 -0.22 – -0.14	-0.21 -0.28 – -0.16
Salmeterol (bid)	0	-0.07 -0.10 – -0.04	-0.07 -0.01 – -0.04	-0.08 -0.11 – -0.05	-0.05 -0.14 – 0.00	-0.06 -0.13 – 0.00	-0.08 -0.17 – -0.02
Indacaterol (75ug qd)	0.07 0.04 – 0.10	0	0.00 -0.02 – 0.02	-0.01 -0.03 – 0.01	0.02 -0.09 – 0.09	0.01 -0.08 – 0.08	-0.01 -0.11 – -0.06
Tiotropium Spiriva (18ug qd)	0.07 0.04 – 0.10	0.00 -0.02 – 0.02	0	-0.01 -0.03 – 0.01	0.02 -0.09 – 0.08	0.01 -0.08 – 0.08	-0.01 -0.11 – 0.06
Glycopyrronium (100ug qd)	0.08 0.05 – 0.11	0.01 -0.01 – 0.03	0.01 -0.01 – 0.03	0	0.03 -0.08 – 0.10	0.02 -0.07 – 0.09	0.00 -0.10 – 0.08
Budesonide (160ug bid)	0.05 0.00 – 0.14	-0.02 -0.09 – 0.09	-0.02 -0.08 – 0.09	-0.03 -0.10 – 0.08	0	-0.01 -0.03 – 0.03	-0.03 -0.07 – 0.01
Fluticasone (bid)	0.06 0.00 – 0.13	-0.01 -0.08 – 0.08	-0.01 -0.08 – 0.08	-0.02 -0.09 – 0.07	0.01 -0.03 – 0.03	0	-0.02 -0.06 – 0.00
Roflumilast (500ug qd)	0.08 0.02 – 0.17	0.01 -0.06 – 0.11	0.01 -0.06 – 0.11	0.00 -0.08 – 0.10	0.03 -0.01 – 0.07	0.02 0.00 – 0.06	0

Drug 1 is superior • Drug 1 is inferior • Not established

Simulated medians and 95% confidence intervals for $r = log\,(ER_{Drug1} / ER_{Drug2})$

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Wrapping it up…

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Discussion

Application of the FEV1 and ER meta models for decision making in clinical drug development:

- Account for differences in study setup, populations and covariate effects:
  - Normalised predictions of true treatment effects
  - Improve design of future studies
- Bridge predictions across Phase 2 & 3 endpoints
- Assess comparative effectiveness across different compounds and treatment combinations

- New studies are published all the time
  - Constant maintenance required to stay up-to-date
  - Possibility to build upon prior work

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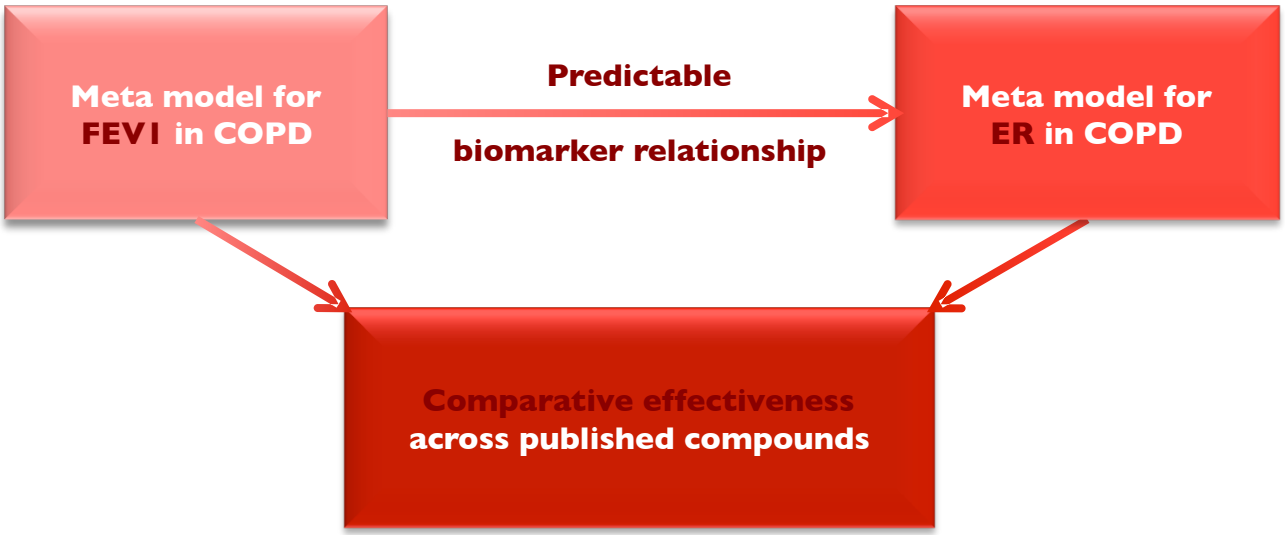
Conclusion

A model based longitudinal network meta-analysis of literature data is a powerful tool to facilitate decision making in clinical drug development.



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THANK YOU! ☺

Questions ?

Comments ?

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