Translating Pharmacometrics to Pharmacoeconomics

ISPOR 18th Annual European Congress

Workshop W11

November 10, 2015

FACULTY

- Scott Marshall, PhD, Senior Director, Global Clinical Pharmacology, Pfizer, Sandwich, UK
- Julia Slejko, PhD, Assistant Professor, Pharmaceutical Health Services Research, University of Maryland, Baltimore
- Richard Willke, PhD, Vice President, Outcomes & Evidence, Pfizer, New York City, USA

AGENDA

- Introduction (Willke)
- Making early clinical and cost effectiveness predictions for novel Gout Therapies: An introduction to Pharmacometrics & System Pharmacology (Marshall)
- Translating Pharmacometrics to Pharmacoeconomics: A COPD example (Slejko)
- Some Points After (Willke)
- Q&A

A Sneak Peek

- Treatment effects on clinical outcomes are key drivers in health economic models
  - But …. actual treatment effects on outcomes aren't available in early drug development

  → treatment effects on biomarkers or surrogate markers usually are
- Pharmacometric Model-Based Meta-Analysis predicts outcomes based on bio/surrogate-marker changes, using data from previous trials of similar drugs
  - Think non-linear meta-regression
- With a drug/dose-specific prediction of outcomes based on bio/surrogate-markers, often with covariate effects included, a more targeted health economic model can be built
- See Hughes & Walley (2001), Milligan et al (2013)

Making early clinical and cost effectiveness predictions for novel Gout Therapies:
An introduction to Pharmacometrics

Scott Marshall PhD
Pharmacometrics
Global Clinical Pharmacology
Global Innovative Pharma Business
Sandwich UK

Overview

- Introduction to Clinical Pharmacology & Pharmacometrics
  - Model informed Drug Discovery and Development (MID3)
  - Overview of Methods
- MID3 applied to Gout
  - Outline of plan and links
  - Cost effectiveness
- Summary

Clinical Pharmacology = Right Dose for Each Patient

- How much ?
- How often ?
- How long ?
- Maximise beneficial effect
- Minimise adverse effects
- Optimal risk- benefit for both population and individual

Better to learn in Phase I (early) than in Phase III (late)

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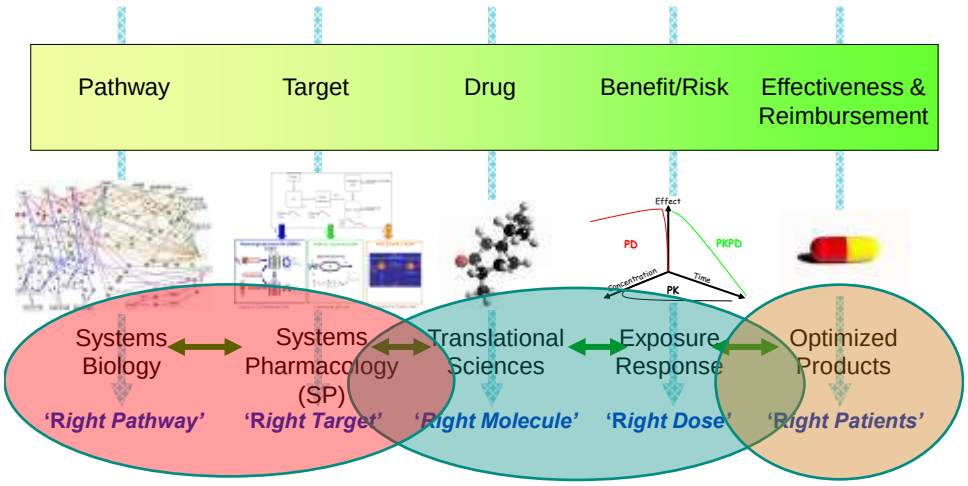
MID3 : Predictions from Pathway to Payer



Systems Models ⇄ Pharmacometrics Models ⇄ CE Models

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MID3: Analysis Techniques

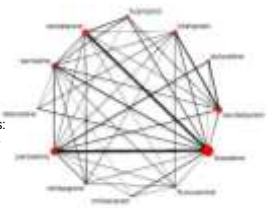
Technique	Empirical (Data Driven)	Mechanistic (P3 Driven)
Dose Time course analysis	++++	++
Population PK /PD	+++ (Empirical)	+++ (Semi Mech)
Meta-analysis	+++ (NMA)	+++ (MBMA)
Disease Progression Modelling	+++	+++
Physiological based PK (PBPK)	+	+++++
Systems Pharmacology	+	+++++

- P3= Physiology, Pharmacology & Pathology

Comparison of NMA & MBMA

NMA

- Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta analysis. Lancet 2009;373:746-58.



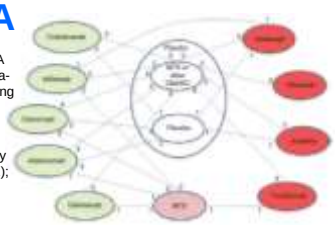
- **Endpoints:** Wide range treated Independently
- **Dose/Time:** Ignored or pooled
- **Interactions:** Statistical Interaction terms
- **Consistency:** Formally tested

Pro
- "Considered" assumption light & Generally accepted

Con
- Loss of knowledge and requires data integration i.e. "assumptions"

MBMA

J W Mandema et al. A Dose–Response Meta-Analysis for Quantifying Relative Efficacy of Biologics in Rheumatoid Arthritis. Clinical Pharmacology & Therapeutics (2011); 90 6, 828–835



- **Endpoints:** Few but integrated
- **Dose/Time:** Integrated across via Model (Emax)
- **Interactions:** Based on Pharmacology
- **Consistency:** Largely ignored

Pro
- Allows integration of data across dose/time/MOA

Con
- Not well known outside Clin Pharm /PMx community
- Method refinement ongoing e.g. to test consistency

Workshop; Session IV Wed 11th Nov
W31: Network Meta-Analysis Models for Dose-Response and Class Effects in Decision Making Brown 2 (L2)

Unmet Need in Gout

Untreated or Mismanaged Gout Can Have Serious Consequences

- Elevations in serum uric acid can result in…
  - –Extremely painful flares
  - –Disabling joint destruction
  - –Increasing recognition of asymptomatic hyperuricemia as a metabolic disorder (increased risk of CV disease)
- Societal Impact
  - –Large and increasing prevalence (diagnosed prevalence ~3.9%, NHANES 2007-2008)[8]
  - –Increasing hospital admissions for gout […suggesting] that the amount of severe gout is increasing, and the burden on the health systems due to gout is increasing[10]

Current Approved Treatments Have Limitations

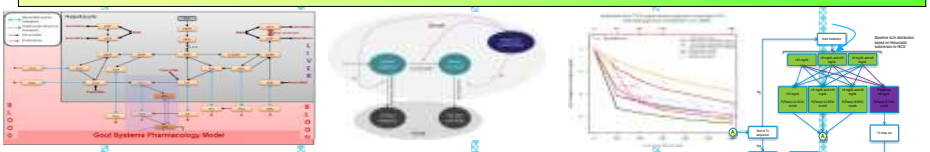
- **Allopurinol** (XOi)
  - Available since 1960s; current SOC
  - Low responder rates (monotherapy): 20%-40%[1,2]
  - Low treatment rates: estimated 30%[3]-50%[9]
  - Potentially life threatening allopurinol hypersensitivity syndrome (AHS) in approximately 2% of patients[4]
- **Uloric/Adrenuric (febuxostat)** (XOi)
  - Same MOA as allopurinol;
  - Similar responder rates to allopurinol (monotherapy): 45% (40 mg)- 50% (80 mg)[1,2,5]
  - CV outcomes study underway in US (CARES trial)[6]
- **Probenecid** (URAT1i)
  - Same MOA as lesinurad Rarely used (<2% of TRxs) due to DDIs, lack of efficacy with low GFRs (<50mg/dL) and dosing regimen (BID/TID)[7]

XOi: xanthine oxidase inhibitor

Full references in notes section

Gout MID3 : Predictions from Pathway to Payer (Overview)

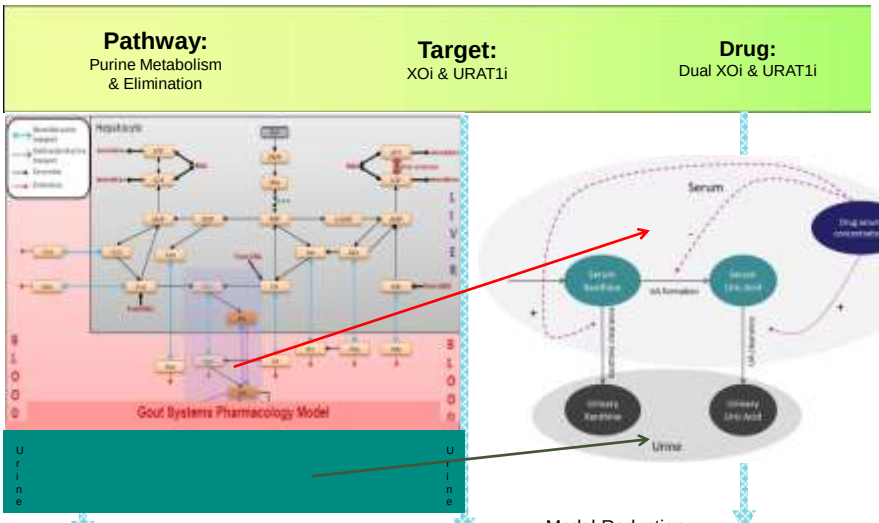
Pathway: Purine Metabolism & Elimination	**Target:** XOi & URAT1i	**Drug:** Dual XOi & URAT1i	**Benefit/Risk:** MBMA: XOi /Urat1i	**Effectiveness & Reimbursement:** NICE febuxostat CE Model



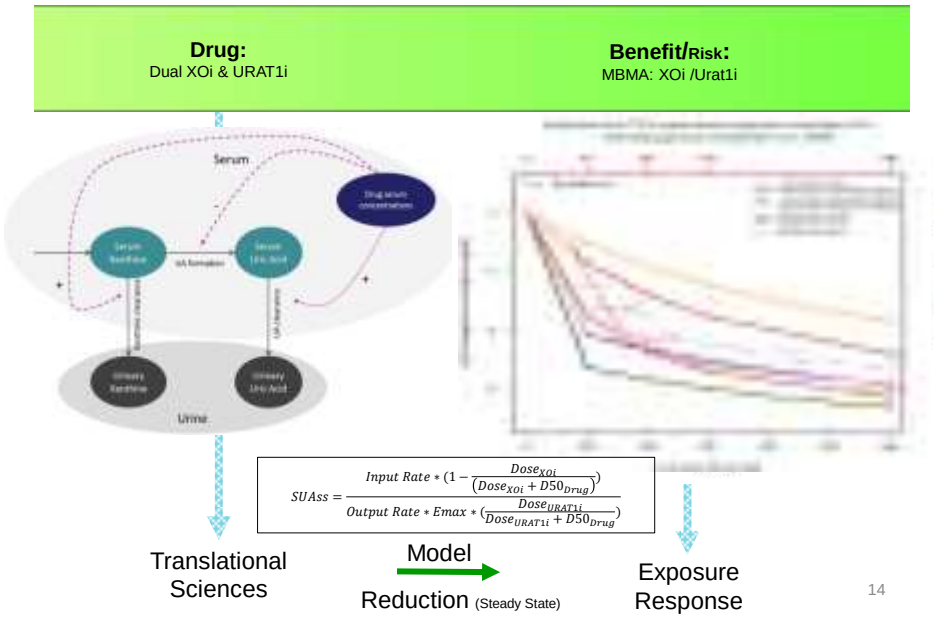
Systems Biology ↔ Systems Pharmacology (SP) ↔ Translational Sciences ↔ Exposure Response ↔ Optimized Products

Step 1: Identify Mechanisms	Step 2: Simplest Mechanistic model	Step 3: Derive CE inputs	Step 4: Derive CE Output

Gout MID3 : Predictions from Pathway to Payer(1)



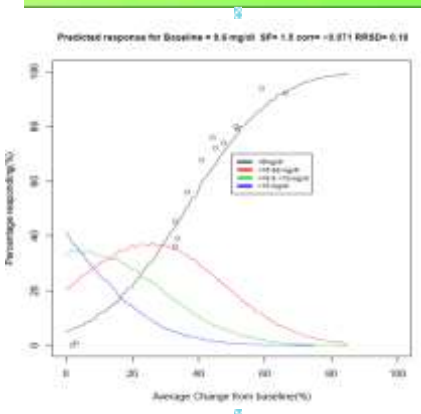
Gout MID3: Predictions from Pathway to Payer(2)

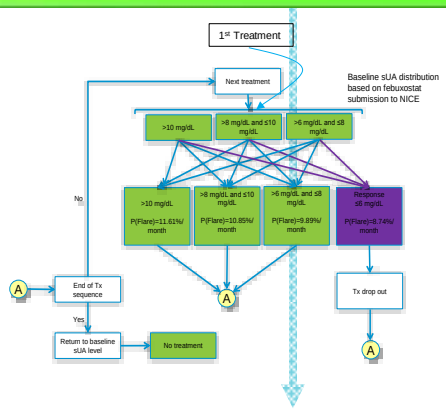


MID3: Predictions from Pathway to Payer(3)

Benefit/Risk:
MBMA: XOi /Urat1i

Effectiveness & Reimbursement:
NICE febuxostat CE Model





Exposure Response

Calibration

Input

Optimized Products

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Cost Effectiveness Model: Results

Based on potential future Generic Febuxostat Price	Δ QALYS	Δ Cost	Cost/QALY*
No ↑Utility w ↓sUA No ↑Resource w ↑sUA	0.001	£1,392	£1,058,607
↑Utility w ↓sUA No ↑Resource w ↑sUA	0.077	£1,392	£18,081
No↑ Utility w ↓sUA ↑Resource w ↑sUA	0.001	£481	£365,747
↑Utility w ↓sUA ↑Resorce w ↑sUA	0.077	£481	£6,247

*red (>), green (<) accepted threshold of £20,000/QALY (NICE)

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Summary

- MID3 provides a framework for making predictions of expected treatment effect and product profile for use in early CE projections
- Early CE projections can directly influence the drug development program/objectives
  - Wider utility of sUA reduction in addition to its impact on Gout Flares needs to be established as part of any future development program
  - EFPIA impact level assessed as **High**
- Potential to set target product profiles for drug discovery based on reverse engineering of CE

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UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

Translating Pharmacometrics to Pharmacoeconomics: COPD

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University of Maryland, Baltimore

Overview

- Motivation for using MBMA
- Review components of COPD MBMA equations.
- Translate MBMA outputs to HE model inputs.
  - Conceptual
  - Technical

COPD Modeling

- Estimating exacerbations is often the crux of COPD models for economic evaluation.
- Existing Options:
  - Exacerbation rate seen in trials (placebo or drug)
  - Estimate with real-world data

Estimate using model-based meta analysis (MBMA) to inform early-stage CEA model for hypothetical drug.

COPD MBMA

- 29 COPD trials. Criteria: ≥500 patients and ≥ 24-week study duration (mostly 1 year)
  - 80 study arms, 198-3,006 patients each → 43,472 patients.
- The meta-analytic model predicted as non-linear functions:
  - **Placebo arm exacerbation rate**
  - **Exacerbation rate ratio between the active and placebo arms**

Ribbing et al. 2015

MBMA Equations

Placebo Exacerbation Rate

Patients %FEV1

Model for Placebo ER:

$$\text{IF(ERhistory)}\quad ERplac_{TV} = ERplac_{pop} \cdot \cdot e^{(\%FEV1-41)\cdot E_{\%FEV1}+(\%ICSwashout-54)\cdot E_{\%ICSwashout}}$$

$$\text{IF(!ERhistory)}\quad ERplac_{TV} = ERplac_{pop} \cdot (1+E_{NO\text{-}ERhist}) \cdot e^{(\%FEV1-49)\cdot E_{\%FEV1}+(\%ICSwashout-44)\cdot E_{\%ICSwashout}}$$

$$ERplac = ERplac_{TV} \cdot (1+\eta),\ \eta \in N($$

Were patients required to have exacerbation history?

Were patients washed out of ICS use?

MBMA Equations

Placebo Exacerbation Rate

Patients %FEV1

Model for Placebo ER:

IF(ERhistory) $ERplac_{TV} = ERplac_{pop} \cdot \cdot e^{(\%FEV1-41)\cdot E_{\%FEV1}+(\%ICSwashout-54)\cdot E_{\%ICSwashout}}$

IF(!ERhistory) $ERplac_{TV} = ERplac_{pop} \cdot (1+E_{NO\text{-}ERhist}) \cdot e^{(\%FEV1-49)\cdot E_{\%FEV1}+(\%ICSwashout-44)\cdot E_{\%ICSwashout}}$

$ERplac = ERplac_{TV} \cdot (1+\eta),\ \eta \in N($

Were patients required to have exacerbation history?

Were patients washed out of ICS use?

Model for drug effect:

$RAT_{ER} = e^{slope_{BD}\cdot\Delta\Delta FEV1_{BD}+slope_{AInaive}\cdot\Delta\Delta FEV1_{AI}\cdot fraction_{ICSnaive}} \cdot \left(1- fraction_{ICSexperienced} \cdot \Delta\Delta FEV1_{AI}{}^{slope_{ICSexperienced}}\right)$

Ratio of exacerbations treatment vs. placebo

Expected drug effect: increase in FEV1

Were patients using ICS?

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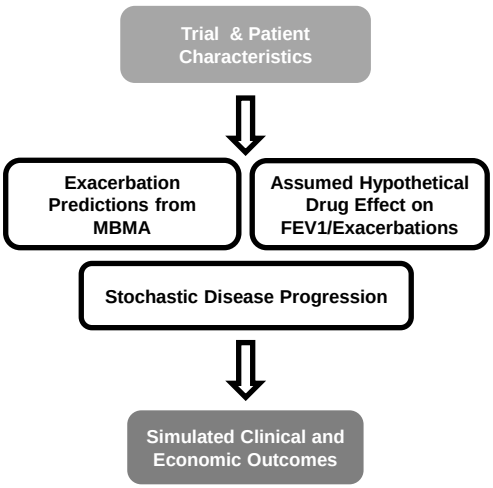
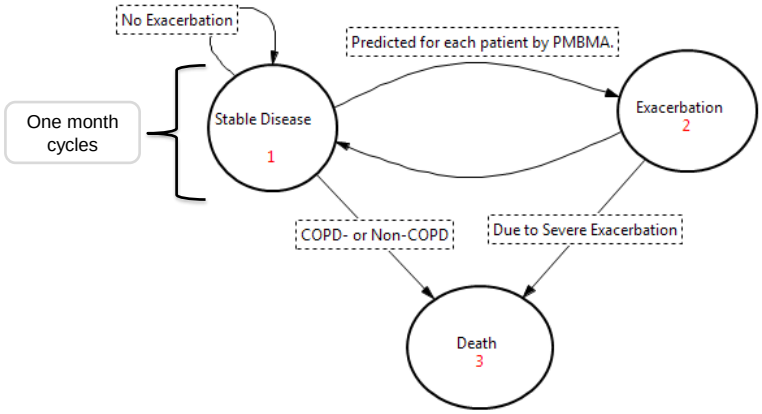
Conceptual Framework

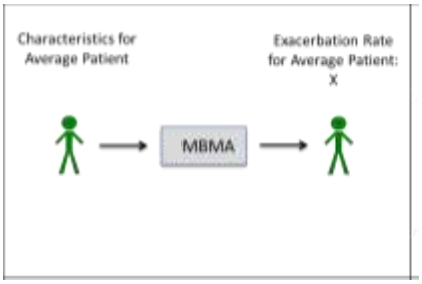


COPD Markov Model



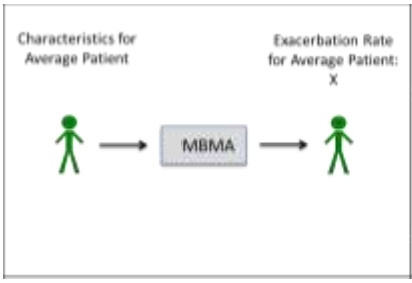
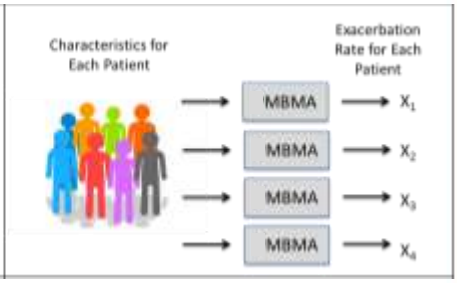
Implementing the MBMA

Cohort Approach



MBMA operates on the cohort level
- Average FEV1 input values
- Average exacerbation rates

Implementing the MBMA

Cohort Approach	Microsimulation Approach
	
MBMA operates on the cohort level • Average FEV1 input values • Average exacerbation rates	If individual patient data available… • Unique FEV1 inputs • Individual exacerbation rates • Calibration may be needed

Trial-Level Characteristics

We created six trial scenarios

	Inhaled Corticosteroid Use		
	Yes		No
	Washed Out of ICS?		
Exacerbation History?	Yes	No	
Yes	x	x	x
No	x	x	x

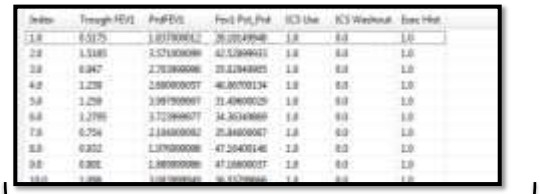
Technical Implementation

- How can individual- and trial-level characteristics be modeled using a Markov framework?

Technical Implementation

- How can individual- and trial-level characteristics be modeled using a Markov framework?
- TreeAge Pro 2014
  - Create Markov microsimulation
  - Patient and cohort characteristics using tables
  - Allows uncertainty at the individual and trial level.

Individual & Trial Characteristics

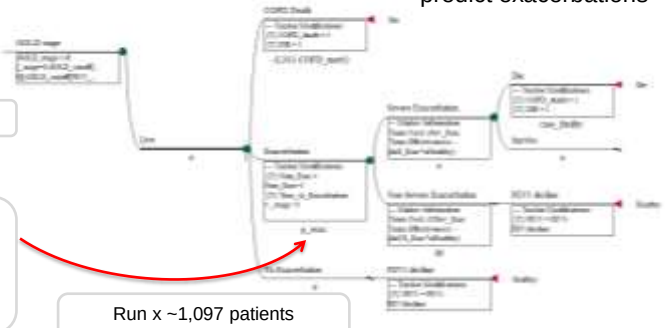


Create Table

- Contains unique values for each patient's FEV1
- Contains single value for trial characteristics
- Feeds into MBMA to predict exacerbations

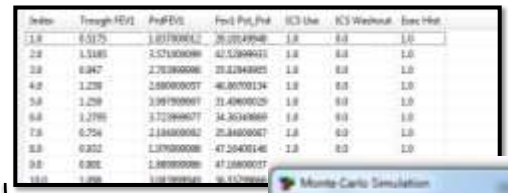
MBMA

Exacerbation Rate for each Patient (Treatment & Placebo)



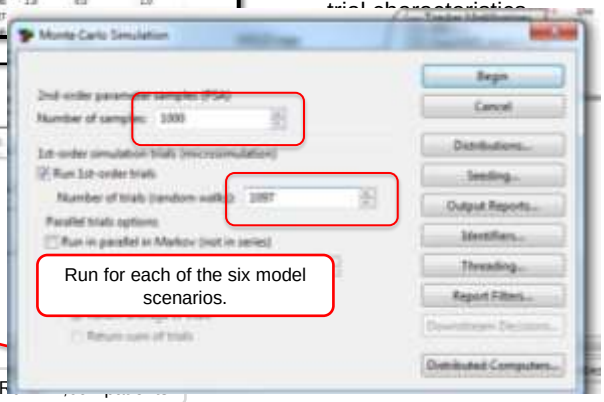
Run x ~1,097 patients (Moderate and Severe cohorts)

Individual & Trial Characteristics



Create Table

- Contains unique values for each patient's FEV1
- Contains single value for trial characteristics



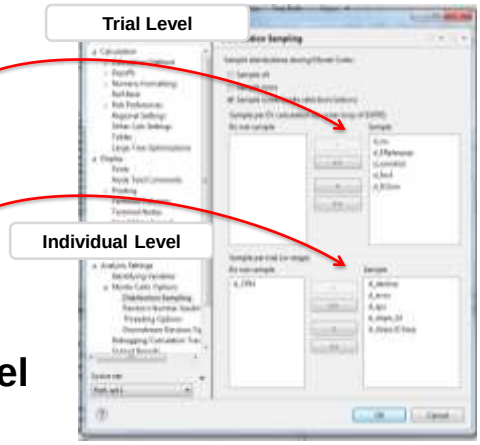
MBMA

Exacerbation Rate for each Patient

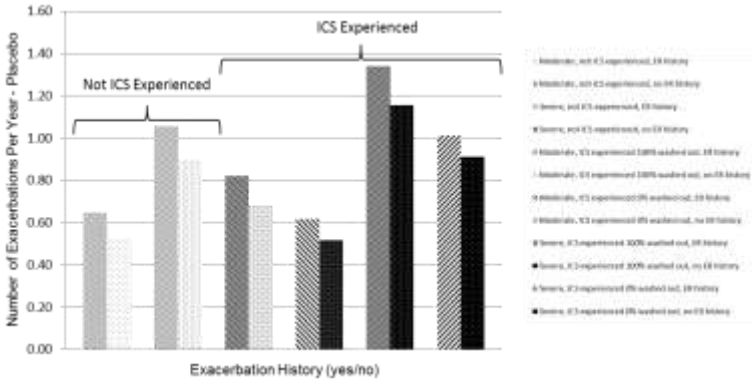
Run for each of the six model scenarios.

Model Uncertainty

- Create distributions for
  - MBMA model coefficients
  - Disease characteristics: FEV1 decline
- **Sample some at individual level, some at trial level**

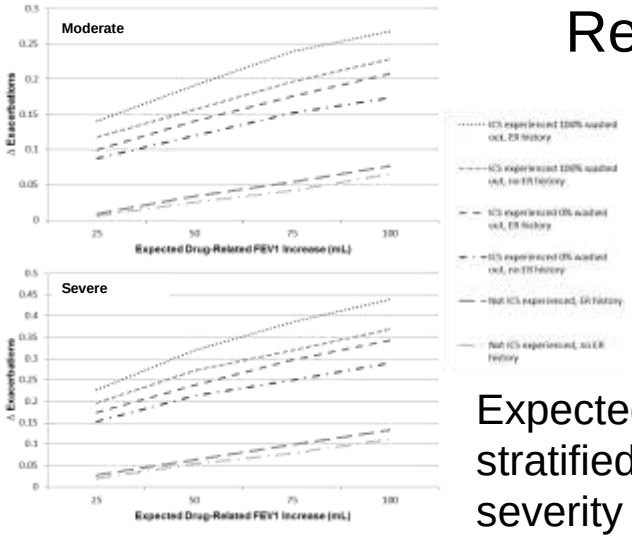


Results



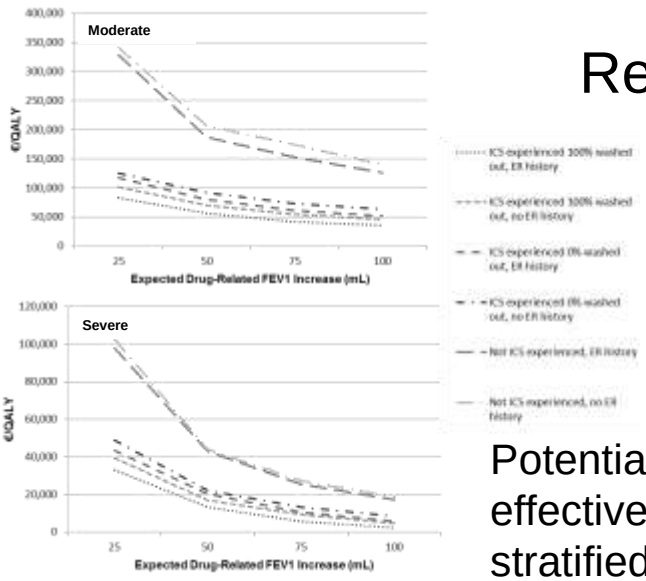
Yearly baseline exacerbations stratified by disease severity and trial scenario.

Results



Expected drug effect stratified by disease severity and trial scenario.

Results



Potential cost effectiveness, stratified by trial characteristics.

Some Points After

- Calibrating the variation in outcomes
- Why do this?
- Questions for Discussion

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Getting the variation right

- Problem – random choices made in the Markov model generate variation in exacerbations that doesn't match what is observed in the trials
- Solution
  1. Use the estimated variances in the MBMA to calculate the underlying (after covariate adjustment) variances in treatment and placebo group exacerbation rates in the trials
  2. Introduce placebo rate and exacerbation rate ratio variation in the HE model at levels that result in exacerbation rate variances that match those estimated from the MBMA in step 1 above.

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Results of replicating the sample-based variance in exacerbations

Differences in 1-yr HE Model results based on use of variance calibration factors

Outcomes	Naive		Calibrated	
	Mean	SD	Mean	SD
Placebo Exac. Rate/yr.	.962	.029	.962	.515
Treatment Exac. Rate/yr	.798	.026	.808	.428
Placebo group costs (€)	1121	44	1120	334
Treatment group costs (€)	1453	41	1461	278
Placebo group QALYs	.725	.0031	.725	.0096
Treatment group QALYs	.732	.0030	.732	.0082
ICER* (€/QALY)	49,133	44,182-54,651	53,714	37,850-75,580

*Median and interquartile range shown

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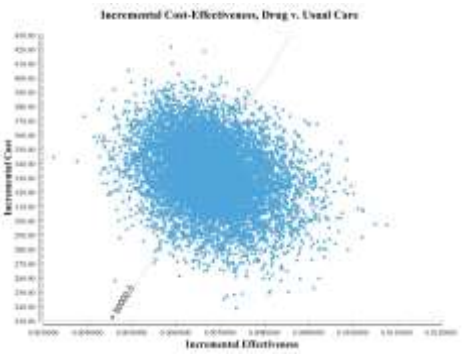
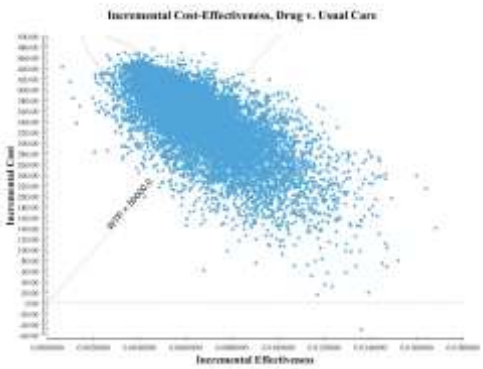
Comparing cases

Naive



Calibrated



Note: ICERs are quite similar between cases

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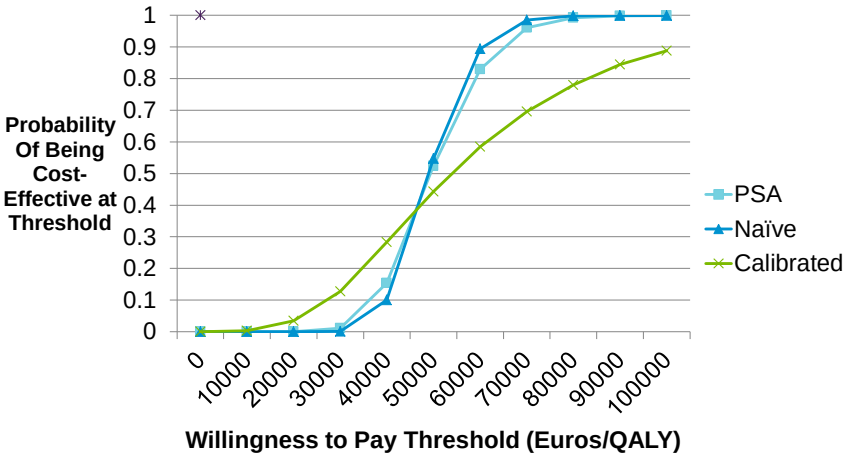
Cost-Effectiveness Acceptability Curves
Comparisons Across Variance Scenarios



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Why Do This?

- MBMA-based early economic models are valuable during drug development:
  - Consistent with pharmacometric predictions of efficacy (safety if needed), based on biomarker results
  - Can be driven by phase II biomarker results
  - Are available at the time key development decisions are being made
  - Can be modified as needed to evaluate different product concepts for hypothetical early assets
  - Can be used to test pricing assumptions for consistency with cost-effectiveness thresholds
  - Can inform development decisions around secondary endpoints, patient subgroups, etc.
- Potential value for HTA/reimbursement as well
  - Dependent on HTA acceptance of MBMA results in place of NMA for indirect treatment comparisons (to allow for inclusion of dose and time effects)

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Questions for Discussion

- Does anyone in audience have their own experience in this area?
- Have you met your pharmacometrics colleagues?
- Have you had any discussions about doing meta-analyses with them?
- Have you constructed any models of this type? Any reflections on that work?
- Have you had any experience using MBMA for regulatory or HTA purposes?

References

- Hughes DA, Walley T. Economic evaluations during early (phase II) drug development: a role for clinical trial simulations? Pharmacoeconomics 2001; 19 (11): 1069-77.
- Milligan PJ, Brown MJ, Marchant B, et al. Model-based drug development: A rational approach to efficiently accelerate drug development. Clin Pharm & Therapeutics 2013; 93:502-14.
- Ribbing J, Korell J, Cerasoli F, Milligan PA, Martin SW, Karlsson MO. Predicting Reductions in COPD Exacerbations from FEV1: A model-based meta-analysis of literature data from randomized clinical trials. Poster presented at American Conference on Pharmacometrics 6 (October, 2015).

References for slide 11

1. Michael A. Becker, M.D., Febuxostat Compared with Allopurinol in Patients with Hyperuricemia and Gout. N Engl J Med 2005;353:2450-61.

2. H. Ralph Schumacher, Jr., Effects of Febuxostat Versus Allopurinol and Placebo in Reducing Serum Urate in Subjects With Hyperuricemia and Gout: A 28-Week, Phase III, Randomized, Double-Blind, Parallel-Group Trial, Arthritis & Rheumatism (Arthritis Care & Research) Vol. 59, No. 11, November 15, 2008, pp 1540–1548

3. W Zhang, EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee For International Clinical Studies Including Therapeutics (ESCISIT) Ann Rheum Dis 2006;65:1312–1324.

4. Edward Roddy, Concordance of the management of chronic gout in a UK primary-care population with the EULAR gout recommendations. Ann Rheum Dis 2007;66:1311–1315.

5. US PI

6. William B. White, MD, CArdiovascular Safety of Febuxostat and Allopurinol in Patients With Gout and Cardiovascular ComoRbiditiES. Am Heart J 2012;164:14-20.

7. N. Lawrence Edwards, ARTHRITIS & RHEUMATISM Vol. 58, No. 9, September 2008, pp 2587–2590 Treatment-Failure Gout: A Moving Target

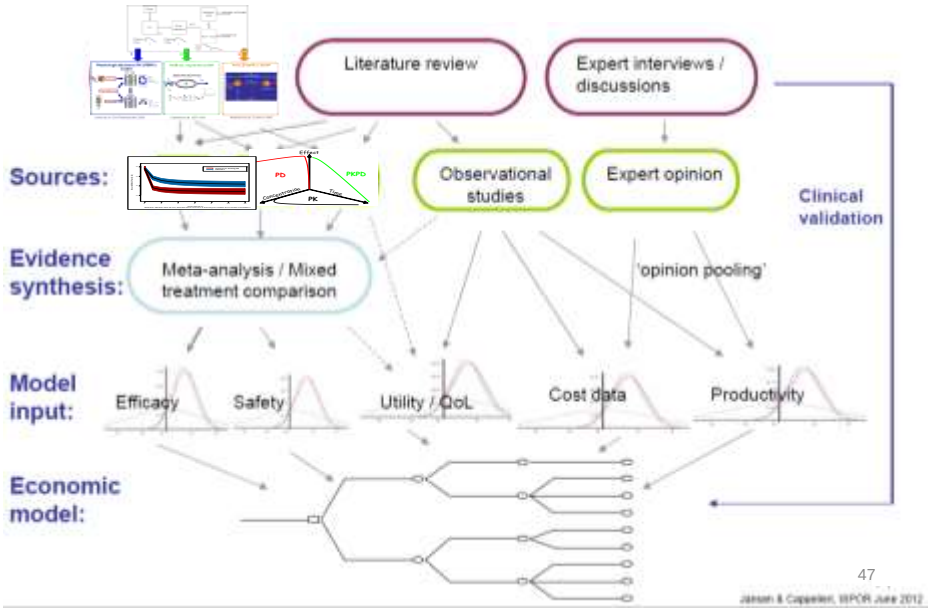
8. Yanyan Zhu, Prevalence of Gout and Hyperuricemia in the US General Population The National Health and Nutrition Examination Survey 2007–2008. ARTHRITIS & RHEUMATISM Vol. 63, No. 10, October 2011, pp 3136–3141

9. IMS data

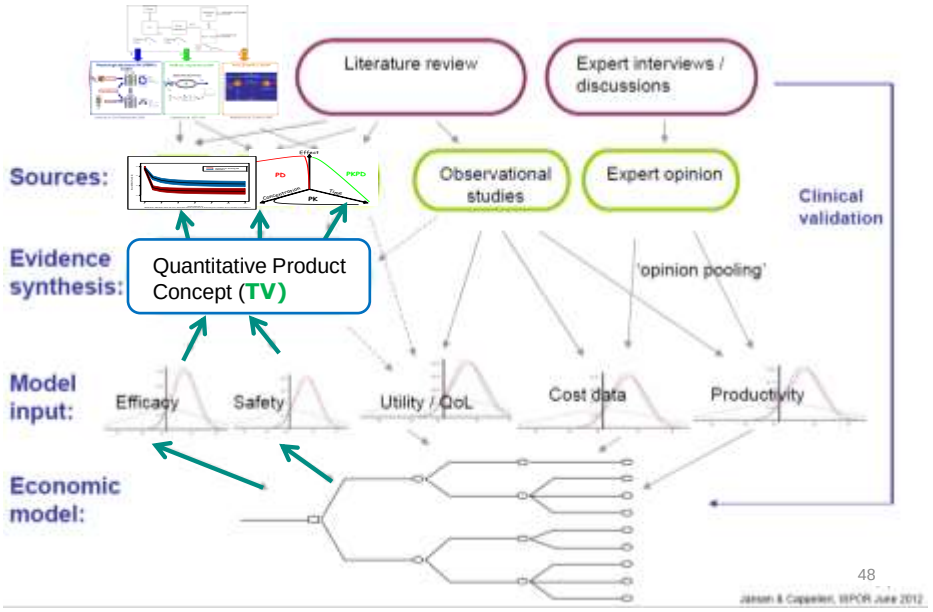
10. Philip C. Robinson, Hospital admissions associated with gout and their co-morbidities in New Zealand and England 1999—2009, *Rheumatology (2012) doi: 10.1093/rheumatology/kes253*

Backup

EQDD driving HTA



HTA driven Product Concepts



Model Informed Drug Discovery & Development
_likely speak to this using next slide

- (i) systems pharmacology
  - Informs therapeutic interventions based on detailed structural knowledge of biological systems.
  - A feature of systems pharmacology is that it focuses on the interplay between pharmacology and the underlying system, allowing predictions of the efficacy and safety of compounds to be based on known or possible mechanisms of action.
- (ii) pharmacometrics
  - Is at “the intersection of PK models, PD models, PD–biomarker–(clinical) outcome models, data visualization, statistics, stochastic simulation, and computer programming”
  - Mathematical models are developed and applied to characterize, explain, and predict PK and PD behavior of therapeutic agents.
  - These are combined with statistical models to quantify the source and the extent of variability and uncertainty in the underlying responses.

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Pharmacometrics Driven Cost Effectiveness

Bangor University non-clinical PhD studentship
MRC North West Hub for Trials Methodology Research (NWHTMR)

Title: Development and application of linked pharmacometric-pharmacoeconomic analyses in clinical drug development

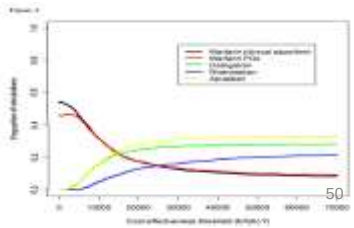
Supervisors: Professor Dyfrig Hughes (lead), Dr Steven Lane (University of Liverpool); **Advisory group:** Professor Munir Pirmohamed, University of Liverpool; Dr Peter Milligan & Dr Richard Willis, Pfizer

Project summary: Model-based drug development uses pharmacometric (quantitative pharmacology) approaches to inform trial design and optimise compound development strategies [1]. This approach aims to reduce late-stage failure and improve the efficiency of drug development. We conceived and subsequently proved the concept of linking such an approach with economic models to provide early estimates of cost-effectiveness, and inform pricing strategies [2-4]. In collaboration with Pfizer, and utilizing the expertise within the NWHTMR, this PhD project will aim to develop case studies for application in clinical drug development. The project will improve methods for strategic, clinical and pricing decisions during phase II/III drug development.

MRC Case award PhD Studentship
Dec 2013

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 94 NUMBER 2 | AUGUST 2013

Comparative Effectiveness of Dabigatran, Rivaroxaban, Apixaban, and Warfarin in the Management of Patients With Nonvalvular Atrial Fibrillation



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Package Insert – Clinical Pharmacology Contributions

Full Prescribing Information (SUTENT example): Contents*

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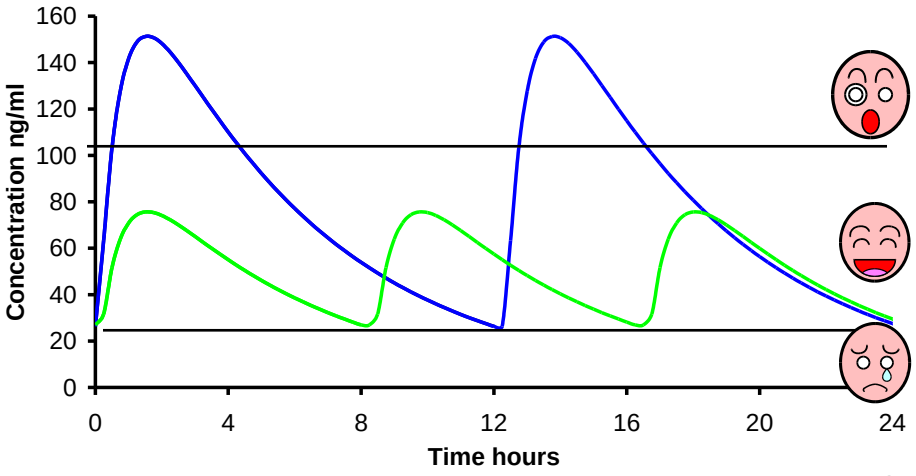
** Sections or subsections omitted from the full prescribing information are not listed.*

Getting the right dose and dose Regimen Twice daily vs Three times daily



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