Pharmacological and economic modelling of follicular lymphoma and stroke prophylaxis

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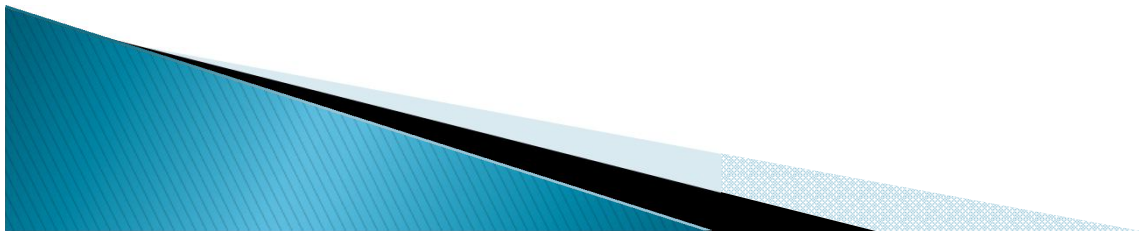
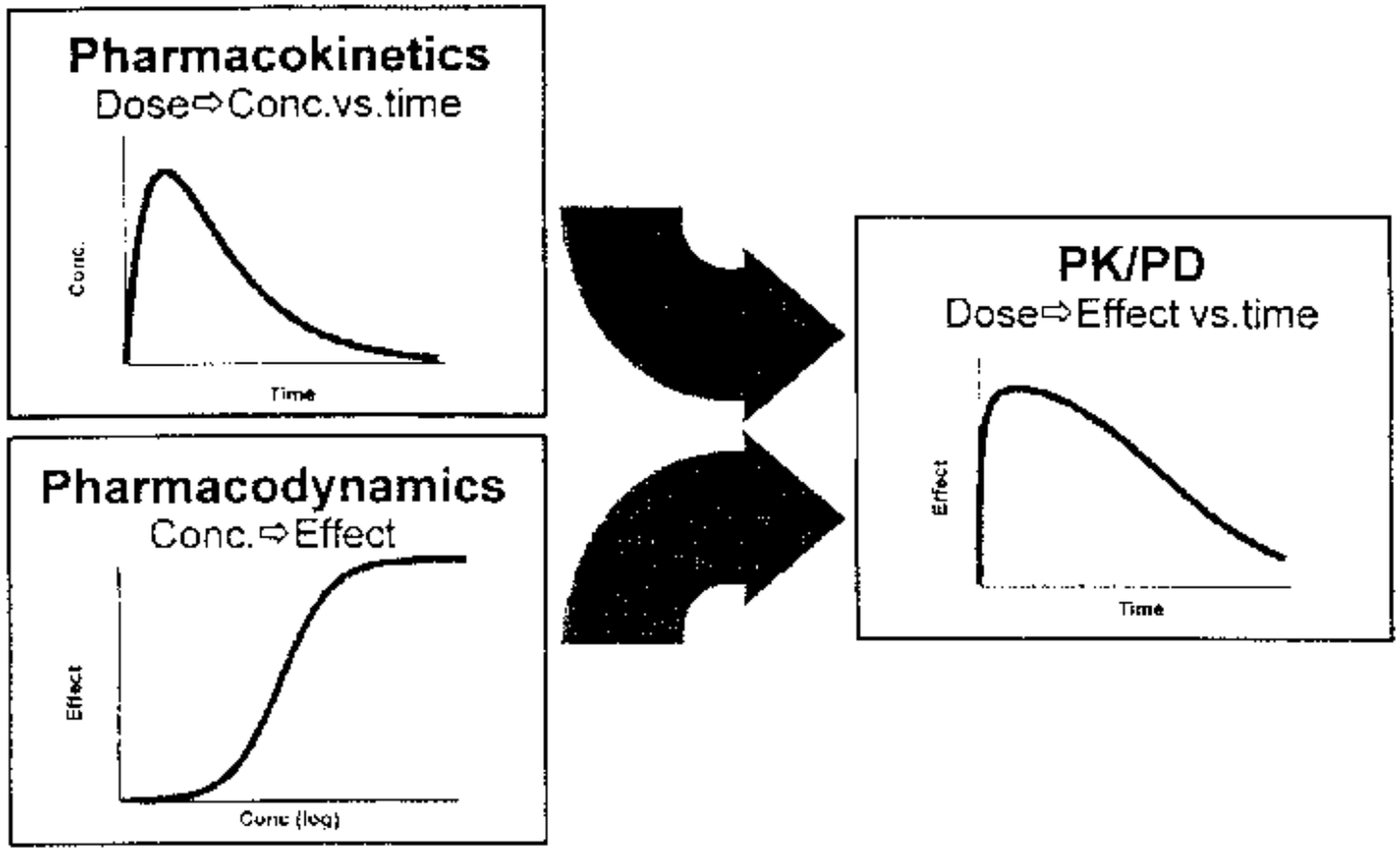
Pharmacokinetics & pharmacodynamics

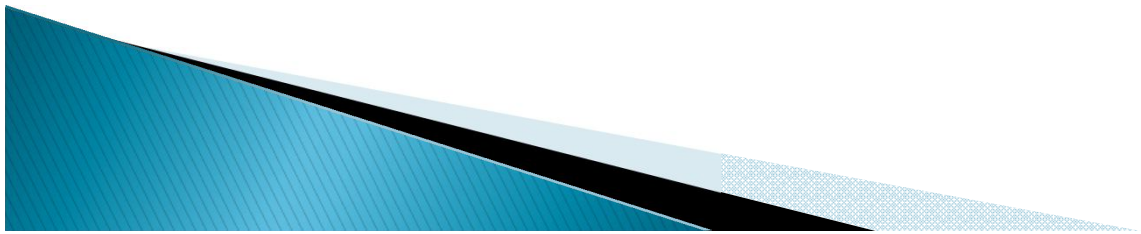
- PK describes the processes of absorption, distribution, metabolism and excretion of drugs.
- Standard mechanistic models link dose with concentration.
- These can be linked to pharmacodynamic models, which link drug concentration and pharmacological effect.
- Combined PKPD models can therefore predict outcome measures from dosing information.




Pharmacokinetics
Dose⇨Conc.vs.time
Conc.
Time
Pharmacodynamics
Conc.⇨Effect
Effect
Conc (log)
PK/PD
Dose⇨Effect vs.time
Effect
Time

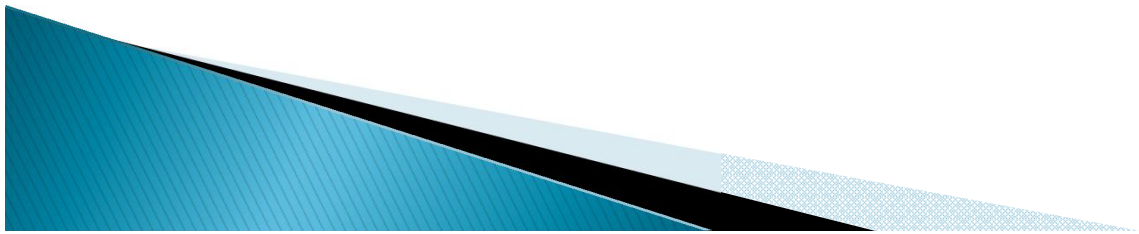
PKPDPE Modelling

- Link together established population PKPD models with health economic models by simulating the outcome of clinical trials.
- £/QALY can thus be reached as an outcome measure.
- Trial design can be made, based on the actual end criteria by which success will ultimately be judged.
- Amenable to Value of Information analysis
  - Informing trial design
  - Identification of subgroups etc.



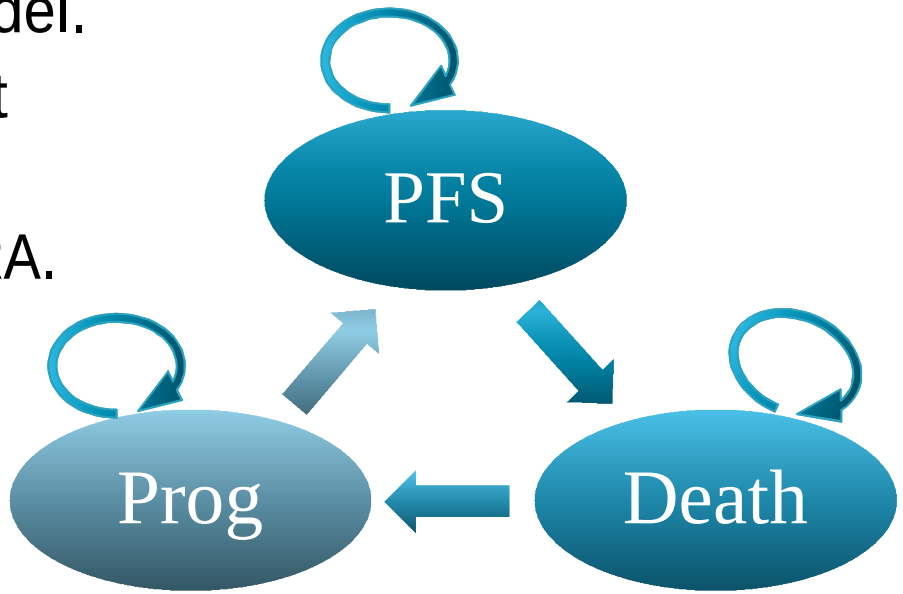
Case Study 1 - Rituximab

- Rituximab is a monoclonal antibody used in the treatment of follicular lymphoma.
- Separate evidence available for its PK, PD (progression-free survival) and cost-effectiveness.
- Aim is to make use of these data to develop a PKPDPE model.
  - Proof of concept exercise.
  - Compare PKPDPE output with industry submission to NICE.



Rituximab Model - overview

- PK model – Ng et al.
  - Two compartment linear model.
  - BSA and gender as significant covariates.
  - Based on 102 patients with RA.
- PD model – Ternant et al.



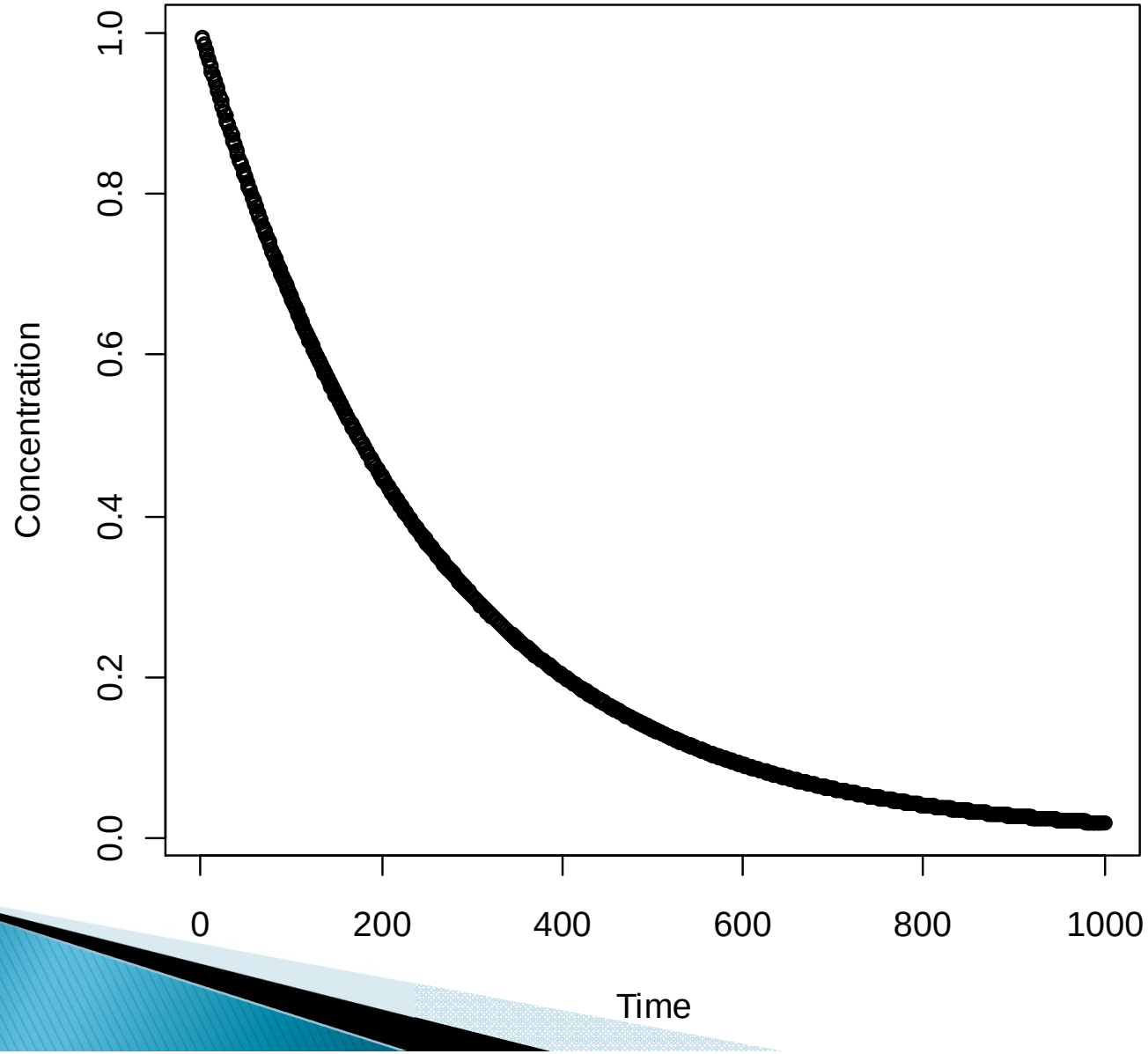
$$Cm(t) = \frac{\int_{t_n}^{t} C(\tau)\,d\tau}{t - t_n}$$

$$PFS(t) = \exp\left(-\left(\lambda_{max}\left(1 - \frac{Cm^{\gamma}}{Cm_{50}{}^{\gamma} + Cm^{\gamma}}\right)\right)t\right)$$

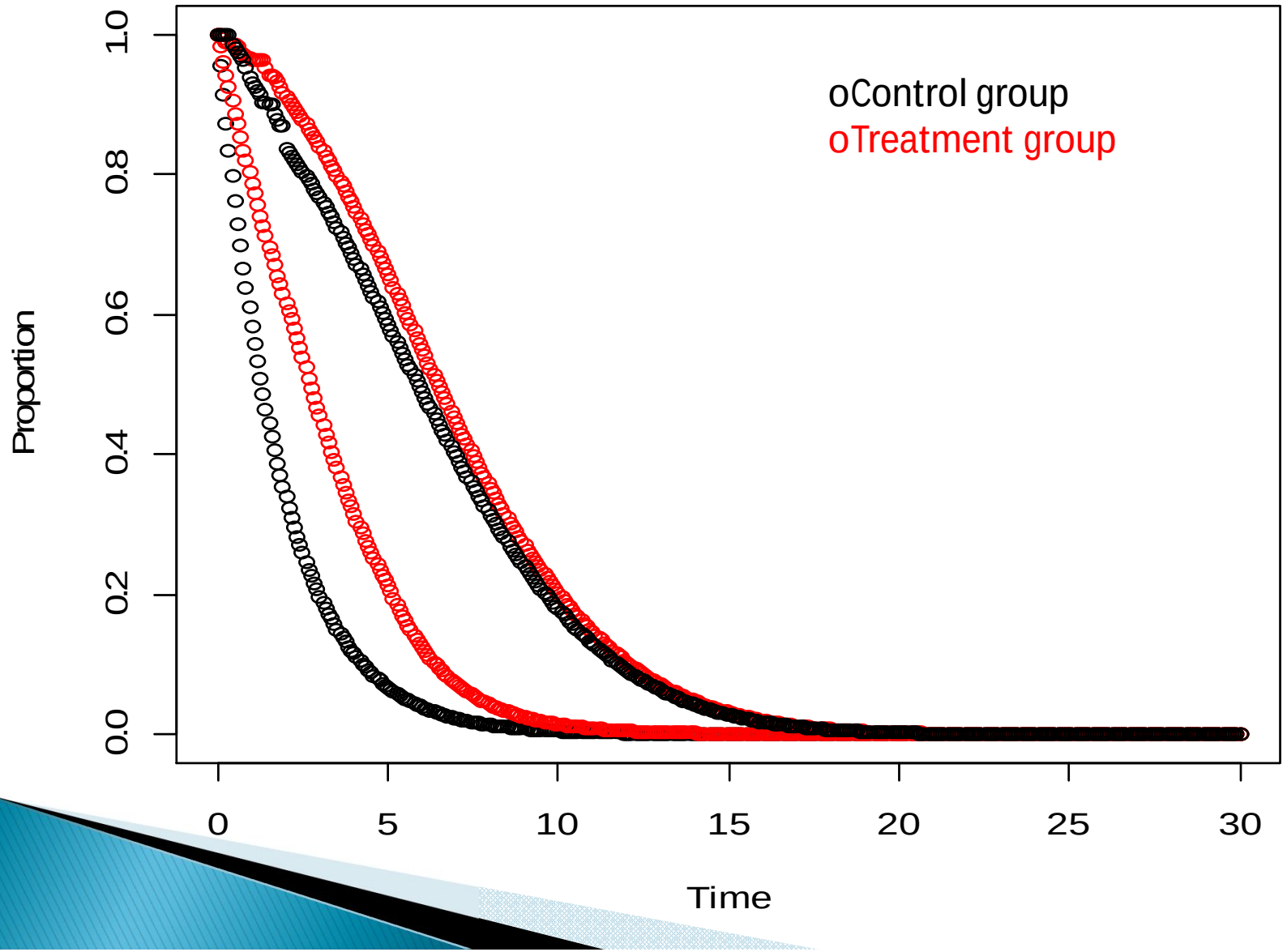
Methods

- Overview:
  - Replicate NICE STA economic model, but substitute trial-reported PFS with PFS derived from PKPD simulation.
- Clinical data:
  - Overall survival data/parameters taken from EORTC 20981 trial.
  - Progression free survival simulated from PKPD model.
- Other parameters are all taken from the NICE STA submission:
  - Trial also provides data on incidences/costs of adverse events.
  - Other costs taken from NHS reference costs.
  - Health utility scores come from an Oxford Outcome Group study.

PK Model – Ng et al



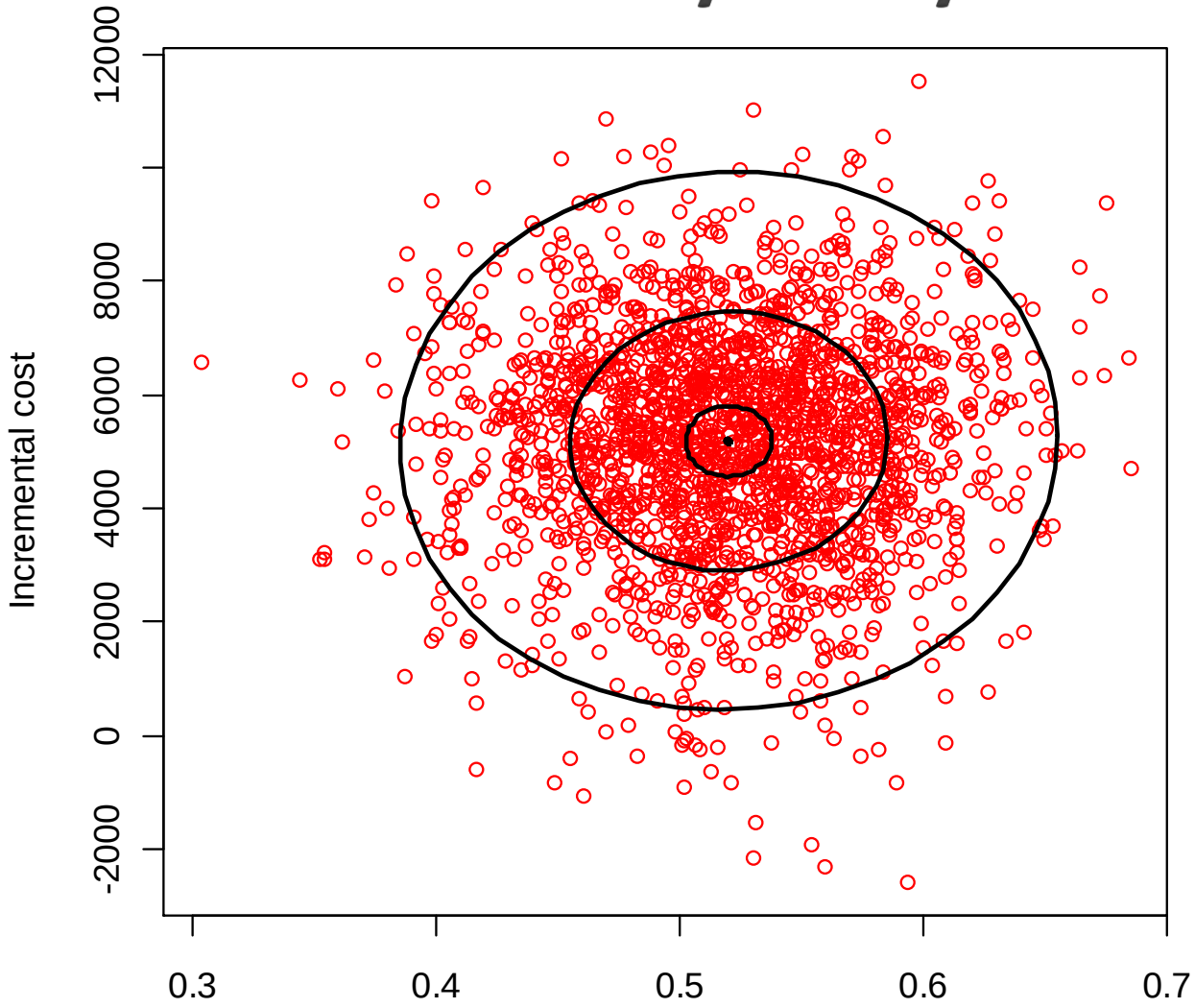
PD Model – Ternant et al



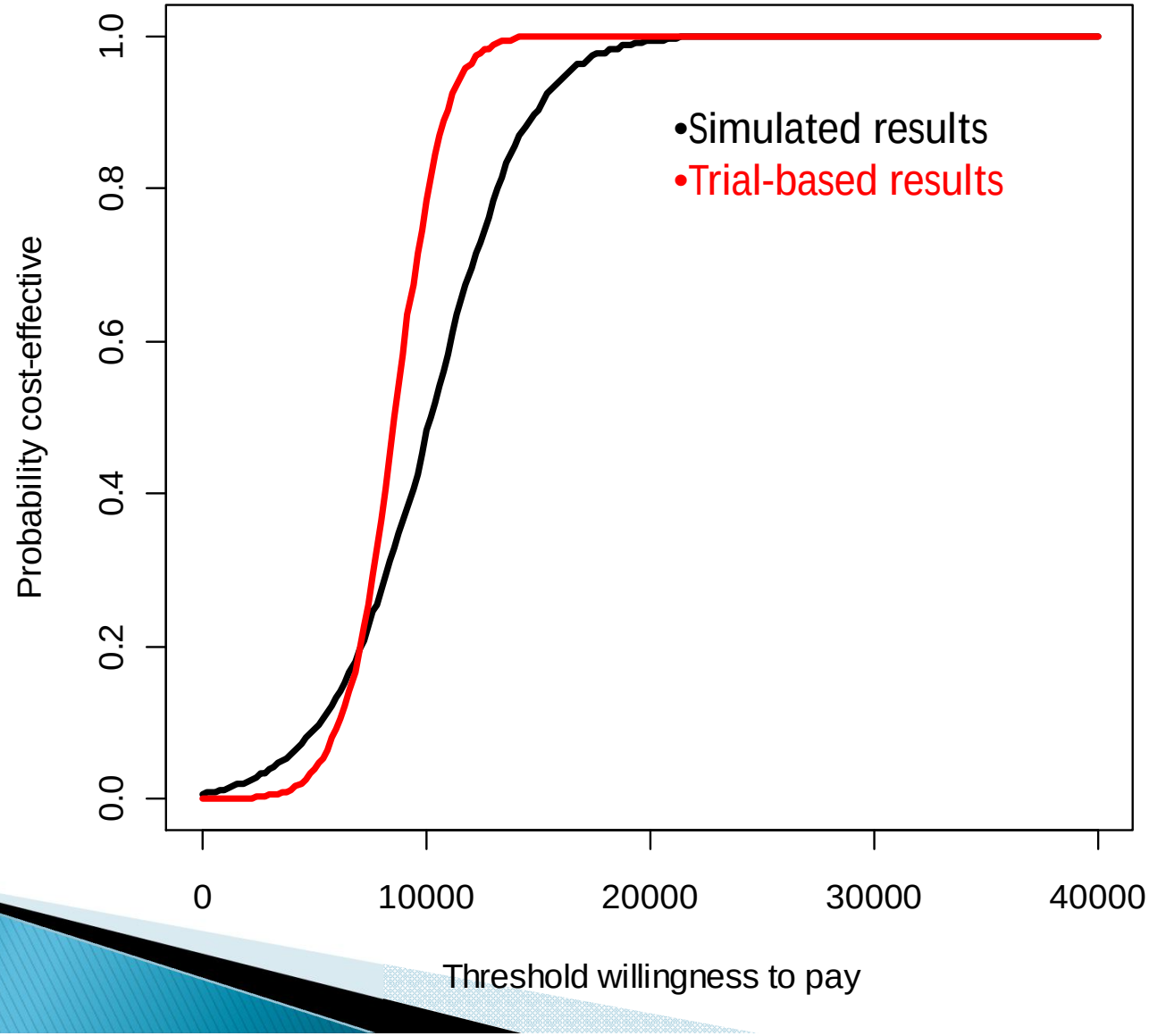
Results

Value	Simulation	Original	95% CR for difference
Median survival – C	5.288	5.214	
Median survival – T	6.267	6.221	
Mean life expectancy – C	5.4026	5.4092	
Mean life expectancy – T	6.5878	6.5998	
Total cost – C	£17,419	£14,722	
Total cost - T	£22,736	£21,608	
Incremental cost	£5,317	£6,886	(-£829,£2,958)
Incremental life years	0.9973	1.0001	
Incremental QALYs	0.5703	0.8919	(0.0027,0.5872)
Incremental cost per QALY	£9,323	£7,721	(-£1,943,£5,955)

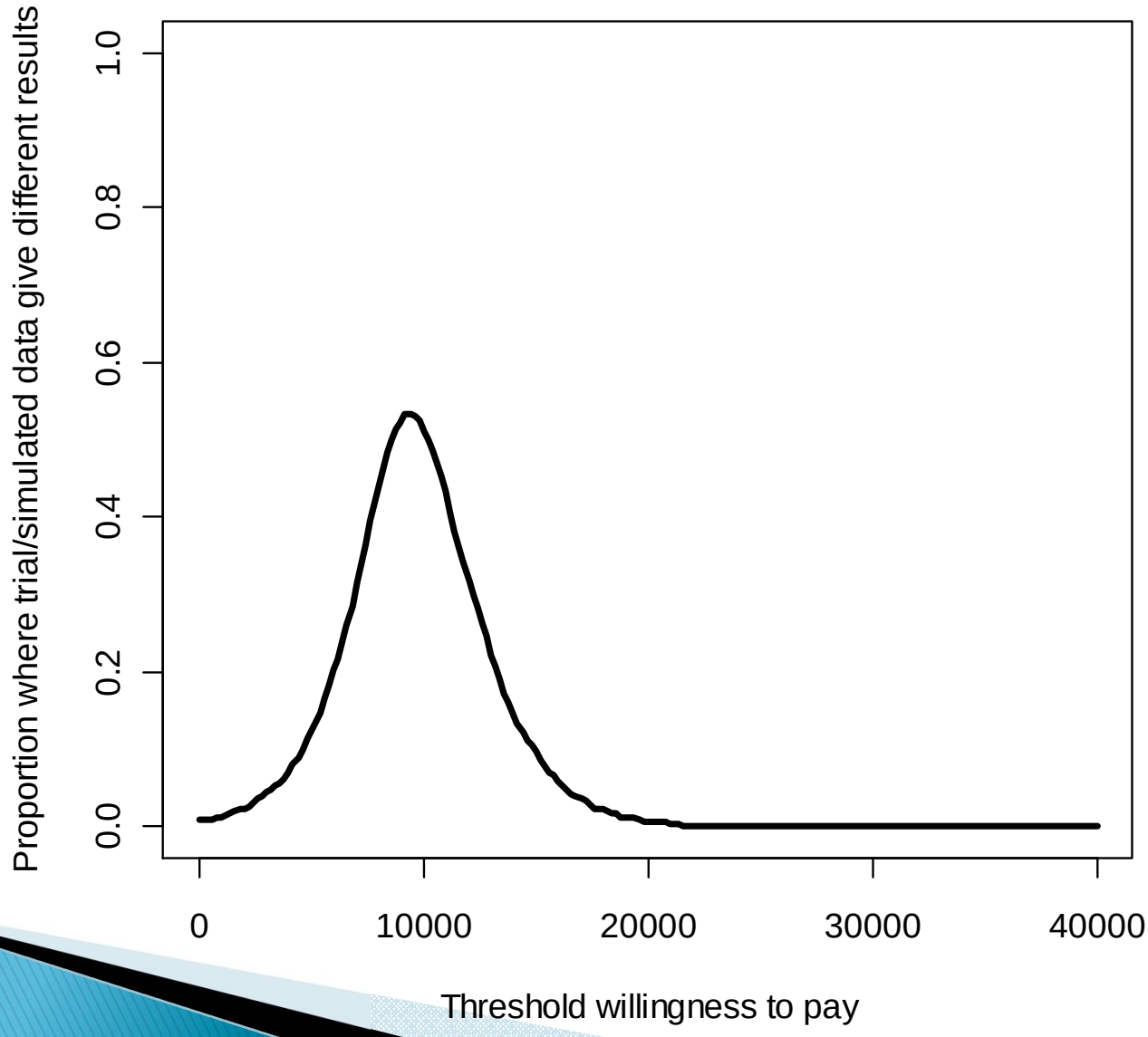
Probabilistic Sensitivity Analysis



Cost-effectiveness Acceptability Curve

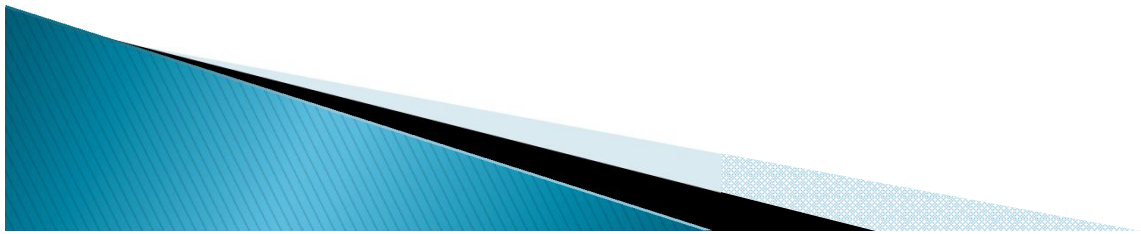


Agreement of modelling approaches



Case study 1b - PACIFICO Trial

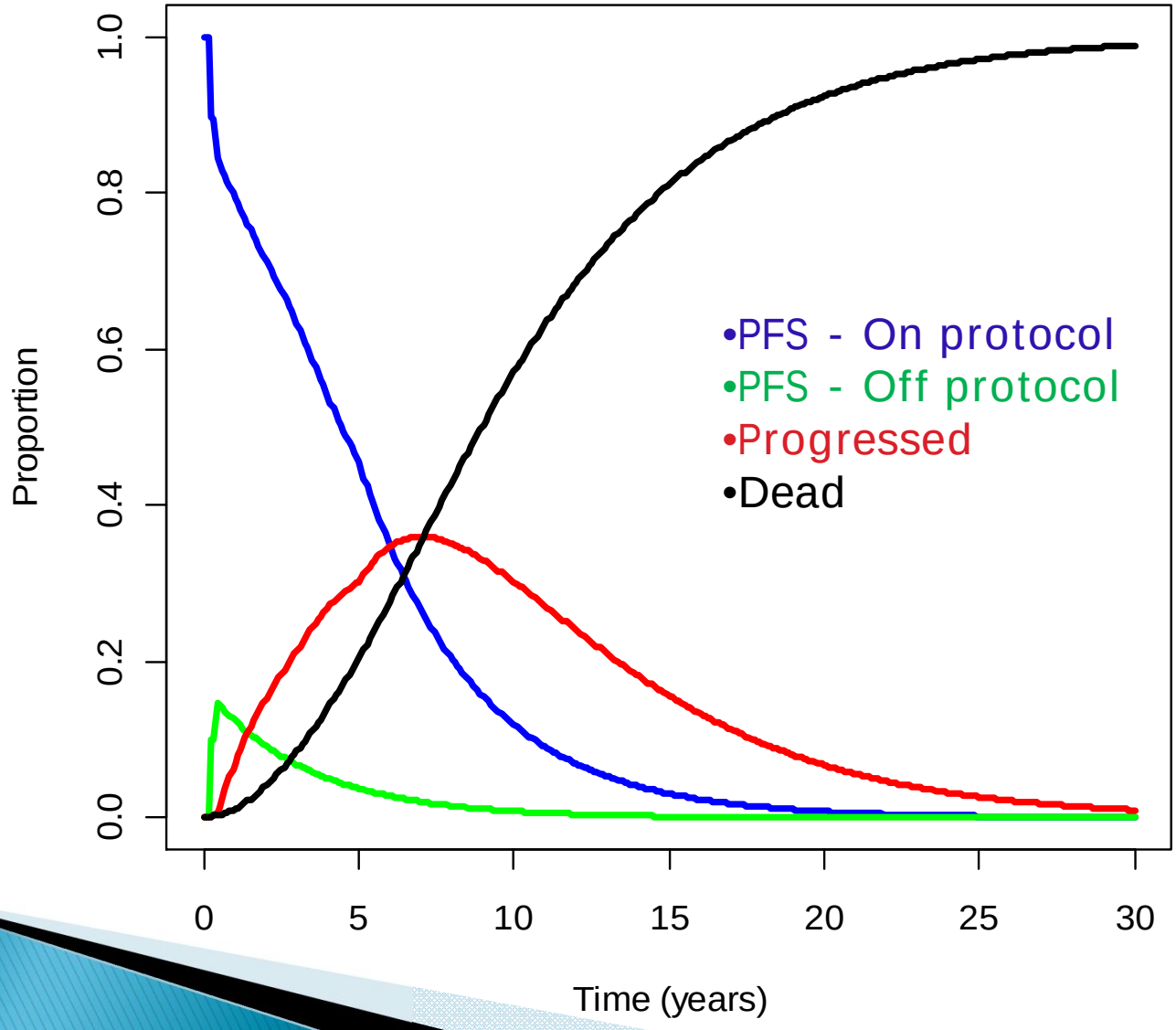
- Phase III multicentre trial comparing two different Rituximab-Chemotherapy induction regimens (R-CVP and R-FC) for Follicular Lymphoma in Older Patients.
  - Currently recruiting
- Rituximab is used in both the induction and maintenance phases of the treatment.



Methods

- Clinical data:
  - Baseline hazards and response rates for the two chemotherapy regimens taken from a trial comparing FC and CVP.
  - A meta-analysis of trials containing FC or CVP was conducted to obtain information on adverse events and the treatment effect of rituximab.
  - PKPD model provides PFS data, which is combined with all-cause mortality data and data on 2nd line chemotherapy.
- Economic data:
  - Extrapolated to a lifetime horizon of analysis.
  - Taken from previously published economic evaluations.

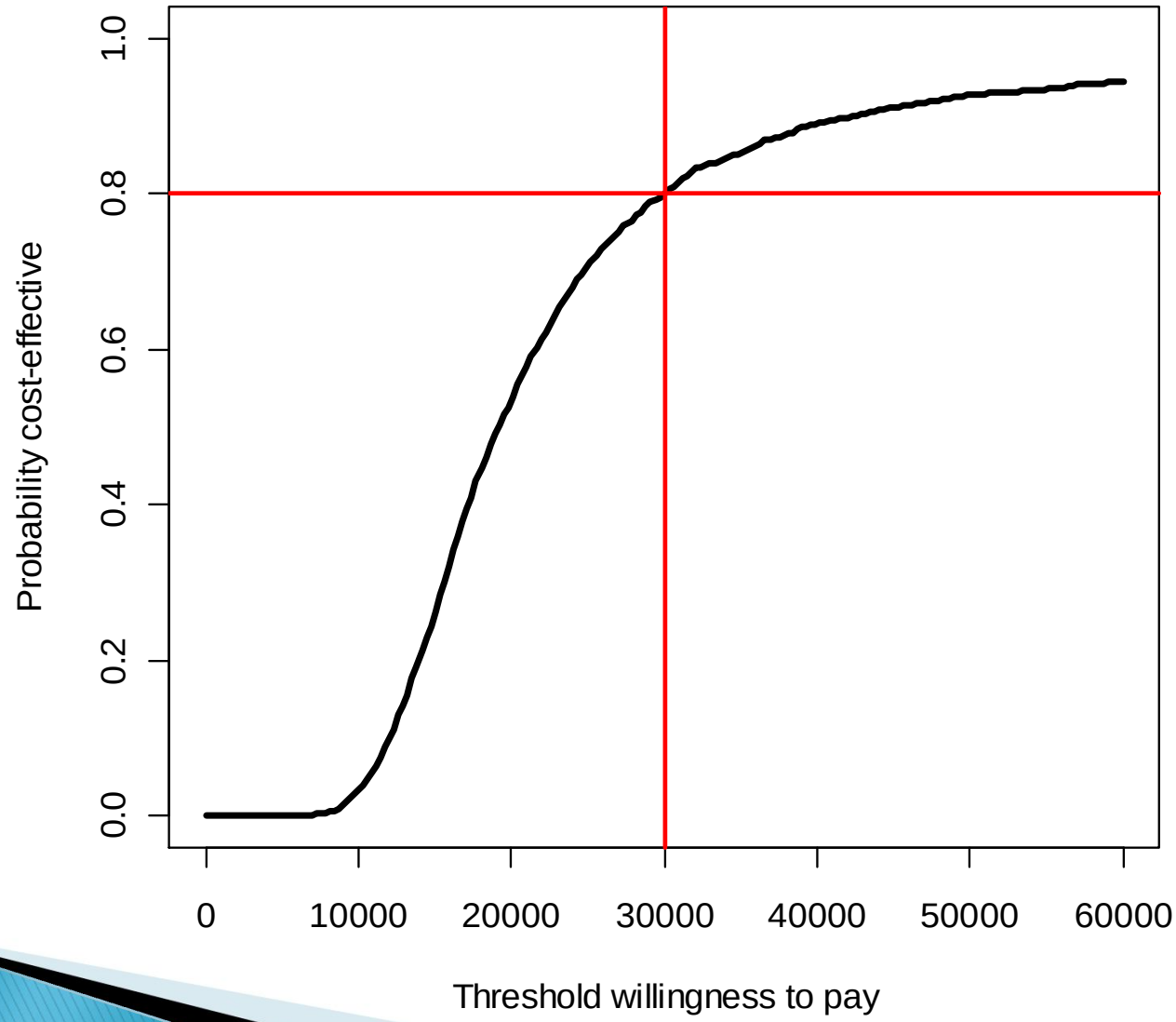
PACIFICO Simulation



Results

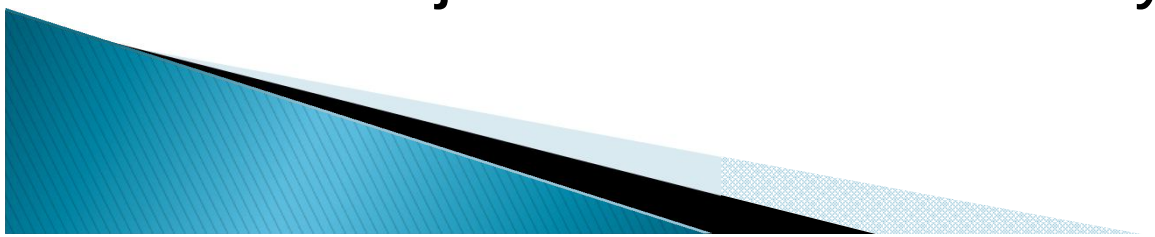
Value	R-CVP	R-FC
Median survival	9.008	9.542
Mean life expectancy	10.1577	10.6678
Total cost	£35,833	£41,401
Incremental cost		£5,568
Incremental life years		0.3260
Incremental QALYs		0.2873
Incremental cost per QALY		£19,376

PACIFICO Simulation



Case study 2 - Warfarin

- Warfarin is the most common oral anticoagulant used for patients with atrial fibrillation.
- For optimal anticoagulation, it is necessary to maintain an international normalised ratio (INR) between 2.0 and 3.0.
  - Deviations outside this range increase the risk of both strokes and haemorrhagic events.
- Due to the considerable between patient variability in response to warfarin, frequent monitoring and dose adjustments are necessary.



Warfarin pharmacogenetics

- Much of this variability can be explained by differences in two genes:
  - CYP2C9 – Responsible for the metabolic clearance of S-warfarin.
  - VKORC1 – Recycles reduced vitamin K
- People with variant alleles are at an increased risk of over-anticoagulation and bleeding.
- Dosing algorithms that take into account these genetic factors may result in better INR control, and hence better clinical outcomes.

Dosing algorithms

- There are three distinct algorithms that are used in warfarin dosing:
  - Loading phase – To achieve correct INR range as quickly as possible without over anti-coagulating.
  - Predicted maintenance dose – To predict the most likely dose to maintain a patient in the desired range in the long term.
  - Maintenance phase – Further dose adjustments are made based on INR at clinic visits.
- Genetic information can be made use of in all three of these stages.

Simulation structure

- A PKPD model of warfarin is used to predict time below, in and above INR range for a cohort of patients in the six months following initiation.
  - This simulation is re-run for all the different dosing algorithms we wish to compare.
- Data from a systematic review was used to link time in range to various clinical endpoints.
- An economic model was used to extrapolate these results to a lifetime horizon and compare different algorithms in terms of costs and QALYs accrued.

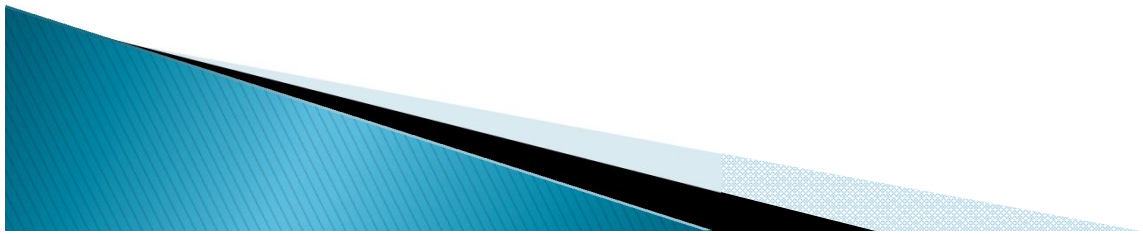
PKPD model

- The model was developed by Hamberg et al and predicts INR measurements based on dose, age and genetic information.
- Patient characteristics based on those of the UK atrial fibrillation population.
- Model allows for explicit incorporation of various forms of non-compliance:
  - Dose time compliance.
  - Missing doses.
  - Treatment discontinuation.

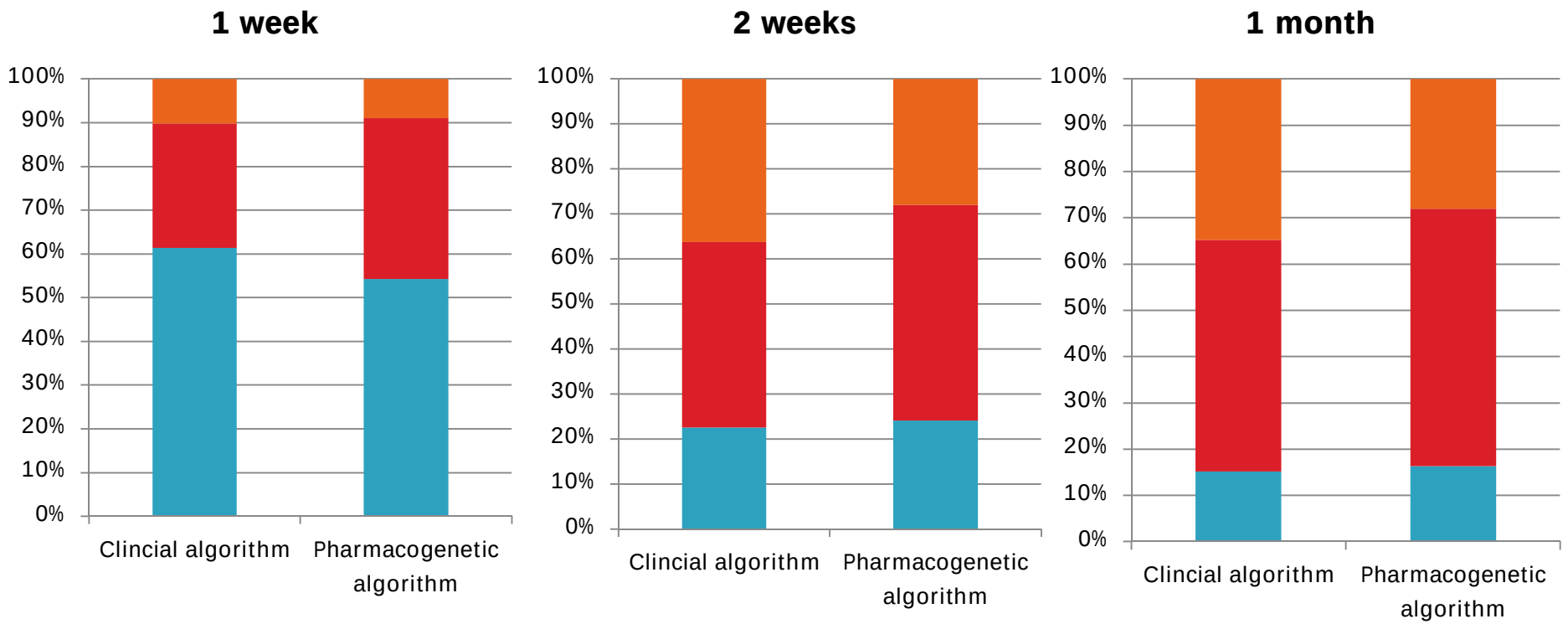
Hamburg et al. Clin Pharmacol Ther. 2010;87:727-34

Algorithm selection - Example

- Loading dose: All patients are given 10mg on days 1 and 2 and 5mg on day 3.
- Predicted maintenance dose: Two IWPC algorithms are used:
  - A clinical algorithm which uses age, height, weight, ethnicity and amiodarone and enzyme inducer use to predict the appropriate maintenance dose.
  - A pharmacogenetic algorithm which uses all these variables and genetic information to predict the maintenance dose.
- Doses adjusted with the Fennerty algorithm.



PKPD results – 3 months



Clinical event model

- Update of a systematic review from 2004.

	TE event odds ratio	Bleed odds ratio
INR < 1.5	4.26 (2.76, 6.81)	1.59 (1.01, 2.51)
1.5 <= INR < 2.0	2.19 (1.85, 2.59)	1.21 (0.78, 1.88)
2 <=INR < 3	1	1
3 <= INR < 3.5	1.05 (0.84, 1.31)	2.01 (1.33, 3.04)
3.5 <= INR < 4.0	1.14 (0.93, 1.40)	3.82 (2.57, 5.66)
INR > 4.0	1.26 (0.71, 2.22)	31.76 (22.76, 44.32)

- These numbers can then be applied to the data from our PKPD simulations to compare event rates.

Reynolds et al. Chest. 2004;126:1938-45

Results

	Clinical algorithms	Pharmacogenetic algorithm
TE event RR	1	1.000473
Bleed event RR	1	0.940997

- We can now, under the assumption that the clinical algorithm represents standard warfarin care, obtain event rates for both algorithms.
- We use a discrete event simulation to extrapolate these events to a lifetime horizon.
- We can thus obtain an incremental cost and incremental health gain associated with genetic testing.

Pink et al. BMJ. 2011;343

Economic modelling

- Event rates with warfarin standard care are taken from large randomised trials containing warfarin as an arm e.g. RE-LY, ROCKET-AF, ARISTOTLE.
- Health state utilities are taken from the standard utility of a patient with atrial fibrillation.
  - Utility decrements (permanent and temporary) are accrued when clinical events occur.
- Costs in the model are warfarin drug and monitoring costs and the costs of managing events.
  - A cost of £20 was assumed for the genetic test.

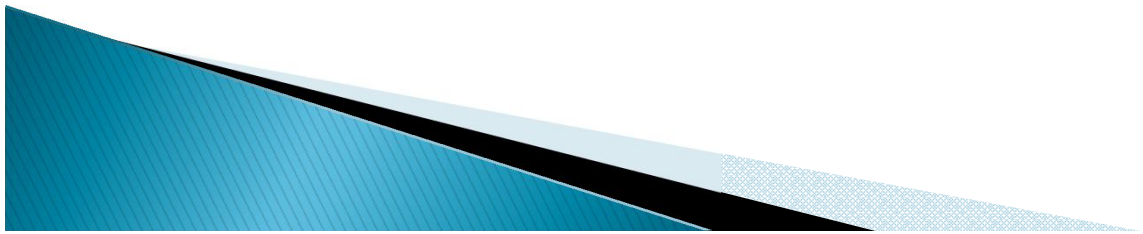
Results

	Clinical algorithm	Pharmacogenetic algorithm
QALYs	5.7209	5.7240
Life years	9.7220	9.7222
Costs (£)	5,880	5,921
ICER (£/QALY)		13,226

- In this particular case, the pharmacogenetic algorithm is not cost-effective (ICER > £30,000/QALY).
- A large number of algorithms can be simulated to look for those with the highest probability of being cost-effective.

Discussion - warfarin

- The most promising candidate algorithms can be selected on the criteria of both effectiveness and cost-effectiveness.
- The mechanistic nature of the model enables:
  - Inter-patient variability and protocol deviations to be explicitly explored.
  - Different patient subgroups to be evaluated separately.
  - Value of information analyses to be performed, looking at the potential value of future research in reducing parameter uncertainty.



Discussion - general

- Clinical trial design - Simulations can help to inform protocol design in many ways.
  - Mechanism-based drug development.
- Inform stop/go decisions.
  - Early estimates of cost-effectiveness.
- Simulations are also useful later in the evaluation process where trials of all available comparators will never become available.