



**HEALTH OUTCOMES MEASUREMENT,
PHARMACOECONOMIC EVALUATION AND
OPTIMIZATION OF DRUG TREATMENT – HOW
DO THESE RELATE TO GENERIC
MEDICINES?**

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FOCUS

- Optimization of drug treatment with generic medicines
- Role of generic medicines as comparators in pharmacoeconomic evaluation
- Role of Real World Data in determining outcomes with generic medicines



OPTIMIZATION OF DRUG TREATMENT WITH GENERIC MEDICINES



BACKGROUND

- Generic phenytoin
- Epanutin^R
- Epilepsy
- Perception of inferiority to original
- Ancient drug



STUDY

The determination and validation of population pharmacokinetic parameters of phenytoin in adult epileptic patients in the Western Cape using nonlinear mixed-effects modeling.

Needed blood samples of phenytoin for PK modelling.

Clinical pharmacokinetic consulting service for phenytoin

8 clinics per week - 2 years



CLINICAL PHARMACOKINETIC SERVICE

Referral by attending doctor

Demographic data

Concurrent medicines

Duration of treatment

History of seizures and frequency

Description of seizures

Alcohol and smoking

Admission to hospital

Toxicity

Seizure diary

Compliance checks

Counselling – missed doses

Tablet counts

Time to Steady state calculation

Blood phenytoin samples

Determination of V_m and K_m

Calculation of dose

Prediction of new PHT conc.

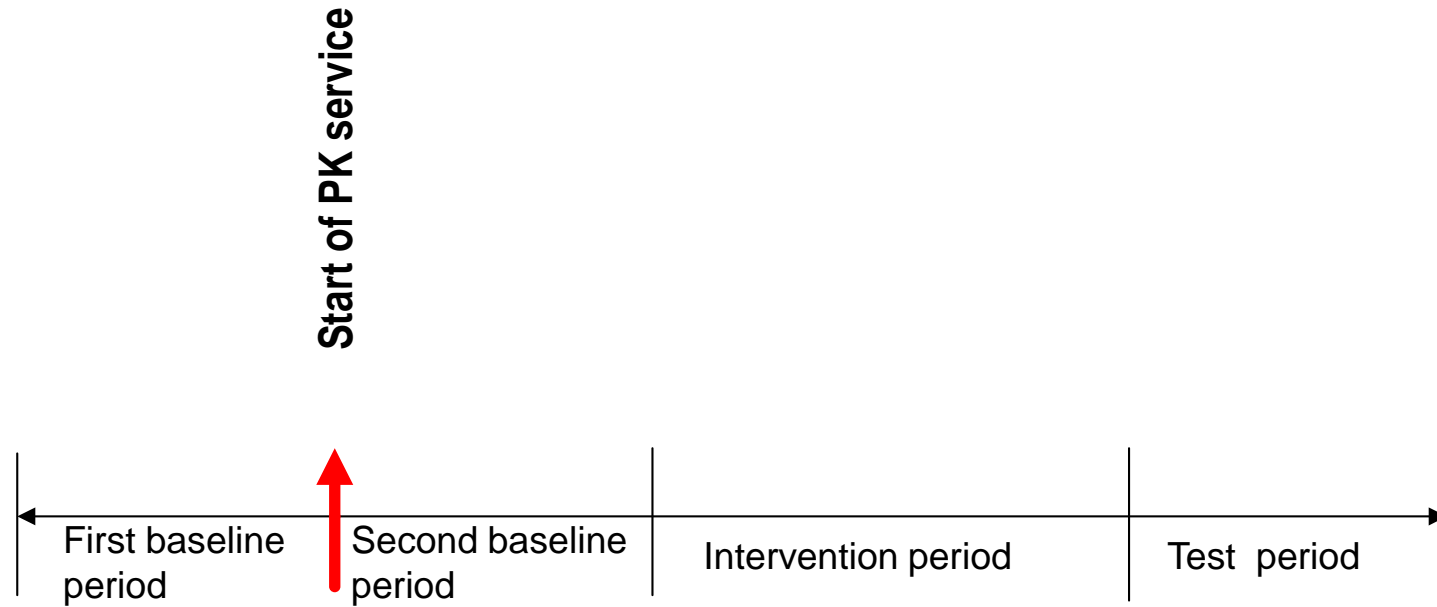
Report to doctor

Phenytoin toxicity – withdraw

Oral loading dose



PRE-POST INTERVENTION: PHENYTOIN



P. Valodia et al, Benefits of a clinical pharmacokinetic service in optimizing phenytoin use in the Western Cape. SAMJ.1998,88:873-875



TOTAL NUMBER OF SEIZURES EXPERIENCED DURING THE FIRST AND SECOND BASELINE PERIODS AND THE TEST PERIOD (195 PATIENTS)

PERIOD	NUMBER OF SEIZURES
First baseline	667
Second baseline	588
Test period	216

P. Valodia et al, Benefits of a clinical pharmacokinetic service in optimizing phenytoin use in the Western Cape.
SAMJ.1998,88:873-875



MEAN SEIZURE FREQUENCY PER MONTH FOR SPECIFIC PERIODS BEFORE AND AFTER THE INITIATION OF THE STUDY (195 PATIENTS)

PERIOD	SEIZURE FREQUENCY PER MONTH	
	Mean	Range
First baseline	3.62	0 - 48
Second baseline	3.15	0 – 29
Test period	1.18	0- 16

P. Valodia et al, Benefits of a clinical pharmacokinetic service in optimizing phenytoin use in the Western Cape.

SAMJ.1998,88:873-875



PERCENTAGE REDUCTION IN SEIZURES

Period	% reduction in seizures
	n = 195
Based on first baseline period	66,4
Based on second baseline period	63,2
Based on the average of first and second baseline periods	64,8



ADVERSE EFFECTS

	% patients
First visit	20,5%
Last visit	3,2 %



DOSE ADJUSTMENTS

	% patients
	n = 332
Dose increased	31,9
Dose decreased	15,1
No change in dose	53,0
Dose adjusted	47,0



Relationship between therapeutic concentration of phenytoin and the percentage of patients optimized at that concentration range.

Therapeutic conc ($\mu\text{mol/l}$)	% Patients
	n = 171
0,0 – 19	0,0
20 – 39	17,0
40 – 59	31,2
60 – 79	30,7
80 – 99	10,9
100- 119	8,6
120 - 139	1,6



$$Cp_{ss} = - \frac{1}{2} \left[\left(\frac{Vm}{Cl} + Km - \frac{R}{Cl} \right) - \sqrt{\left(\frac{Vm}{Cl} + Km - \frac{R}{Cl} \right)^2 + \frac{4 \cdot R \cdot Km}{Cl}} \right]$$

$$Vm = (\theta_1 * WT + \theta_2) RACE * SMK * ALC * SEX * AGE * EXP \tau_1$$

where RACE = θ_4 if coloured, otherwise = 1

SMK = θ_5 if smoker, otherwise = 1

ALC = θ_6 if drinker, otherwise = 1

SEX = θ_7 if male, otherwise = 1

AGE = θ_{10} if ≥ 65 years, otherwise = 1

$$Km = \theta_2 * RACE * AGE * EXP \tau_2$$

where RACE = θ_7 if coloured, otherwise = 1

AGE = θ_{11} if ≥ 65 years, otherwise = 1

$$Cl = \theta_8 * EXP \tau_3$$

P. Valodia et al, Factors influencing the population pharmacokinetic parameters of phenytoin using nonlinear mixed-effects modelling in adult epileptic patients in South Africa, *Therapeutic Drug Monitoring*, 1999, **21**:57-62.



COST SAVINGS

	Price (per month)	Claims (2008)	Total cost
Epanutin	R 234	12018	R 2,8 m
Phenytoin sod	R 53	1965	R 0,1 m
Savings			R 2,2 m



Value

Generic phenytoin effective – optimization is required.

Generic phenytoin is still infrequently used.

Use existing drugs known to be effective



ROLE OF GENERICS AS COMPARATORS IN PHARMACO- ECONOMIC EVALUATION



REGULATIONS RELATING TO A TRANSPARENT PRICING SYSTEM FOR MEDICINES AND SCHEDULED SUBSTANCES (30 APRIL 2004)

Section 14 (5):

DG may request in writing:

Details as to the comparative efficacy, safety and **cost effectiveness** of the medicine or Scheduled substance relative to that of other medicines or Scheduled substances in the same therapeutic class compiled in a manner consistent with guidelines published by the Director-General in the Gazette from time to time.



PHARMACOECONOMIC ANALYSES

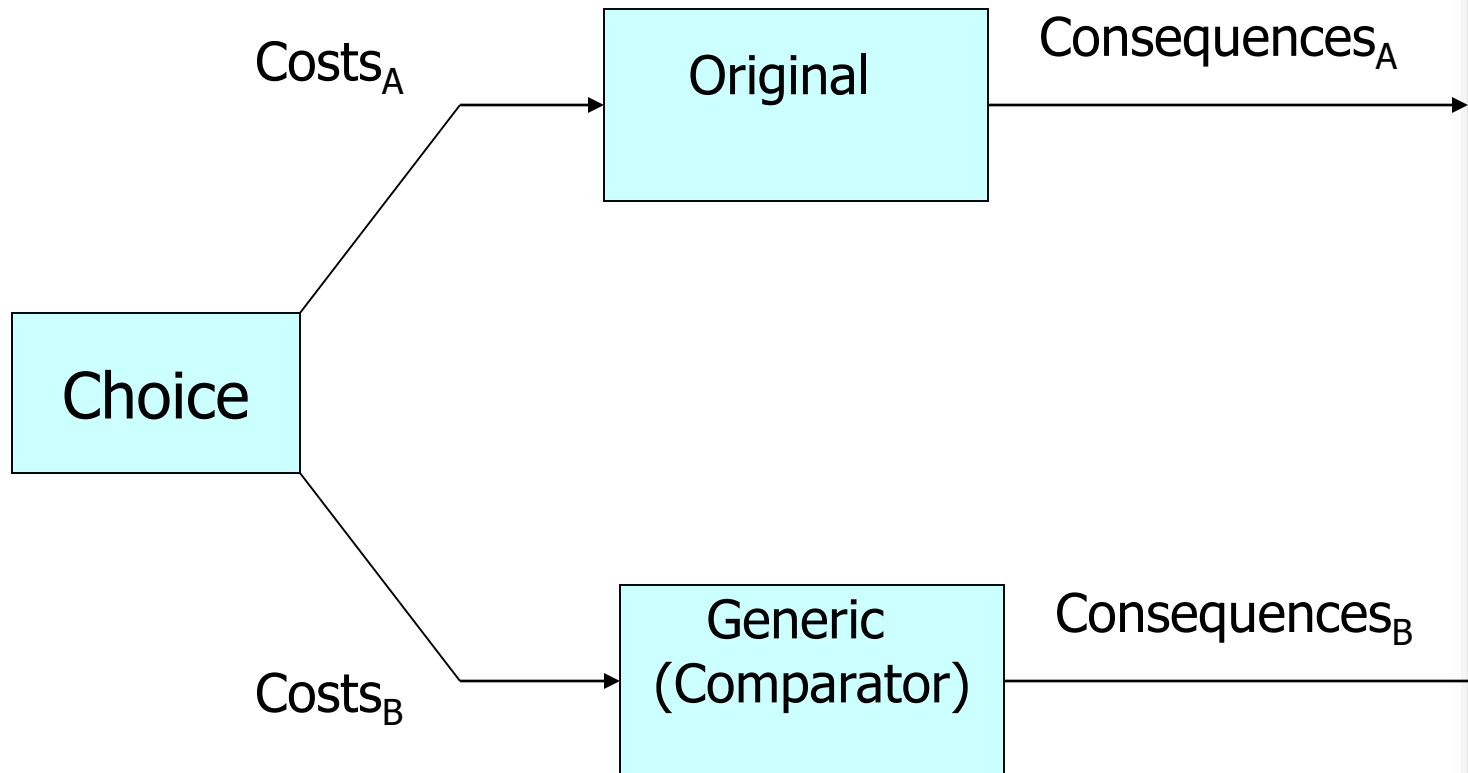
(1) Cost minimization

	Cost	Outcome
Original	R 200	↓ 12 mm Hg
Generic	R 100	↓ 12 mm Hg

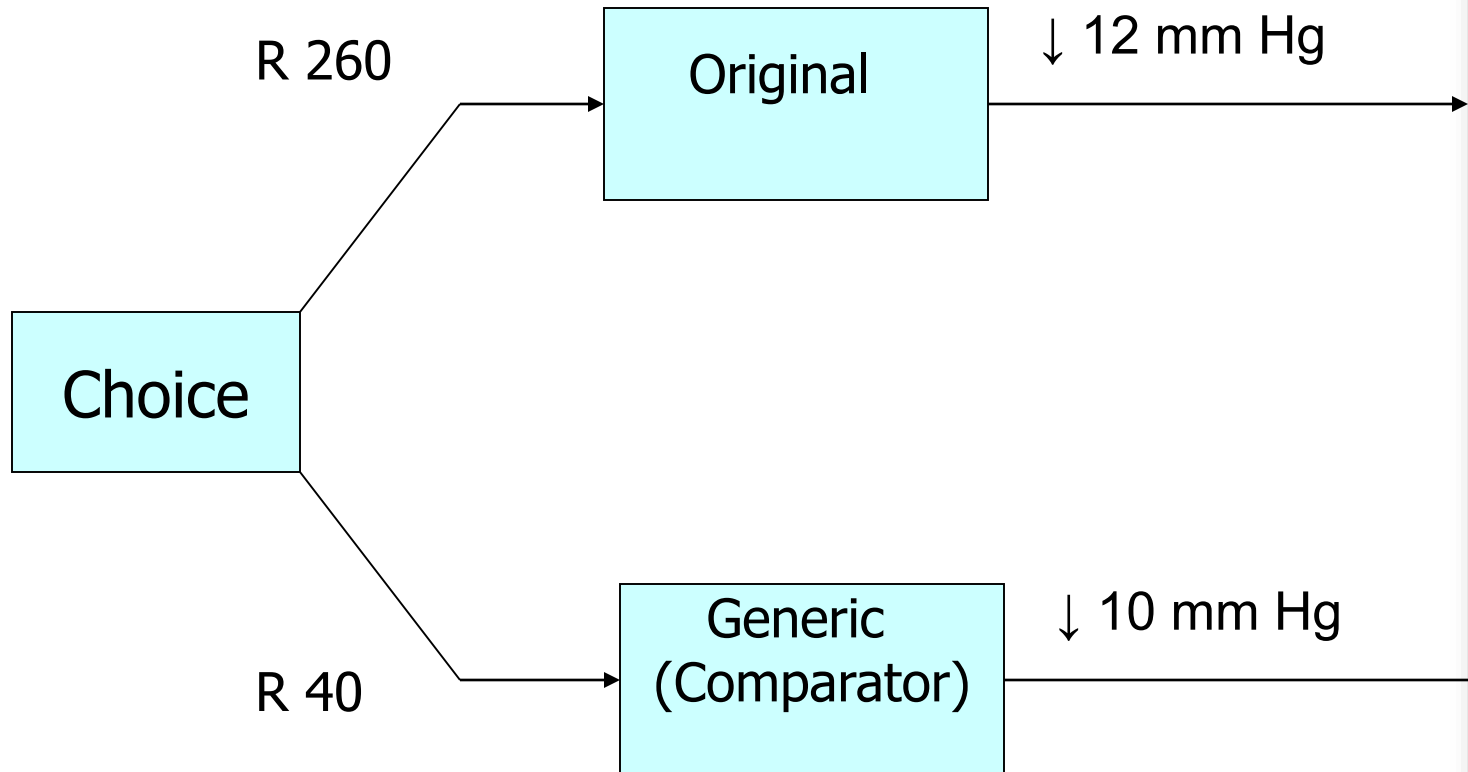
(2) Cost effectiveness



Economic Evaluation always involves a comparative analysis of alternative courses of action



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QUESTIONS

Do you think that we allocate scarce resources wisely, fairly and efficiently?

Are we ready to ration more extensively?



VALUE

The role of generic drugs as comparators in PE evaluation will become important.

Need a better understanding of the relationship between cost and the value a generic medicine delivers.



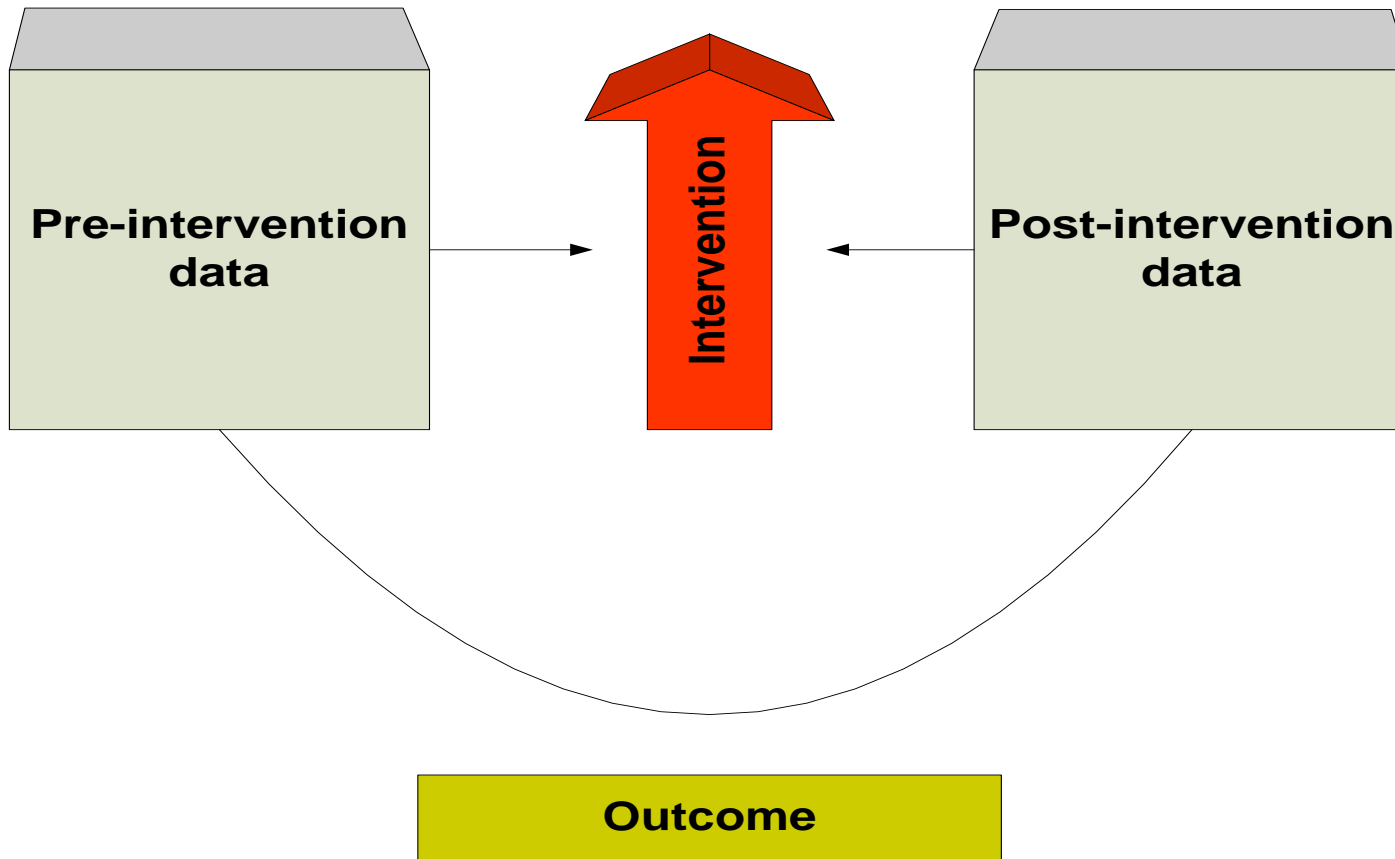
ROLE OF REAL WORLD DATA IN DETERMINING OUTCOMES WITH GENERICS



DEFINITION : OUTCOMES RESEARCH

A **scientific** discipline that evaluates the effect of **health care interventions** on patient-related, if not **patient specific**, **economic, clinical** and **humanistic** outcomes.





VALUE

- Opportunity to use RWD to determine outcomes with generic medicines.
- Maximizes the use of all available data
- OR allows tracking and management of individual patients with generic medicines.



FINAL COMMENTS

- Value of generic medicines not fully realized.
- The value of generic medicines as comparators in cost-effectiveness analyses requires more attention.
- Exploit the use of RWD to support the value of generic medicines using outcomes research methods.

