Experience in offering a clinical pharmacokinetic service for epilepsy management and the measurement of health outcomes

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BACKGROUND

- Non-linear pharmacokinetics
- 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 Vm and Km
Calculation of dose
Prediction of new PHT conc.
Report to doctor
Phenytoin toxicity – withdraw
Oral loading dose

Phenytoin kinetics

$$Vm = \frac{S.F.R}{Cp_{ss}} Km + S.F.R$$

$$Km = \frac{R_2 - R_1}{\frac{R_1}{Cp_{ss1}} - \frac{R_2}{Cp_{ss2}}}$$

$$R = \frac{Vm\ x\ Cp_{ss}\ x\ \tau}{(Km + Cp_{ss})(S)(F)}$$

$$Cp_{ss} = \frac{Km + (S)(F)(R)}{Vm - (S)(F)(R)}$$

Phenytoin kinetics

$$t_{90\%} = \frac{Km \times Vd}{(Vm - S.F.R)^2} \times (2.303Vm - 0.9S.F.R)$$

$$LD = Vd\,(CP_{desired} - CP_{achieved})$$

Phenytoin Kinetics

- Therapeutic range: 40-80 µmol/l
- Collect serum PHT conc at steady-state
- Time to steady-state 5 days to 6 weeks
- Daily dose should not exceed individual's Vm
- Trough concentration
- Following a change in PHT dose, the time required to reach a new steady-state concentration should be determined.
- Total PHT concentration assumes normal protein binding

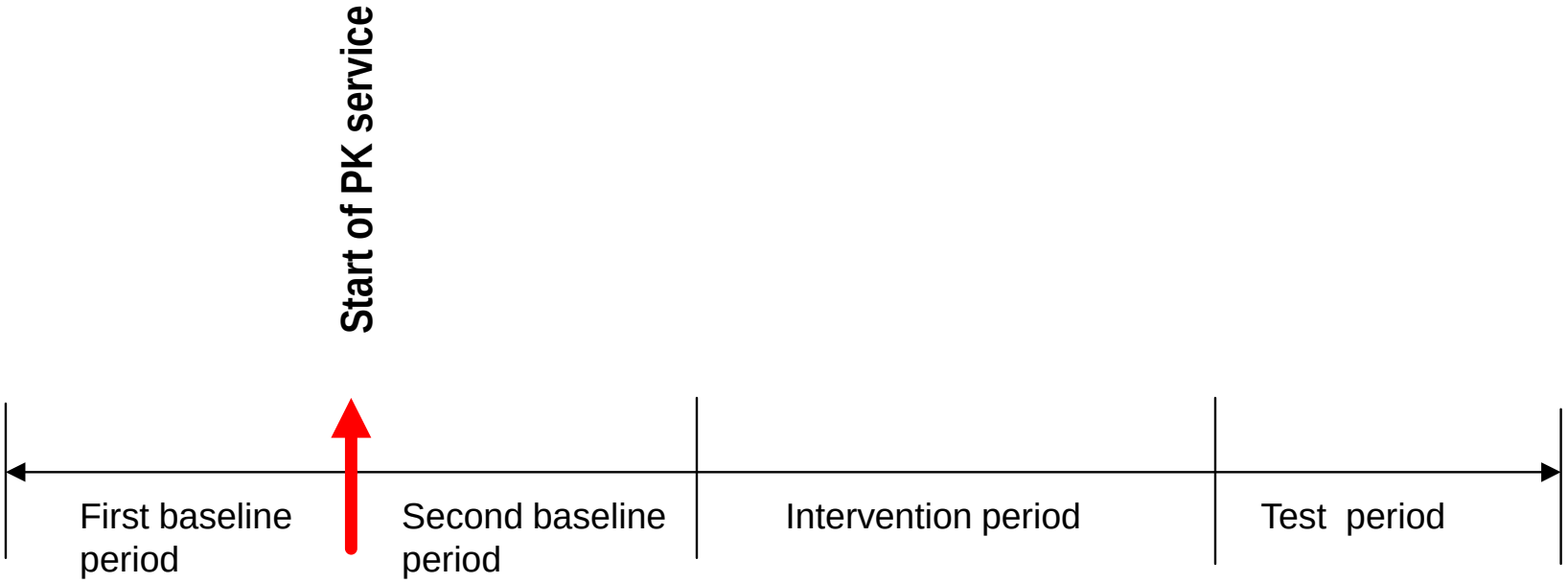
Phenytoin Kinetics

- Withdraw phenytoin over few weeks
- Upward adjustment of phenytoin dose after 5 -12 month due to auto-induction.
- Phenytoin sodium and Phenytoin acid
- Re-optimized after change in brand
- Delay blood sample if compliance is suboptimal
- Ensure compliance before increasing dose

Phenytoin kinetics

- If patient has seizures at the time corresponding to the trough serum concentration, seizure frequency may be decreased by shortening the dosage interval without necessarily changing the daily dose.
- Transient symptoms of toxicity associated with high peak concentration may be avoided by decreasing the dose and shortening the dosing interval, without necessarily having to alter the daily 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

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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

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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 (µmol/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

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

Vm = $(\theta_1 * WT * \theta_3)$ RACE* SMK * ALC * SEX * AGE * EXPn_1

Where
RACE = θ_4 if coloured, otherwise = 1
SMK = θ_5 if smoker, otherwise = 1
ALC = θ_8 if drinker, otherwise =1
SEX = θ_9 if male, otherwise = 1
AGE = θ_{10} if ≥ 65 years, otherwise = 1

$Km =$ θ_2* RACE * AGE * EXPn_2

where
RACE = θ_7 if coloured, otherwise = 1
AGE = θ_{11} if ≥ 65 years, otherwise = 1

$Cl =$ $\theta_{11} * \mathrm{EXP}n_3$

P. Valodia et al. Factors influencing the population pharmacokinetic parameters of phenytoin using non-linear 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

Measuring the value of clinical pharmacy services

Methods to measure value

- Health outcomes
- Benchmarking
- Return on investment
- Trend analysis (using moving average)
- Claims cost versus inflation over time (year to year)
- Other: Total population approach, survival analysis

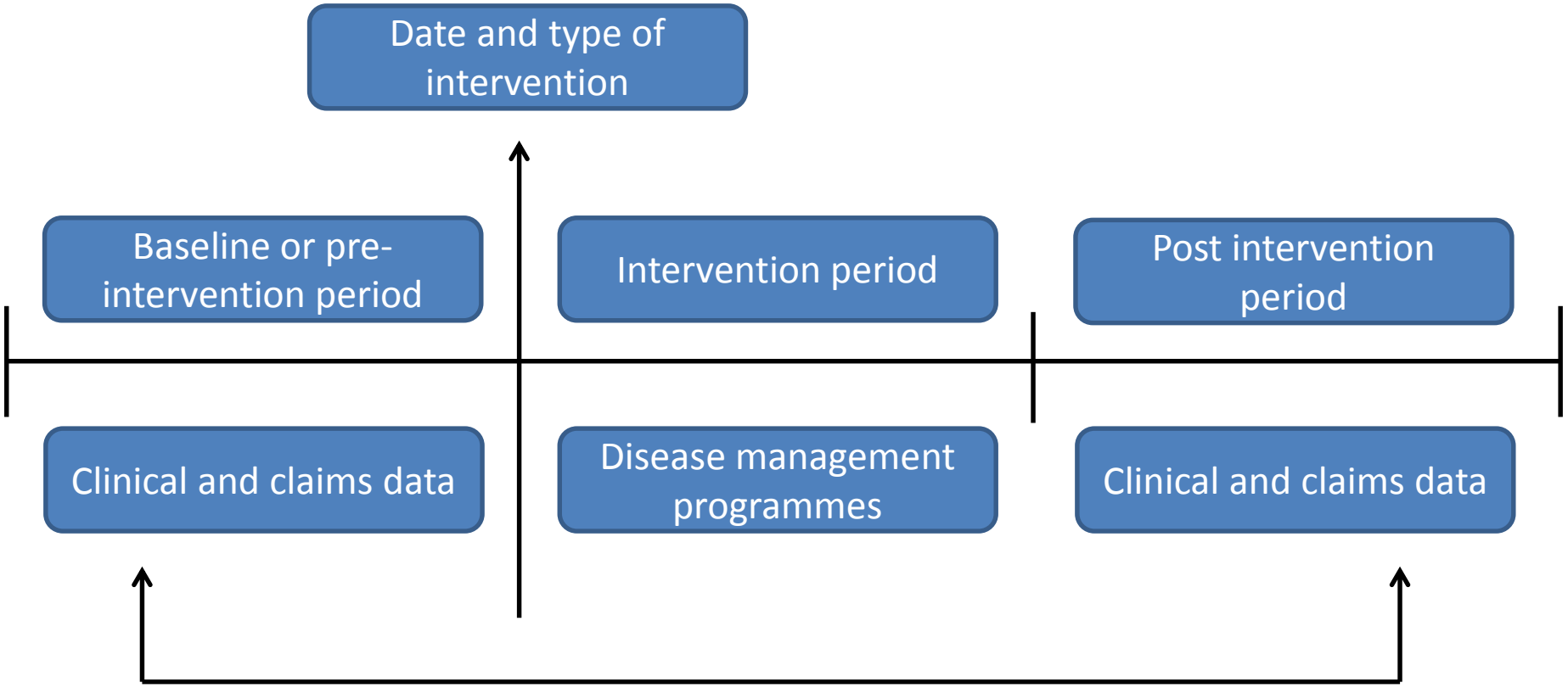
Use combination of methods

Definition: Health Outcomes

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

ISPOR BOOK OF TERMS

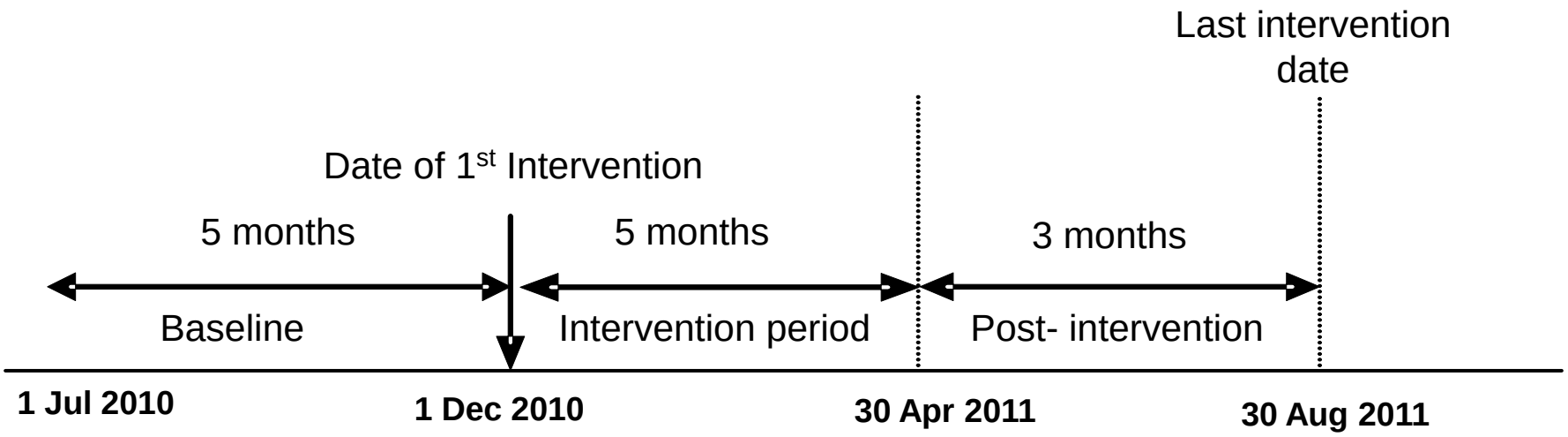
Health Outcomes Assessment



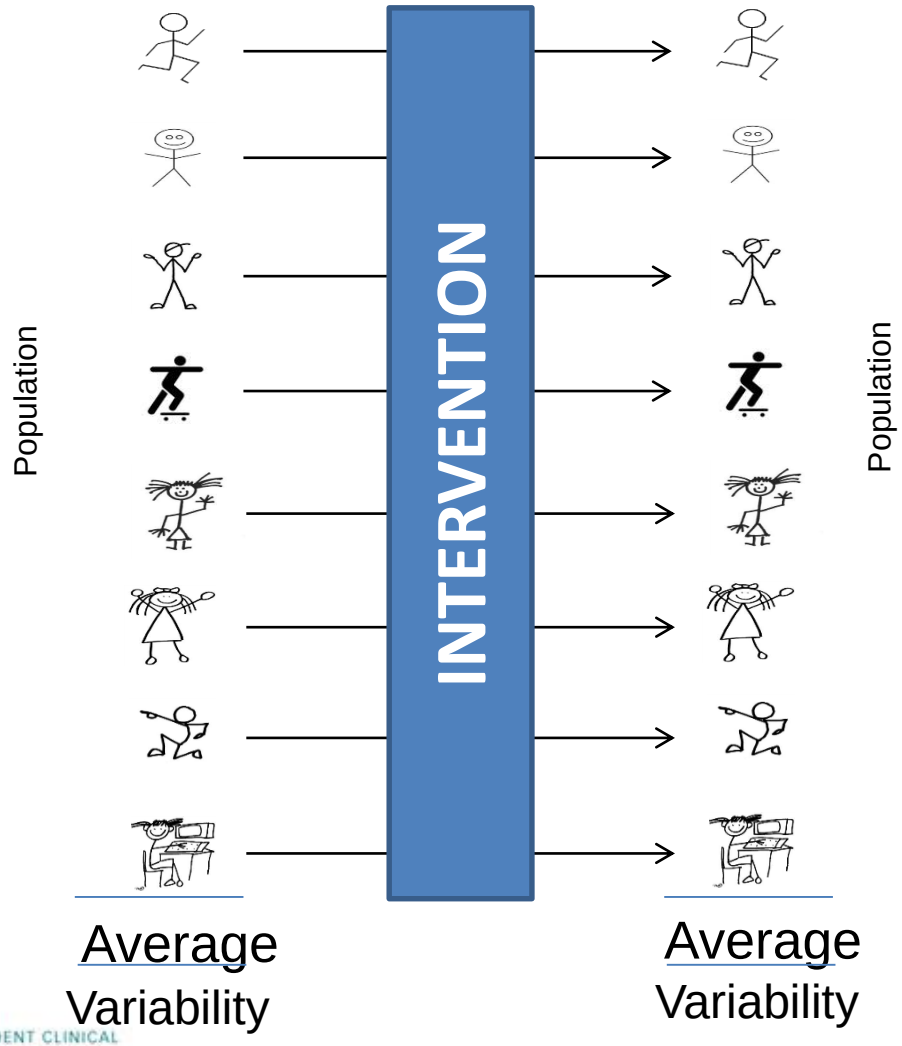
Difference = Outcome

Value of clinical pharmacy service

PRE- AND POST INTERVENTION



Population vs Individual Health Outcomes Assessment



Measure Change

A

B

C

D

E

F

G

H

Asthma: Health Outcomes

Clinical

- Categorization of uncontrolled, partially control and controlled patients
- Frequency of symptoms
- Severity of symptoms
- Number of symptoms
- Number of asthma attacks
- Number of emergency room visits.
- Number of asthma related hospital days
- Number of nebulisations
- Number GP consults
- Number specialists consults
- Asthma related admissions

Economic

- Savings due to reduced hospitalizations
- Savings due to reduced emergency room visits
- Savings due to decrease hospital nebulisations
- Savings due to decrease in consultation costs
- Savings due to decrease specialist visits
- Savings due to increased productivity (less absenteeism)

Humanistic

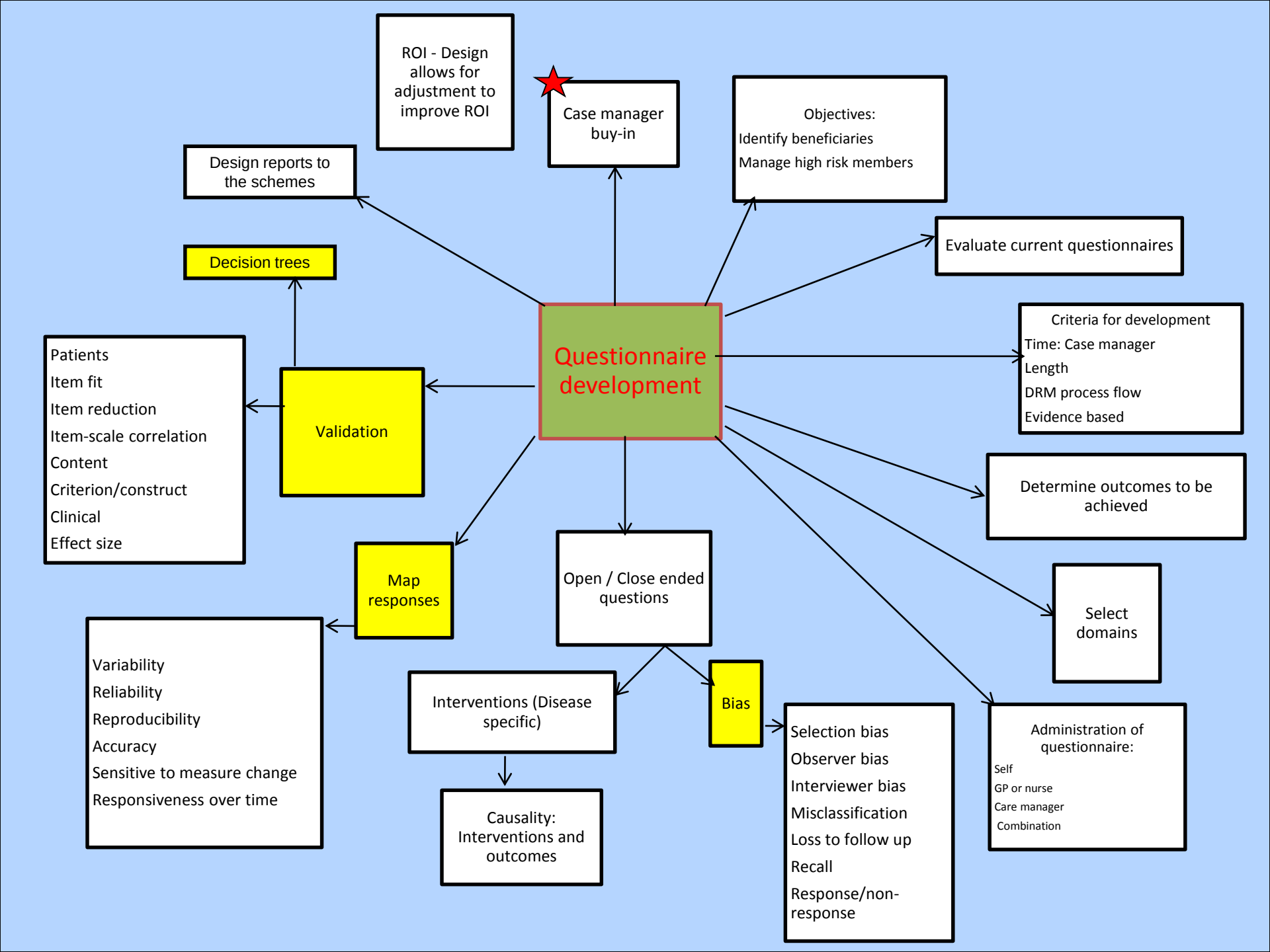
- Improved quality of life
- Improved patient satisfaction
- Improved compliance
- Improved understanding of inhaler use
- Improved understanding of personal treatment plan
- Improved ability to use as peak flow meter
- Smoking cessation
- Avoidance of trigger factors
- Increase use of a spacer device when required

Challenges with measuring health outcomes

- Definition of health outcomes
- Careful planning of data collection
- Availability of good baseline information
- Selection bias
- Missing data points
- Validation of ICD10 and CPT codes
- Matching of control groups
- Regression to the mean
- Clinical and statistical differences
- Inter- and intra-scheme variability

Challenges

- A priori specification of confounding variables
- Interpretation – denominator effect, RTTM
- Development of questionnaires sensitive to changes over time
- Integration and automation of all systems
- Development of intelligent health systems
- Disease specific clinical measurement
- Not all information is extractable
- Develop impactibility models


Questionnaire development
ROI - Design allows for adjustment to improve ROI
Case manager buy-in
Objectives:
Identify beneficiaries
Manage high risk members
Design reports to the schemes
Evaluate current questionnaires
Decision trees
Criteria for development
Time: Case manager
Length
DRM process flow
Evidence based
Patients
Item fit
Item reduction
Item-scale correlation
Content
Criterion/construct
Clinical
Effect size
Validation
Determine outcomes to be achieved
Map responses
Open / Close ended questions
Select domains
Variability
Reliability
Reproducibility
Accuracy
Sensitive to measure change
Responsiveness over time
Interventions (Disease specific)
Bias
Causality: Interventions and outcomes
Selection bias
Observer bias
Interviewer bias
Misclassification
Loss to follow up
Recall
Response/non-response
Administration of questionnaire:
Self
GP or nurse
Care manager
Combination

Way forward

- Continually measure the effectiveness of the work of clinical pharmacists to make an impact.
- Implement a phased approach