Measuring Potential Return on Investment in Pharmacovigilance: A Framework

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Benefits: Medicines are Among the Most Important Health Interventions

- Rx-Related "Best Buys" in Health:
  - Vaccinate children
  - Prevent and treat childhood pneumonia, diarrhea, and malaria
  - Attack the spread of HIV, including providing antiretroviral medications
  - Treat TB patients

Disease Control Priorities Project, www.dcp2.org

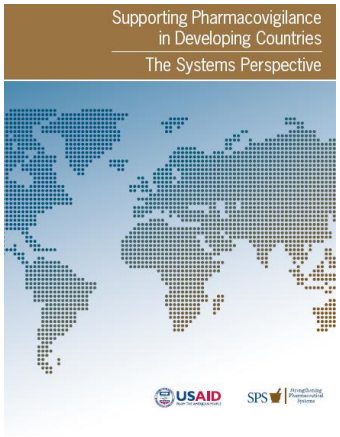
Examples of Serious and Unexpected Adverse Drug Reactions

Medicine	Adverse reaction
Chloramphenicol	Aplastic anaemia
Clioquinol	Myelooptic neuropathy (SMON)
Erythromycin estolate	Cholestatic hepatitis
Fluothane	Hepatocellular hepatitis
Methyldopa	Hemolytic anemia
Oral contraceptives	Thromboembolism
Practolol	Sclerosing peritonitis
Reserpine	Depression
Statins	Rhabdomyolisis
Thalidomide	Congenital malformations

Source: WHO Policy Perspectives on Medicines: Pharmacovigilance-ensuring the safe use of medicines. Geneva: WHO, October 2004.

What is Pharmacovigilance?

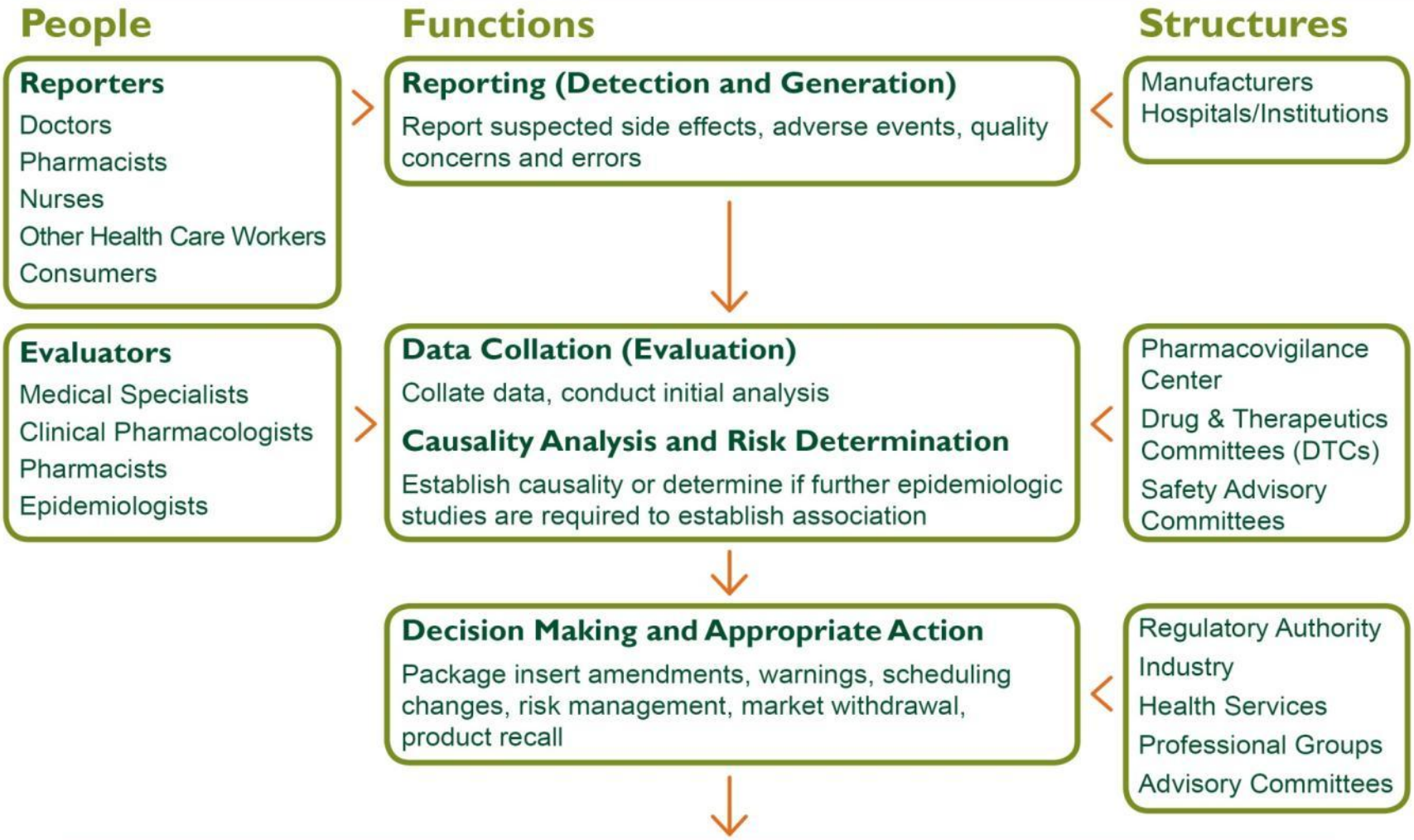
- The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible medicine-related problems (WHO)



Context & Need for Pharmacovigilance

- Rapid scale-up of medicine-centric public health delivery programs
- New medicines in pipeline – drugs & vaccines
- Short- and long-term toxicities
- Product quality issues
- Emergence of drug resistance
- Vulnerable, understudied populations

The Pharmacovigilance Framework



Sources of Safety Information

- Premarketing studies in humans
- Preclinical studies
- Spontaneous reporting of adverse events
- Stimulated reporting of adverse events
- Active surveillance – prospective cohort, records linkage, registries
- Medical literature, including pharmacy journals
- Alerts from other regulatory agencies and WHO
- Media

Risk Management Options

- No change
- Monitor experience while watching and waiting
- More intensive data gathering
- Restrict product availability
- Suspend procurement of products
- Withdraw product from local approved or essential medicines list
- Communicate new or reinforced information to health professionals and the public
- Modify treatment guidelines

Pharmacovigilance Potential Tangible Benefits

- PV can protect the public's health by identifying risks and risk factors of adverse drug events (ADEs) in a timely manner and acting upon such information to prevent or mitigate risks

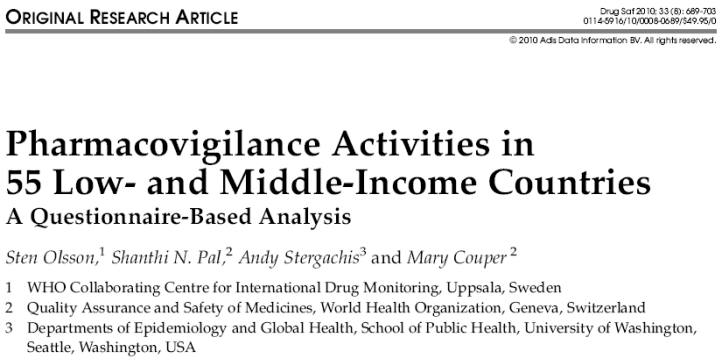
- PV can identify previously undetected ADEs and detects and can prevent irrational use of medicines, medication errors, and medical product defects

- Information collected through PV allows for the assessment of the risks and benefits throughout a medicine's life-cycle

- However many low- and middle-income countries lack fully-functional PV programs

Pharmacovigilance in LMICs

- Gaps in infrastructure, resources, training, and methodologies
- Low number of AE reports
- Limited active surveillance
- Few countries allocate budgets to PV, but some public health programs and donor organizations are supporting PV activities
- PV usually conducted separately in many countries through parallel and often poorly coordinated systems
- PV has not kept pace



ORIGINAL RESEARCH ARTICLE

Drug Saf 2010; 33 (8): 689-703
0114-5916/10/0008-0689/$49.95/0

Pharmacovigilance Activities in 55 Low- and Middle-Income Countries
A Questionnaire-Based Analysis

Sten Olsson,[1] *Shanthi N. Pal*,[2] *Andy Stergachis*[3] and *Mary Couper*[2]

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2 Quality Assurance and Safety of Medicines, World Health Organization, Geneva, Switzerland
3 Departments of Epidemiology and Global Health, School of Public Health, University of Washington, Seattle, Washington, USA

Kuemmerle *et al. Malaria Journal* 2011, **10**:57
http://www.malariajournal.com/content/10/1/57

MALARIA JOURNAL

RESEARCH Open Access

Assessment of global reporting of adverse drug reactions for anti-malarials, including artemisinin-based combination therapy, to the WHO Programme for International Drug Monitoring

Andrea Kuemmerle[1,2,3], Alex NO Dodoo[4], Sten Olsson[5], Jan Van Erps[6], Christian Burri[1,2], Paul S Lalvani[7*]

- Malaria-endemic countries submitted only 1.2% of all of the ADR reports
- Only 60 out of 21,312 ADR reports were related to ACTs, 51 of which were coming from four sub-Saharan African countries.

Resource Constraints and Investment Decisions

- LMICs (and increasingly development partners) face severe resource constraints and must prioritize among competing priorities
- Given that the set up of PV capacity and maintenance of PV activity is potentially costly :
  - Should policy makers invest scarce resources in PV?
  - What is the potential return on investment (ROI) for money spent on PV? i.e. How many $ would be gained for every $ spent on PV?
  - How would the potential ROI in PV systems compare with other public health investments?
- Rigorous assessments of the ROI in national PV systems have not been reported in the literature

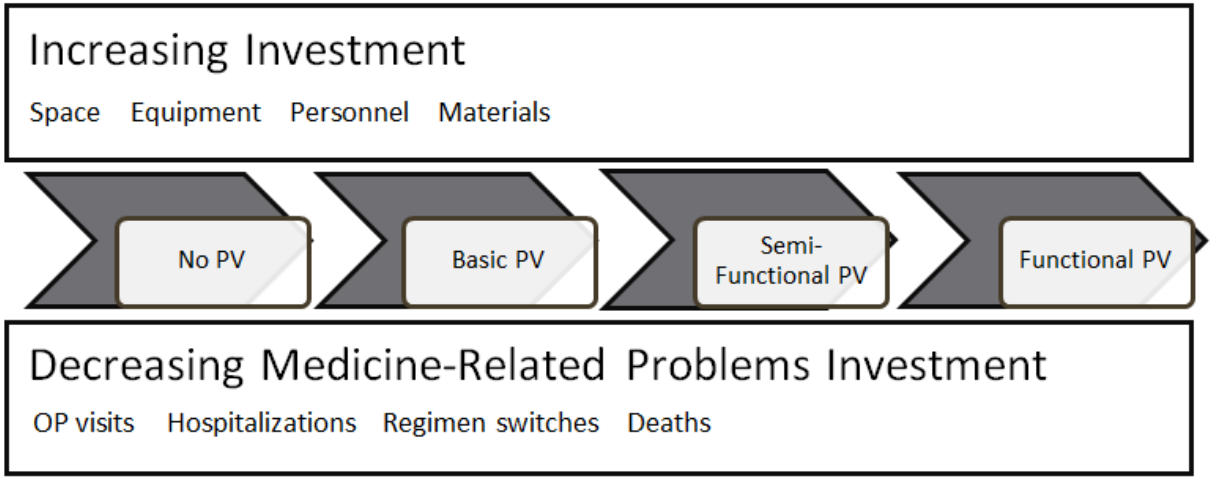
Objectives

- To provide a framework for policy makers and development partners at the country level to assess the potential return on investment (ROI) on resources spent on pharmacovigilance
- (To develop a generic analytic tool that is customizable at the country level using context-relevant data)

Model and Methods

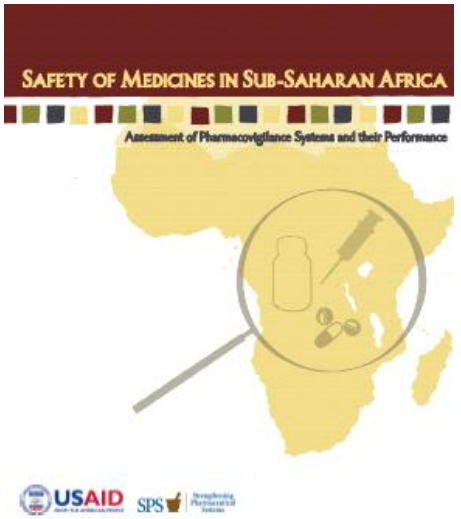
- We developed a framework for a decision analytic return on investment (ROI) model
- The model compares the four PV classification groups:
  - (1) no PV, (2) basic PV, (3) semi-functional PV, and (4) functional PV.
- The investment represents an itemized costing of resources needed to set up and maintain different levels of PV activity
- The returns represent the monetized reduction in ADR-related out-patient visits and hospitalizations, reduction in mortality, and reduction in ADR-related regimen switches
- ROI = Net Benefit/Incremental Cost

Framework


Increasing Investment
Space Equipment Personnel Materials
No PV
Basic PV
Semi-Functional PV
Functional PV
Decreasing Medicine-Related Problems Investment
OP visits Hospitalizations Regimen switches Deaths

Areas of Performance of PV Systems

- Policy, law, and regulation
- System, structure, and stakeholder coordination
- Signal generation and data management
- Risk assessment and evaluation
- Risk management and communication

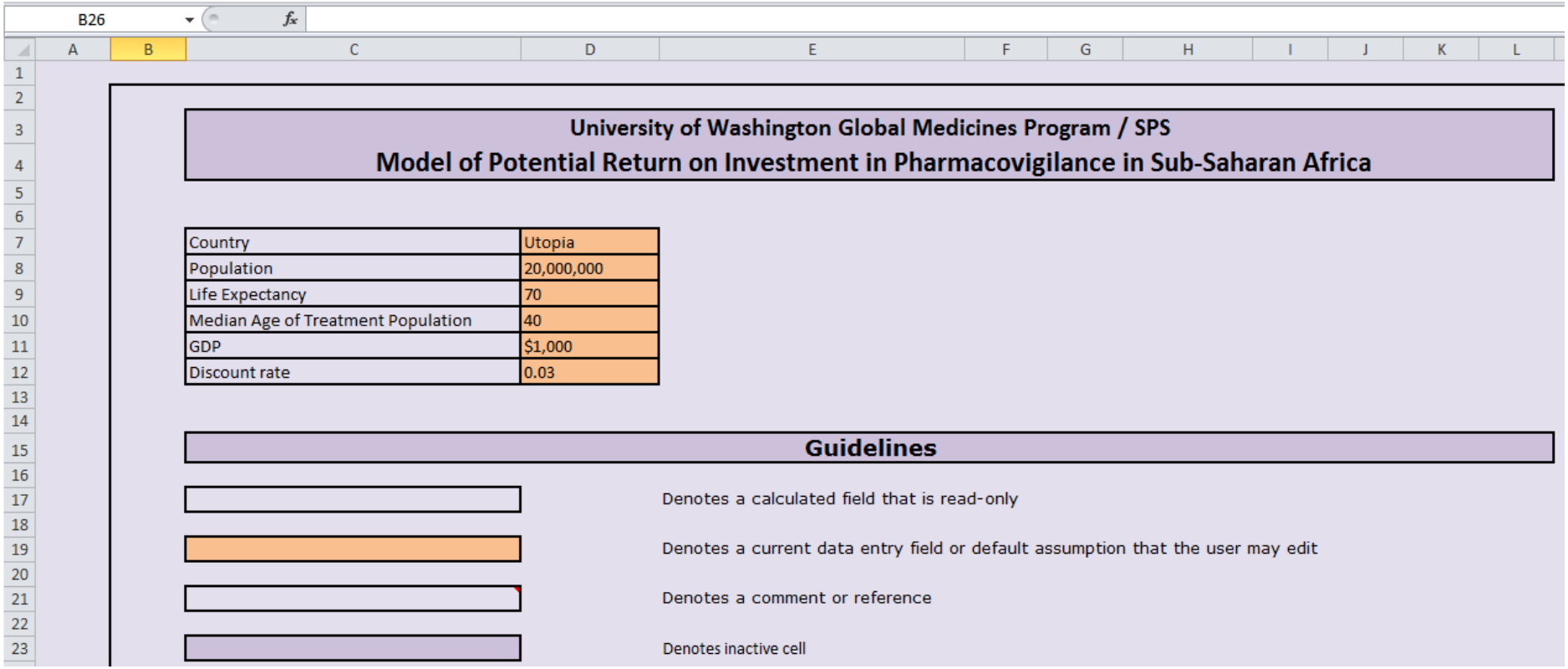


Classification

- Group 1—Countries have no capacity or only minimal capacity for PV
- Group 2—Countries have basic structure in place
- Group 3—Countries have the capacity to collect and evaluate safety data on the basis of legal and organizational structure
- Group 4—Countries have performing PV systems to detect, evaluate, and prevent medicine safety issues

Model introduction page

(Figures are placeholders for demo only)



University of Washington Global Medicines Program / SPS

Model of Potential Return on Investment in Pharmacovigilance in Sub-Saharan Africa

Country	Utopia
Population	20,000,000
Life Expectancy	70
Median Age of Treatment Population	40
GDP	$1,000
Discount rate	0.03

Guidelines

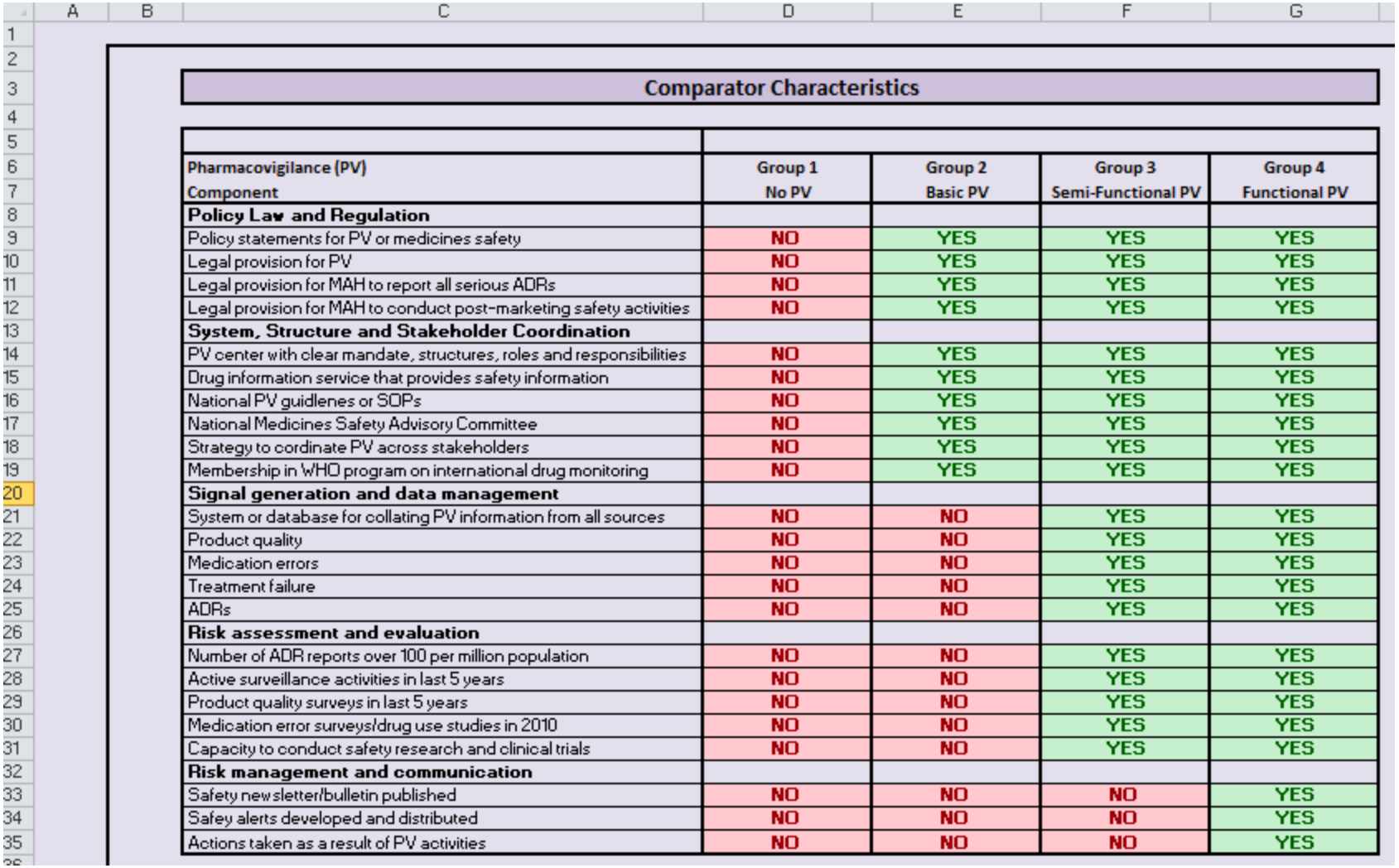
Denotes a calculated field that is read-only

Denotes a current data entry field or default assumption that the user may edit

Denotes a comment or reference

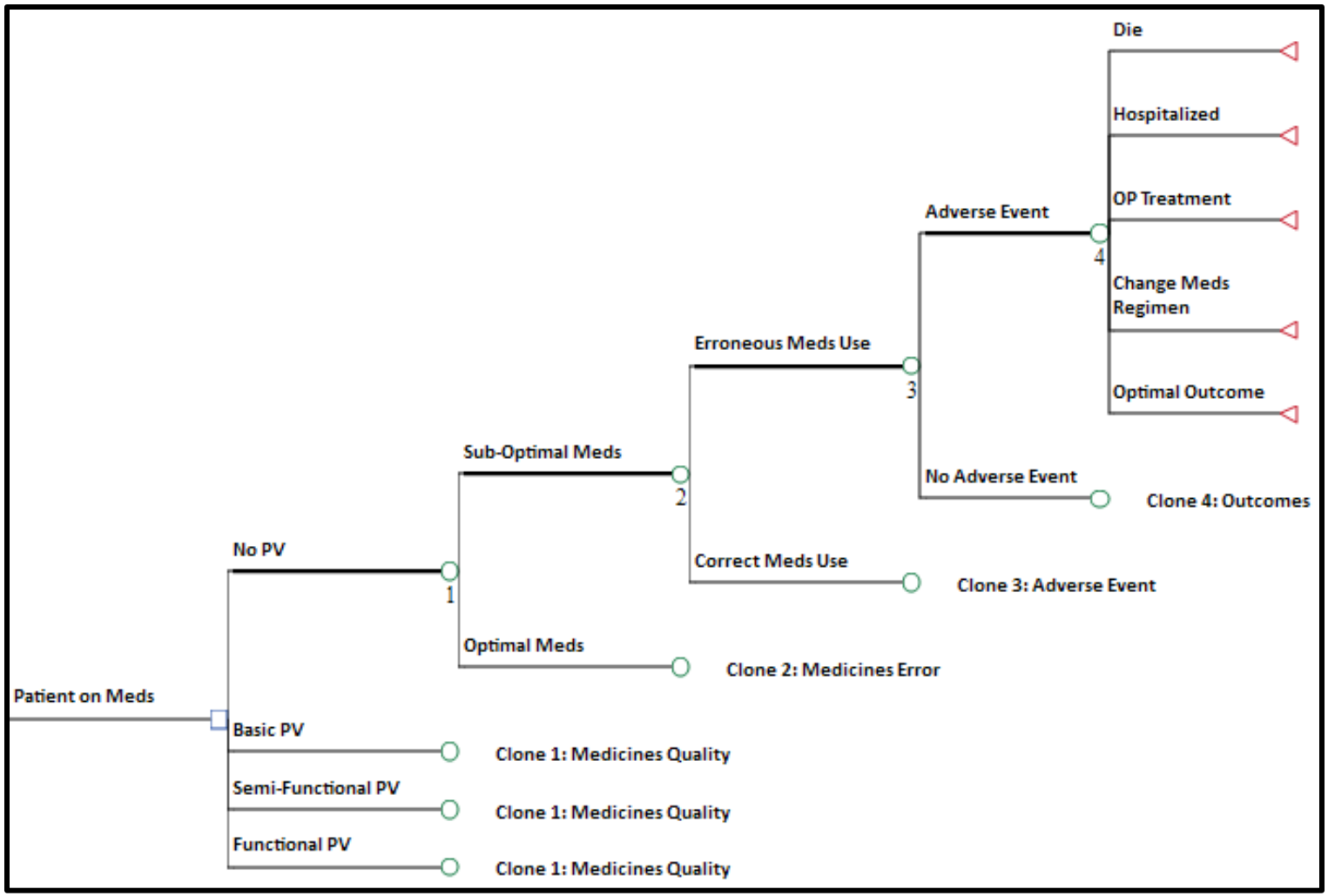
Denotes inactive cell

Comparators



Comparator Characteristics				
Pharmacovigilance (PV) Component	Group 1 No PV	Group 2 Basic PV	Group 3 Semi-Functional PV	Group 4 Functional PV
Policy Law and Regulation				
Policy statements for PV or medicines safety	NO	YES	YES	YES
Legal provision for PV	NO	YES	YES	YES
Legal provision for MAH to report all serious ADRs	NO	YES	YES	YES
Legal provision for MAH to conduct post-marketing safety activities	NO	YES	YES	YES
System, Structure and Stakeholder Coordination				
PV center with clear mandate, structures, roles and responsibilities	NO	YES	YES	YES
Drug information service that provides safety information	NO	YES	YES	YES
National PV guidlenes or SOPs	NO	YES	YES	YES
National Medicines Safety Advisory Committee	NO	YES	YES	YES
Strategy to cordinate PV across stakeholders	NO	YES	YES	YES
Membership in WHO program on international drug monitoring	NO	YES	YES	YES
Signal generation and data management				
System or database for collating PV information from all sources	NO	NO	YES	YES
Product quality	NO	NO	YES	YES
Medication errors	NO	NO	YES	YES
Treatment failure	NO	NO	YES	YES
ADRs	NO	NO	YES	YES
Risk assessment and evaluation				
Number of ADR reports over 100 per million population	NO	NO	YES	YES
Active surveillance activities in last 5 years	NO	NO	YES	YES
Product quality surveys in last 5 years	NO	NO	YES	YES
Medication error surveys/drug use studies in 2010	NO	NO	YES	YES
Capacity to conduct safety research and clinical trials	NO	NO	YES	YES
Risk management and communication				
Safety newsletter/bulletin published	NO	NO	NO	YES
Safey alerts developed and distributed	NO	NO	NO	YES
Actions taken as a result of PV activities	NO	NO	NO	YES

Decision Analytic Model Diagram



Probabilities

(Figures are placeholders for demo only)

PROBABILITIES

Percent reduction in events (No PV = baseline)	No PV	Basic PV	Semi-Functional PV	Functional PV
Sub-optimal medicines	Baseline	0.0%	0.0%	0.0%
Erroneous medication use	Baseline	0.0%	0.0%	0.0%
Adverse drug event	Baseline	0.0%	10.0%	40.0%
Death	Baseline	1.0%	10.0%	20.0%
Hospitalization	Baseline	5.0%	20.0%	40.0%
Out patient treatment	Baseline	10.0%	20.0%	30.0%
Regimen change	Baseline	10.0%	20.0%	30.0%

Probabilities	No PV	Basic PV	Semi-Functional PV	Functional PV
Medicines Quality				
Sub-optimal quality	30.0%	30.0%	30.0%	30.0%
Optimal quality	70.0%	70.0%	70.0%	70.0%
Medication Error				
Erroneous medication use	30.0%	30.0%	30.0%	30.0%
Correct medication use	70.0%	70.0%	70.0%	70.0%
Adverse Events				
Adverse event	30.0%	30.0%	27.0%	18.0%
No adverse event	70.0%	70.0%	73.0%	82.0%
Outcomes				
Adverse event				
Death	2.0%	2.0%	1.8%	1.6%
Hospitalization	5.0%	4.8%	4.0%	3.0%
Out patient treatment	10.0%	9.0%	8.0%	7.0%
Regimen change	10.0%	9.0%	8.0%	7.0%
Optimal treatment outcome	73.0%	75.3%	78.2%	81.4%
No adverse event				

Investment

(Figures are placeholders for demo only)

	RESOURCE NEEDS				UNIT COSTS				ANNUAL INVESTME		
	No PV Group 1	Basic PV Group 2	Semi-Functional PV Group 3	Functional PV Group 4	No PV Group 1	Basic PV Group 2	Semi-Functional PV Group 3	Functional PV Group 4	No PV Group 1	Basic PV Group 2	emi-Fun Gro
Fixed/Set Up Costs											
Equipment	0	1	1	1	$2,000	$2,000	$3,000	$3,500	$0	$2,000	$3
Office furniture (Sets)	0	1	1	1	$7,000	$7,000	$7,000	$10,000	$0	$7,000	$7
IT systems and equipment (Sets)	0	1	1	1	$50,000	$50,000	$50,000	$50,000	$0	$50,000	$5
Communication systems and equipment (Sets)	0	1	1	1	$20,000	$20,000	$20,000	$20,000	$0	$20,000	$2
Vehicles	0	2	4	6	$0	$50,000	$50,000	$50,000	$0	$100,000	$2
Books (Sets)	0	1	2	3	$0	$1	$1	$2	$0	$1	
Other 1	0	1	2	3	$0	$1	$1	$1	$0	$1	
Other 2	0	1	2	3	$0	$1	$1	$2	$0	$1	
Recurrent (Monthly) Costs											
Office space (Square meters)	0	100	200	300	$10	$10	$10	$15	$0	$12,000	$24
Personnel											
Doctors	0	1	2	3	$0	$1	$2	$3	$0	$12	$
Pharmacists	0	1	2	3	$0	$1	$2	$3	$0	$12	$
Nurses	0	1	4	6	$0	$1	$4	$6	$0	$12	$
Other health workers	0	1	4	6	$0	$1	$4	$6	$0	$12	$
Clinical pharmacologists	0	1	1	2	$0	$1	$1	$2	$0	$12	$
Epidemiologists	0	1	1	2	$0	$1	$1	$2	$0	$12	$
Other	0	1	1	1	$0	$1	$1	$1	$0	$12	$
Materials and supplies											
Utilities	0	1	2	3	$0	$1	$2	$3	$0	$12	$
Travel	0	1	2	3	$0	$1	$2	$3	$0	$12	$
Mass media	0	1	2	3	$0	$1	$2	$3	$0	$12	$
Meetings	0	1	2	3	$0	$1	$2	$3	$0	$12	$
Serial publications	0	1	2	3	$0	$1	$2	$3	$0	$12	$
Web hosting	0	1	1	2	$0	$1	$1	$2	$0	$12	$
Database subscriptions	0	1	1	1	$0	$1	$1	$1	$0	$12	$
Other 1	0	1	1	2	$0	$1	$1	$2	$0	$12	$
Other 2	0	1	2	2	$0	$1	$2	$2	$0	$12	$
									$0	$191,195	$30

Examples of Resources Required for Implementing PV at the National Level

Capital resources

- Equipment
- Office furniture
- IT equipment
- Vehicles
- Books

Recurrent (monthly) resources

- Office space (sq. meter)
- Personnel
  - *Physicians*
  - *Pharmacists*
  - *Nurses*
  - *Clinical pharmacologist*
  - *Epidemiologist*
  - *Driver*
  - *Support staff*
- Materials and supplies
  - *Utilities*
  - *Travel*
  - *Mass media*
  - *Meetings*
  - *Serial publications*
  - *Web hosting*
  - *Database subscriptions*

Return

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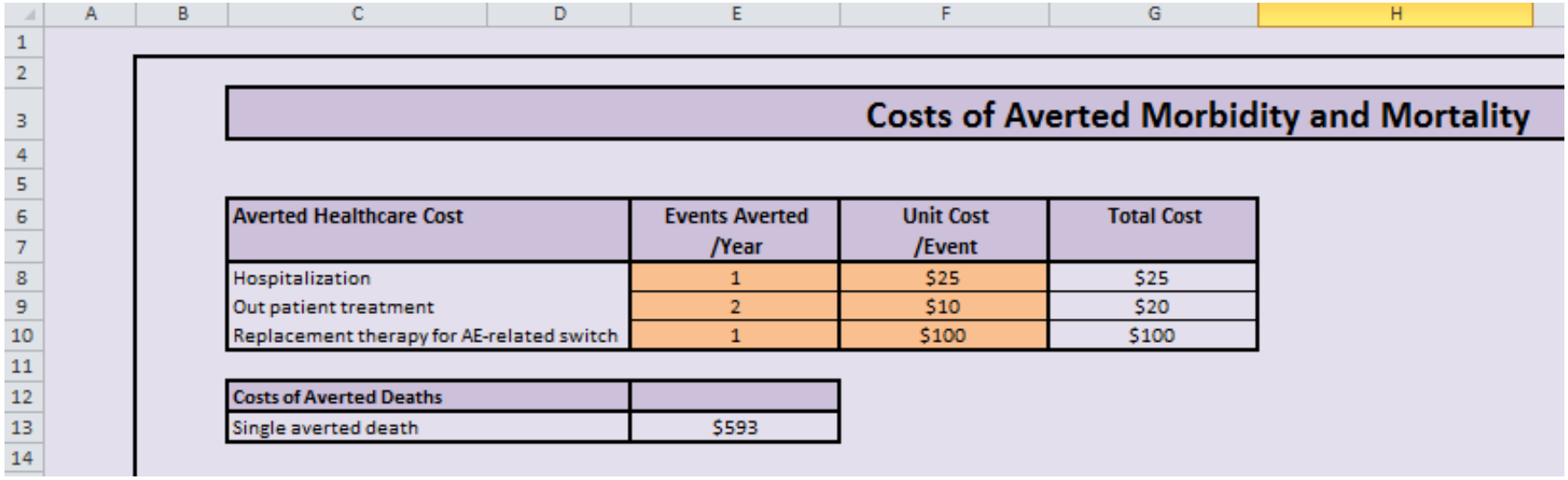

Costs of Averted Morbidity and Mortality

Averted Healthcare Cost	Events Averted /Year	Unit Cost /Event	Total Cost
Hospitalization	1	$25	$25
Out patient treatment	2	$10	$20
Replacement therapy for AE-related switch	1	$100	$100

Costs of Averted Deaths	
Single averted death	$593

Model Engine

(Figures are placeholders for demo only)

Group 1 (No PV)															
pSubOpMed	Description	pMedError	Description	pAdvEvent	Description	pOutcome	Description	Product	Mortality	Mort Product	Hospitalization	Hosp Product	OP visit	OP Product	Regimen Change
0.3	Sub-optimal meds	0.3	Erroneous	0.3	Adverse Event	0.0200	Die	0.0005	1.0000	0.0005	0.0000	0.0000	0.0000	0.0000	0.0000
0.3	Sub-optimal meds	0.3	Erroneous	0.3	Adverse Event	0.0500	Hospitalized	0.0014	0.0000	0.0000	1.0000	0.0014	0.0000	0.0000	0.0000
0.3	Sub-optimal meds	0.3	Erroneous	0.3	Adverse Event	0.1000	Out-patient Treatment	0.0027	0.0000	0.0000	0.0000	0.0000	1.0000	0.0027	0.0000
0.3	Sub-optimal meds	0.3	Erroneous	0.3	Adverse Event	0.1000	Regimen Change	0.0027	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000
0.3	Sub-optimal meds	0.3	Erroneous	0.3	Adverse Event	0.7300	Optimal Outcome	0.0197	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
0.3	Sub-optimal meds	0.3	Erroneous	0.7	No Adverse Event	0.0200	Die	0.0013	1.0000	0.0013	0.0000	0.0000	0.0000	0.0000	0.0000
0.3	Sub-optimal meds	0.3	Erroneous	0.7	No Adverse Event	0.0500	Hospitalized	0.0032	0.0000	0.0000	1.0000	0.0032	0.0000	0.0000	0.0000
0.3	Sub-optimal meds	0.3	Erroneous	0.7	No Adverse Event	0.1000	Out-patient Treatment	0.0063	0.0000	0.0000	0.0000	0.0000	1.0000	0.0063	0.0000
0.3	Sub-optimal meds	0.3	Erroneous	0.7	No Adverse Event	0.1000	Regimen Change	0.0063	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000
0.3	Sub-optimal meds	0.3	Erroneous	0.7	No Adverse Event	0.7300	Optimal Outcome	0.0460	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
0.3	Sub-optimal meds	0.7	Correct	0.3	Adverse Event	0.0200	Die	0.0013	1.0000	0.0013	0.0000	0.0000	0.0000	0.0000	0.0000
0.3	Sub-optimal meds	0.7	Correct	0.3	Adverse Event	0.0500	Hospitalized	0.0032	0.0000	0.0000	1.0000	0.0032	0.0000	0.0000	0.0000
0.3	Sub-optimal meds	0.7	Correct	0.3	Adverse Event	0.1000	Out-patient Treatment	0.0063	0.0000	0.0000	0.0000	0.0000	1.0000	0.0063	0.0000
0.3	Sub-optimal meds	0.7	Correct	0.3	Adverse Event	0.1000	Regimen Change	0.0063	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000
0.3	Sub-optimal meds	0.7	Correct	0.3	Adverse Event	0.7300	Optimal Outcome	0.0460	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
0.3	Sub-optimal meds	0.7	Correct	0.7	No Adverse Event	0.0200	Die	0.0029	1.0000	0.0029	0.0000	0.0000	0.0000	0.0000	0.0000
0.3	Sub-optimal meds	0.7	Correct	0.7	No Adverse Event	0.0500	Hospitalized	0.0074	0.0000	0.0000	1.0000	0.0074	0.0000	0.0000	0.0000
0.3	Sub-optimal meds	0.7	Correct	0.7	No Adverse Event	0.1000	Out-patient Treatment	0.0147	0.0000	0.0000	0.0000	0.0000	1.0000	0.0147	0.0000
0.3	Sub-optimal meds	0.7	Correct	0.7	No Adverse Event	0.1000	Regimen Change	0.0147	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000

Hypothetical Results

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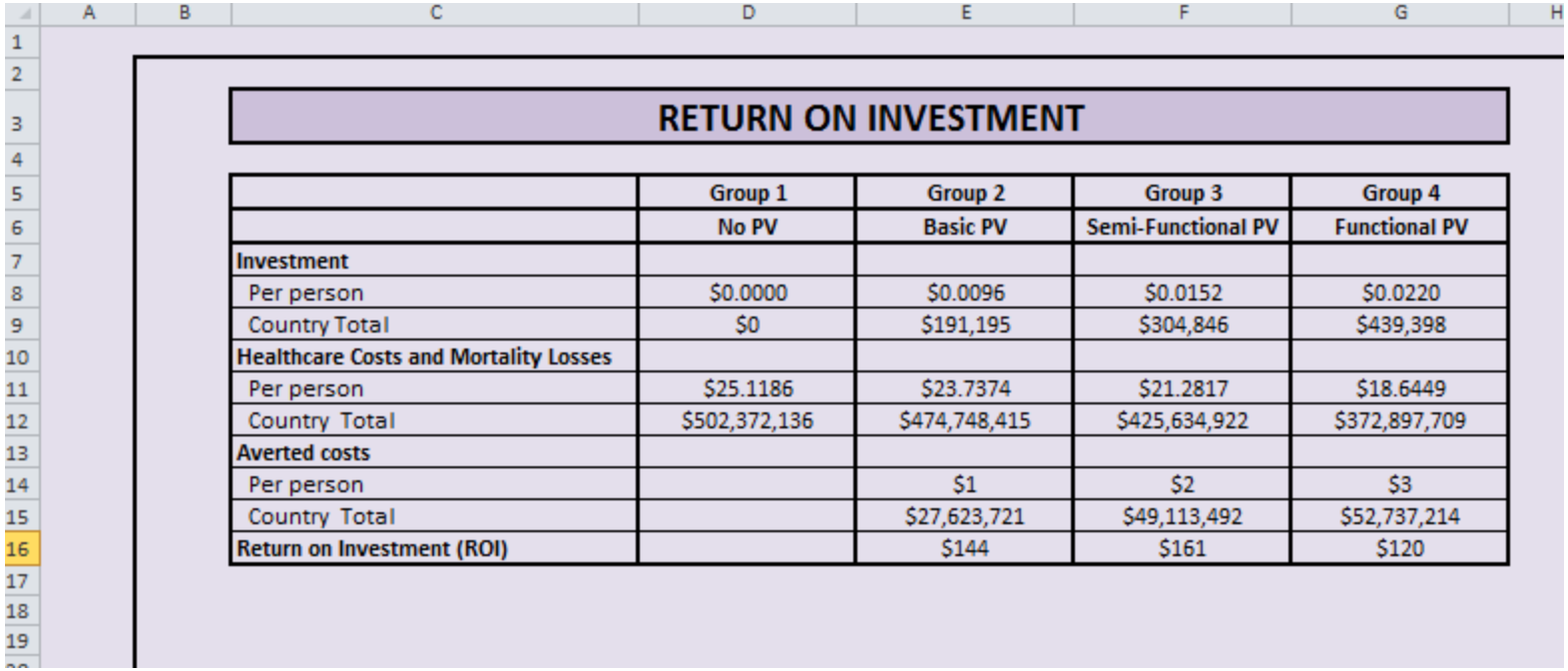
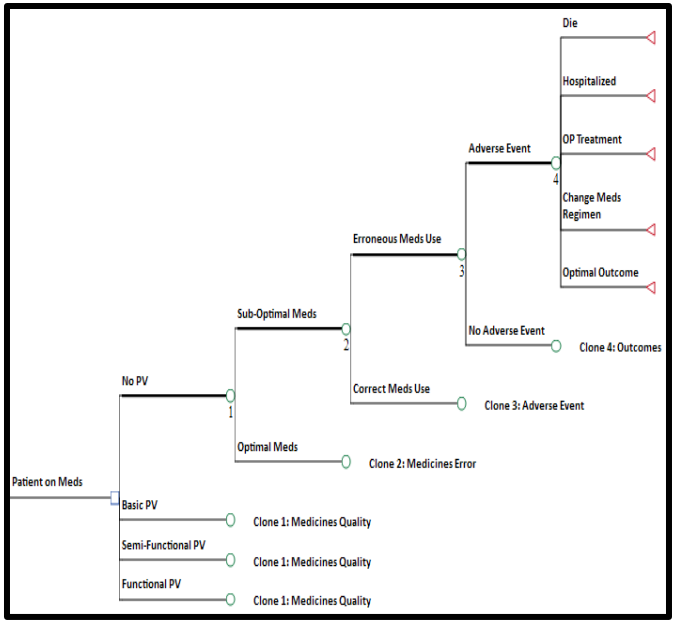


RETURN ON INVESTMENT				
	Group 1	Group 2	Group 3	Group 4
	No PV	Basic PV	Semi-Functional PV	Functional PV
Investment				
Per person	$0.0000	$0.0096	$0.0152	$0.0220
Country Total	$0	$191,195	$304,846	$439,398
Healthcare Costs and Mortality Losses				
Per person	$25.1186	$23.7374	$21.2817	$18.6449
Country Total	$502,372,136	$474,748,415	$425,634,922	$372,897,709
Averted costs				
Per person		$1	$2	$3
Country Total		$27,623,721	$49,113,492	$52,737,214
Return on Investment (ROI)		$144	$161	$120

Summary

- We developed a framework for a decision analytic return on investment (ROI) model that compares four PV classification groups
- The investment represents an itemized costing of resources needed to set up & maintain different levels of PV activity
- The returns represent reductions in ADR-related out-patient visits and hospitalizations, reduction in mortality, and reduction in ADR-related regimen switches
- More work is needed



The Cost-Effectiveness of Periodic Safety Update Reports for Biologicals in Europe

JC Bouvy[1,2], HC Ebbers[1], H Schellekens[3,4] and MA Koopmanschap[2]

We analyzed the cost-effectiveness of all Periodic Safety Update Reports (PSURs) submitted for biologicals in Europe from 1995 to 2009 by comparing two regulatory scenarios: full regulation (PSUR reporting) and limited regulation (no PSUR reporting, but all other parts of the pharmacovigilance framework remain in place). During this period, PSUR reporting resulted in the detection of 2 out of a total of 24 urgent safety issues for biologicals: (i) distant spread of botulinum toxin and (ii) edema/fluid collection associated with off-label use of dibotermin-alfa. We used Markov-chain life tables to calculate costs and health effects of PSURs. The incremental cost-effectiveness ratio (ICER) of full regulation (PSUR reporting) vs. limited regulation (no PSUR reporting) for the base-case scenario was €342,110 per quality-adjusted life year (QALY) gained. It is possible to assess the cost-effectiveness of regulatory requirements using the same methods as those used in assessing the cost-effectiveness of medical interventions.

Clin Pharmacol Ther. 2013 May;93(5):433-42.

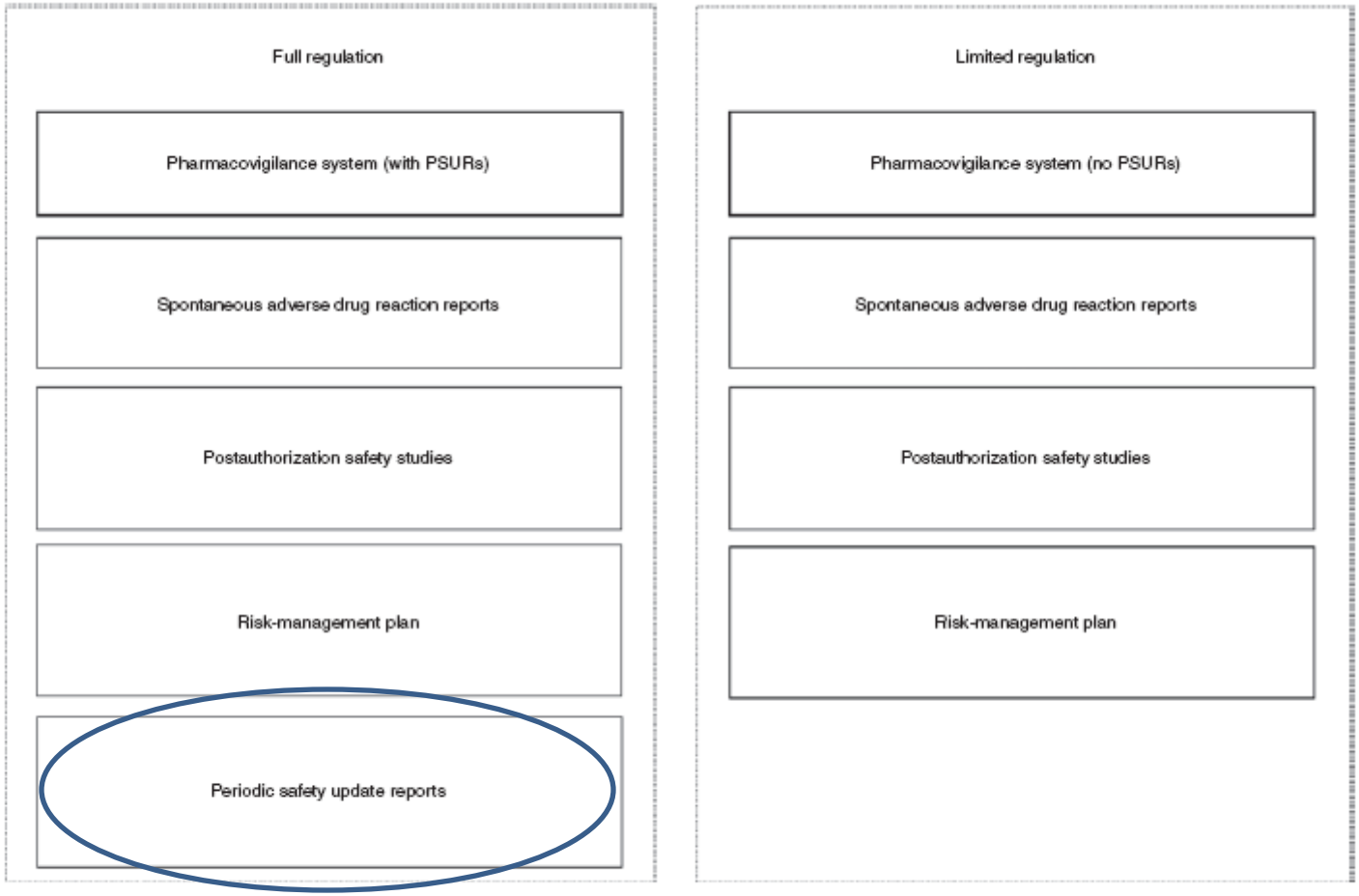


Figure 2 Two regulatory scenarios. PSUR, Periodic Safety Update Report.

The total estimated limited-regulation costs were €31,298,691 with QALYs of 434,566 (Table 1). The ICERs were calculated as follows:

$$\text{ICER} = \frac{\Sigma_{t=0}^{T} \text{costs full regulation} - \Sigma_{t=0}^{T} \text{costs limited regulation}}{\Sigma_{t=0}^{T} \text{QALYs full regulation} - \Sigma_{t=0}^{T} \text{QALYs limited regulation}} \quad (1)$$

The total incremental costs of full regulation vs. limited regulation were €13,450,264 and total incremental QALYs were 39. The ICER of full regulation vs. limited regulation for the base-case scenario (with assumed risk reduction of 25%) was €343,110 per QALY gained (not discounted; see Methods section). The total societal (direct and indirect) costs avoided by the full-regulation scenario were €1,807,104, but the additional total regulatory costs of full regulation were €15,257,368.

The discounting of costs and effects resulted in an ICER of €335,802 if calculated from 1995 onward vs. €366,524 if calculated from 2012 onward. When the European Medicines Agency (EMA) fees were used to estimate PSUR costs (1995–2009, corrected for inflation) the ICER was €1,192,362. When only

Available Metrics for PV

- Minimum Requirements for a Functional Pharmacovigilance System. The Global Fund and the WHO
- Indicator-Based PV Assessment Tool (IPAT)
- Proposed Set of Indicators for Monitoring and Evaluation of Pharmacovigilance Activities (ICIUM 2011 Presentation)
- Miscellaneous Others

pdf.usaid.gov/pdf_docs/PNADS167.pdf

Monitoring and Evaluation Framework Comprehensive HIV and AIDS Care, Management and Treatment Plan for South Africa: Public Health Program

Table 14: Pharmacovigilance	Frequency
• Percentage of spontaneous adverse events (ADE) reports	Annually
• Percentage of ART related ADE experienced at sentinel sites in children	Annually
• Percentage of ART related ADE experienced at sentinel sites in adults	Annually
• Number of patients on treatment with regimens that had to be switched due to serious ADE	Annually
• Percentage of patient discontinuing ART due to ADE	Annually
• Specific mortality rate attributable to specific drugs	Annually
• Specific mortality rate attributable to ART regimen (1a, 1b, 2)	Annually
• Specific morbidity rate attributable to ART regimen (all severe & mild cases)	Annually
• Regimen change rate	Annually
• Discontinuation of treatment rate	Annually
• Adherence rate to treatment	Annually
• Cause specific mortality rates (ART and TM)	Annually

www.hst.org.za/uploads/files/monitorevaluation.pdf

Key Inputs Needed to be Estimated

1. Monetary value of the investment,
2. Probability of different events including reductions in adverse events due to increased PV activity, and
3. Costs of different averted outcomes such as mortality, hospitalizations, and OP visits.

Next Steps Needed

- Data from systematic reviews of the literature, database analyses, and Delphi surveys with panels of experts
- Framework should be tested using real-world data for validity and assumptions
- ??Software-based user-friendly and interactive tool that is customizable for use at the national level

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Back-up Slide

Figure 33. PV systems' capacity in SSA countries