

# BONE TARGETING AGENTS IN PREVENTION OF SKELETAL RELATED EVENTS IN METASTATIC CANCERS OF SOLID TUMOURS : AN ECONOMIC EVALUATION

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5th International Conference on Public Health 2019 (ICOPH 2019)

“Promoting Global Health Equity towards a Sustainable Future”

10th – 12th July 2019 | Kuala Lumpur | Malaysia

# Introduction

Approximately

**70%**

patients with Stage IV  
cancer affected by  
bone metastases

**5** most common cancers  
that metastases to bone



## Skeletal related events (SRE)

Skeletal complications  
from bone metastases

- Spinal cord compression
- Pathological fracture
- Need for bone radiation and bone surgery
- Hypercalcaemia
- Bone pain

# what we already know

Bone targeting agents (**biphosphonates** and **denosumab**) has been used as **treatment** for bone metastases with SREs

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**NICE** : **biphosphonates** can be offered to patients with lung ca, advanced breast ca, metastatic ca with spinal cord compression

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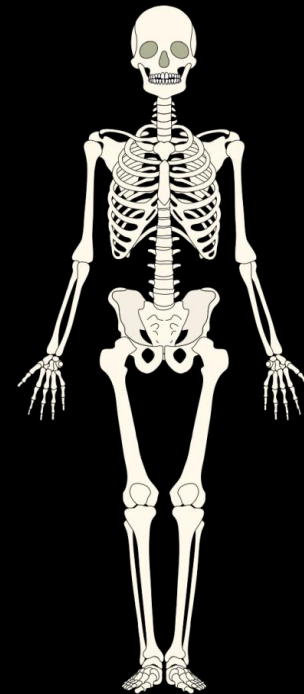
**MOH Drug Formulary (2018)** :

- **Ibandronic acid** and **Denosumab** was approved for treatment of **post-menopausal osteoporosis**
  - **Zoledronic acid** was approved for prevention of SREs only in patients with **multiple myeloma** involving multiple bone lesions
- 



# what we want to know

Are bone targeting agents  
**safe, effective & cost-effective** in  
**preventing** skeletal-related events  
among patients with metastatic  
cancers of solid tumours?



# From SR and meta-analysis

01

BTAs significantly delayed time-to-first SREs and reduced the risk of first & subsequent SREs in all cancers except NSCLC

02

Among all biphosphonates, Zoledronic acid has the highest effectiveness in delaying first SREs in breast and lung cancer

03

No significant difference in terms of SRE prevention between 12-weekly and 4-weekly IV Zoledronic Acid

04

Denosumab was superior than ZA in **delaying the time to first SRE** (HR=0.82, 95%CI 0.78, 0.87) and **reducing the risk of first SRE** (RR=0.83, 95%CI 0.77, 0.87)



# Objectives of E.E.



to assess the **cost-effectiveness of bone targeting agents** in prevention of skeletal-related events in metastatic cancer of solid tumours



to calculate the **incremental cost-effectiveness ratio (ICER)** of Zoledronic Acid and Denosumab with current best supportive care in prevention of SREs among patients with metastatic solid tumours



to estimate the **financial implications** when patients with bone metastases secondary to solid tumours transitioned from usual care (no prophylaxis) to bone targeting agent as SRE-prophylaxis

# Methodology & Model Structure



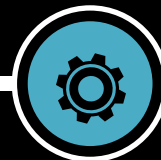
# Methodology



Literature-based  
Markov model



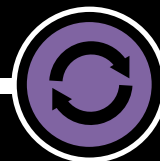
Population : primary solid  
tumour with bone mets



Seven health states in  
two disease conditions:  
stable & progressive



Perspective :  
Ministry of Health Malaysia



Transition cycle : 3-month  
Time horizon : lifetime



# Interventions

Usual Care /  
Best Supportive Care  
(no prophylaxis)

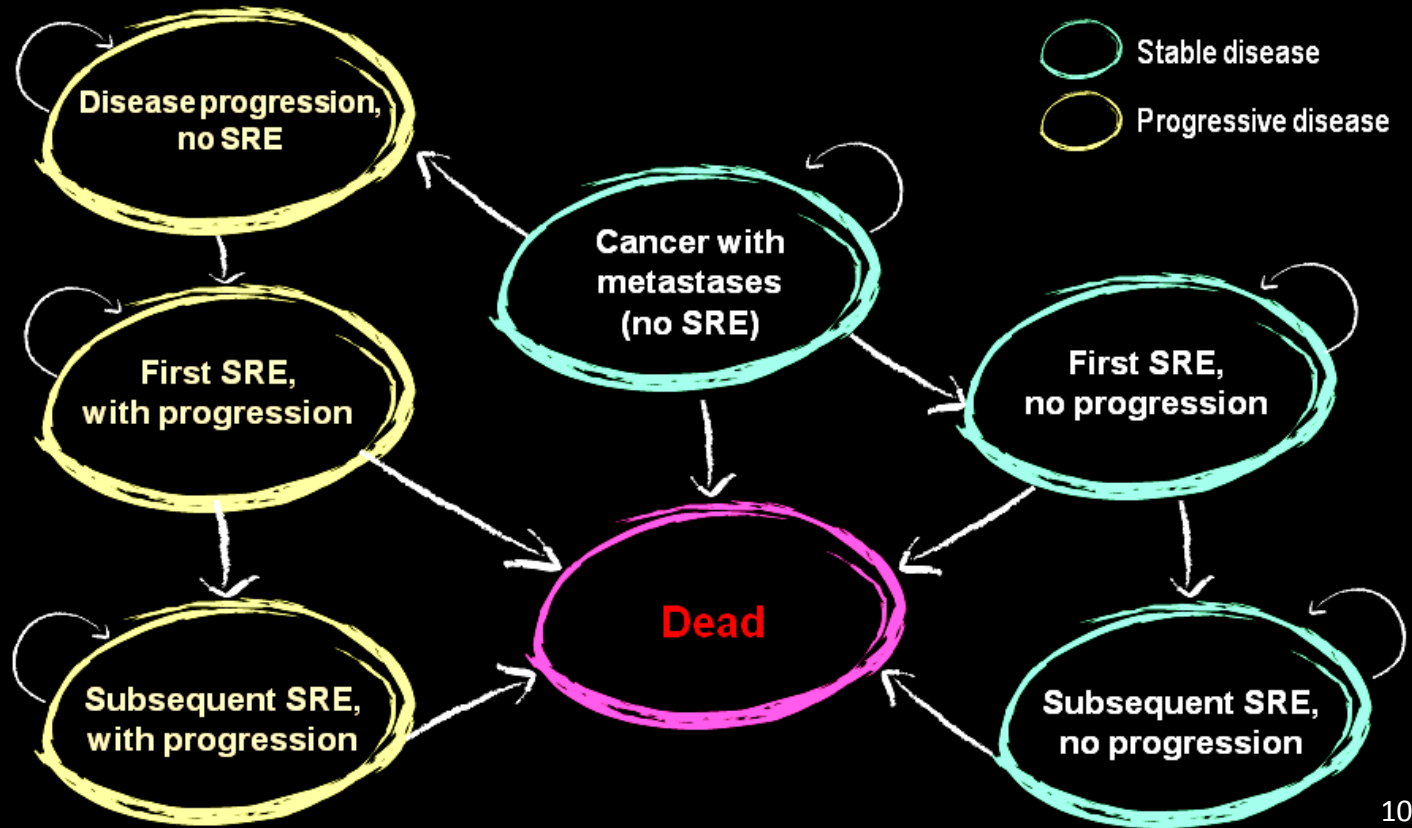
**VS**

SC Denosumab  
120mg, 4-weekly

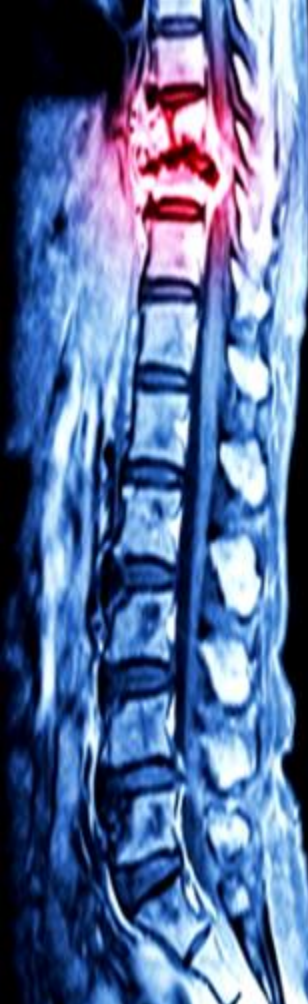
**VS**

IV Zoledronic Acid  
4mg, 12-weekly

# Model Structure



# Simulated Clinical Pathways

- 
- All patients entered the model after confirming presence of bone metastases (cancer with metastases, no SRE) and managed according to standard care (with or without BTA).
  - In the cohorts of patients receiving bone targeting agent, it was given as prevention and treatment of SRE. Tablet calcium supplementation was also given.
  - Patients would either remain in stable metastatic disease or having disease progression before experiencing the first episode of SRE and/or subsequent SRE.
  - The health outcome and economic impact related to drug-induced severe adverse events were not included in the model due to its rarity (<1%).<sup>3</sup>
  - In patients receiving ZA, renal profile was performed prior to each treatment in view of possible complication of renal toxicity.
  - All patients received palliative care. Follow-up in oncology specialists clinic was 3-monthly.
  - Death was only possible due to metastatic cancer and not other causes.

# ASSumptions

- The same BTA is given as prevention and treatment of SRE in the cohort (no switch of treatment once patient has SRE).
- The quality of life benefits (utility) of all bone targeting agents were assumed to be similar.
- Utility values in disease progression states are lower than in stable metastases.
- SRE did not change the mortality rate.
- No more than one SRE could occur within each cycle (maximum SRE that may occur in a year is 4 times)
- The type of subsequent SRE was not dependent on the first SRE.
- Stable and progressive metastases states incur the same cost.
- Average cost of SRE-related treatments is the same (regardless first or subsequent SRE.)



# Clinical Parameters

Parameter	Usual care	ZA	Denosumab	Reference
Median time to first SRE in months (SD)	11 (0.8)	17.1 (1.1)	20.7 (1.6)	1, 2, 4, 5
Skeletal morbidity rate	3.05	1.71	1.20	1, 3
Risk of hypocalcaemia	-	6%	13%	4
Increased risk of having first SRE and subsequent SRE due to progression	2.14	2.14	2.14	1
<b><i>Transitional probabilities</i></b>				
From stable metastases to disease progression	0.221	0.221	0.221	1
First SRE among patients without progression	0.245	0.115	0.096	1, 2
Subsequent SRE among patients without progression	0.355	0.167	0.137	1, 2
From any health states to death	0.271	0.271	0.271	1



# Utility Inputs

- Obtained from a time trade-off study by Dranitsaris and Hsu (1999), the only published estimate of utilities for bone targeting agents and SRE for patients with advanced breast cancer receiving Pamidronate (also used by other EE).
- Compared with utility value from **ACTION study** on health-related QoL among cancer survivors in Southeast Asia including Malaysia.

Health states	Base-case value	95%CI	Reference
No SRE, receive BTA	0.64	0.53 - 0.76	3, 6, 7
No SRE, receive usual care	0.56	0.45 - 0.68	3, 6, 7
SRE, receive BTA	0.46	0.37 - 0.54	3, 6, 7
SRE, receive usual care	0.31	0.23 - 0.38	3, 6, 7
Stage IV with progressive disease	0.39	0.33 - 0.45	9
Stage IV at diagnosis	0.65	SD = 0.24	8

# Cost & Resource Data

Cost description	Base case estimate	Reference / Source
Tablet calcium carbonate 500mg (per month)	RM 180.00	MOH Consumer Price Guide <sup>10</sup> (2018)
Renal profile (per test)	RM 5.00 (third class charge)	MOH Investigation Charges <sup>11</sup> (2018)
Total cost IV Zoledronic acid 4mg (per dose)	RM 472.00	National Cancer Institute, Lee WC et al (2016) <sup>12</sup>
Total cost SC Denosumab 120mg (per dose)	RM 1,239.14	National Cancer Institute, Lee WC et al (2016) <sup>12</sup>
Stable / Progressive Stage IV disease (per year)	RM 21,830.77	MalaysianDRG (severity illness 2), Dranitsaris G et al (2011) <sup>13</sup> , Zainal R et al (2014) <sup>14</sup>
Average cost of first SRE related treatment	RM 5,132.04	MalaysianDRG (severity illness 2), Hwa YS et al (2011) <sup>15</sup>



# Sensitivity Analysis

- **Deterministic** : 1-way sensitivity analysis
- **Input parameters for SA:**
  - annual discounting rate (0-5%)
  - transition probability of subsequent SRE in BTA group (per cycle)
  - utility values for usual care and BTA groups
  - cost of first SRE-related managements
  - cost of stable / progressive Stage IV disease
- **Varying input parameters** :
  - specified range / standard deviation
  - UL & LL of 95% confidence interval

# Results





# Base-Case Results

Strategies	Total cost per patient	Total QALY per patient	Increment. cost	Increment. QALY	ICER (compared to usual care)
Usual care	RM 32,544.36	1.6235	-	-	-
ZA	RM 37,314.89	2.5836	RM 4,770.53	0.9601	RM 4,968.87
Denosumab	RM 57,231.09	2.7582	RM 24,686.73	1.1348	RM 21,754.66

*\*over the lifetime of the patients cohort (approximately 7 years)*

1 GDP per capita per QALY gained for Malaysia  
(USD 10,500 = MYR 42,688)

**The lower the ICER,  
the better**

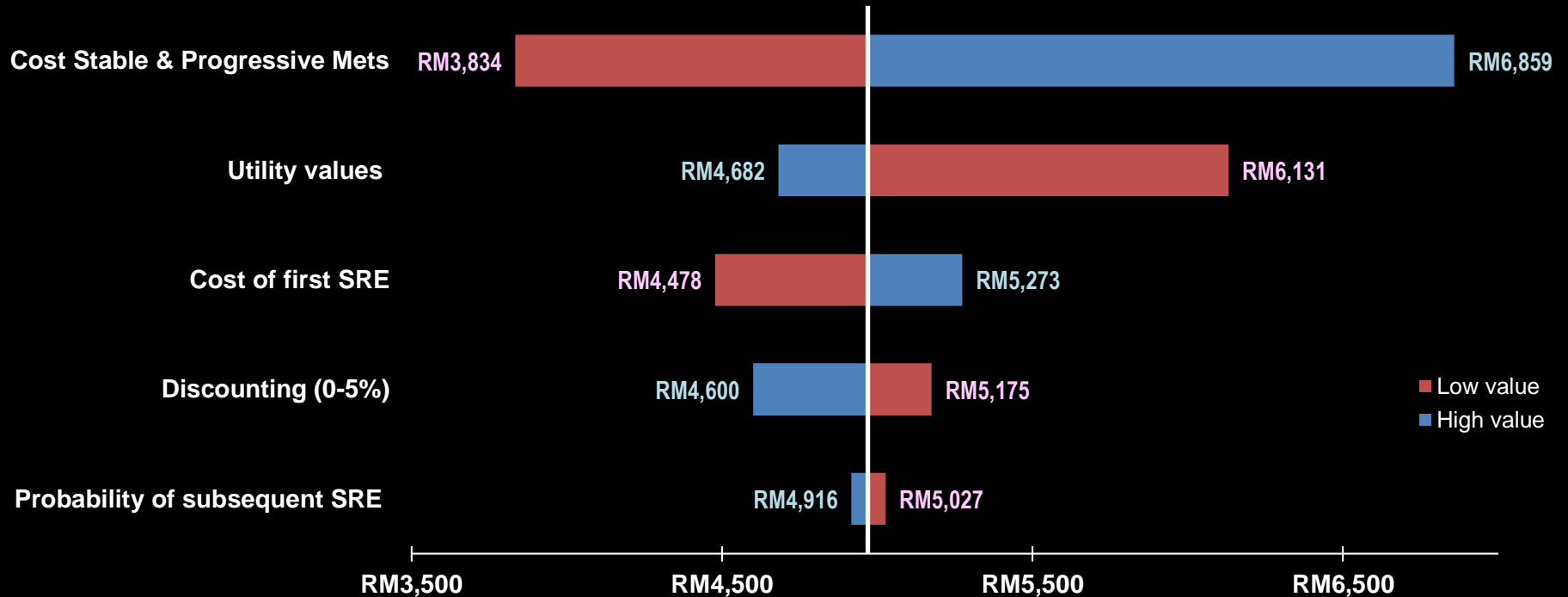


# Sensitivity Analysis Results

Parameters	95% CI limit / Range / SD	ICER of lower value input	ICER of higher value input
Annual discounting rate	0 – 5%	RM 5,174.74	RM 4,600.12
Transition probability of subsequent SRE in patients without progression (zoledronic acid group)	SD = 0.019	RM 5,026.56	RM 4,915.89
Utility values for usual care and zoledronic acid groups	Refer to <b>Table 2</b>	RM 6,131.09	RM 4,681.52
Cost of first SRE-related managements	RM 1,845 - RM 8,745	RM 4,478.36	RM 5,273.47
Total cost of stable and progressive Stage IV disease	RM 17,710 - RM 31,552	<b>RM 3,834.01</b>	<b>RM 6,858.80</b>

# Tornado Diagram :

## 1-way sensitivity analysis



\* Central axis = base-case ICER (RM 4,968.87)

# Financial Implications

Transition from usual care (no BTA) to Zoledronic Acid as SRE-prophylaxis in primary solid tumor patients with bone metastases

70% patients with Stage IV breast or prostate ca affected by metastatic disease to the bone <sup>16,17</sup>

01

\*Total number of Stage IV patients in 13 solid tumour cancers  
**14,671**

02

\*Average number of Stage IV patients / year

**2,934**

03

Approximate Stage IV patients with bone mets  
(70% x 2,934)

04

**2,054**



# Financial Implications

12-weekly Zoledronic Acid

**RM 4,289.82**

per patient per year

**RM 8.8 million**

Total financial implication  
per year

4-weekly Zoledronic Acid

**RM 9,081.90**

per patient per year

**RM 18.7 million**

Total financial implication  
per year



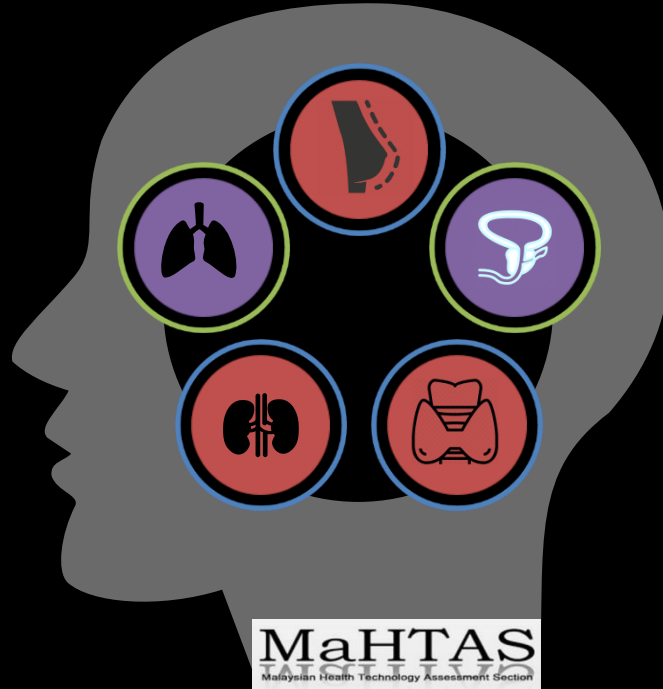
Cost savings = 53%

# Scenario Analysis

5

most common primary  
cancers that metastases  
to the bone

**N = 1,084**



## Strategy

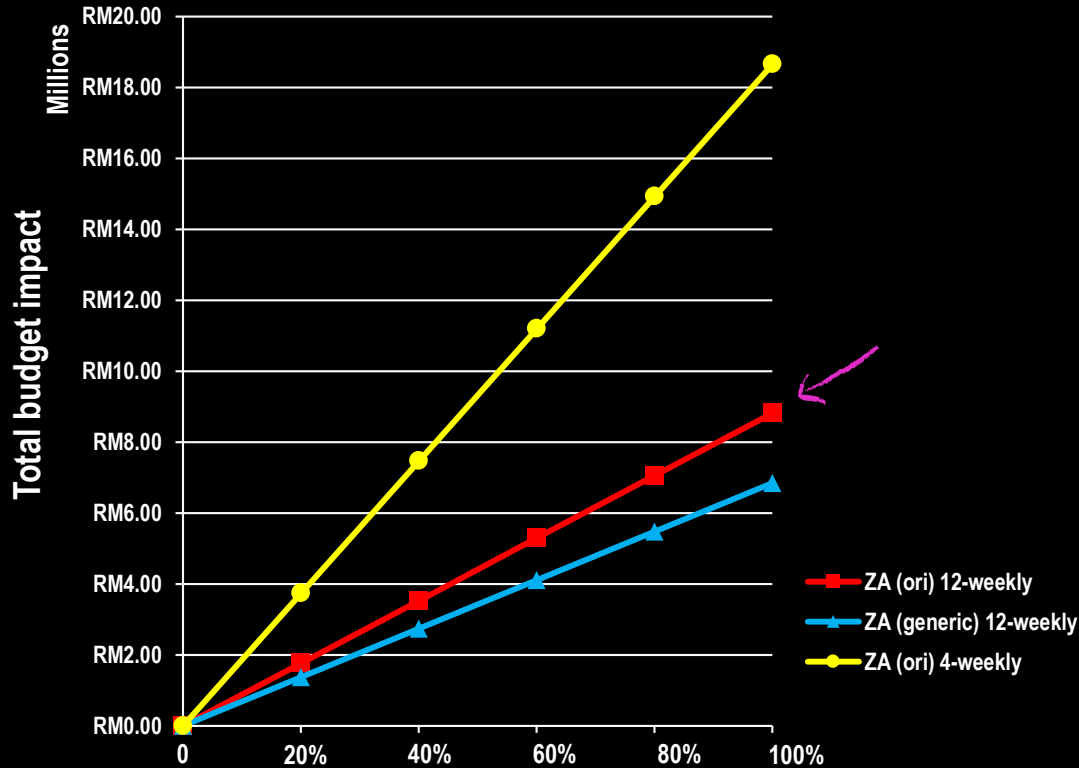
12-weekly ZA (ori) SRE-  
prophylaxis to these patients  
first before widening the  
coverage

**RM 4.6 million**

Total financial implication  
per year



# Total budget impact following transition from usual care to different strategies of SRE-prophylaxis with zoledronic acid



Proportion of patients switching from usual care to prophylactic ZA

**12-weekly**  
Vs  
**4-weekly**

**Total cost-savings**  
RM 2.0 million to RM 9.8 million for every 20% patient transition

**Generic**  
Vs  
**Originator**

**Total cost-savings**  
RM 394,356 to RM 2.0 million for every 20% patient transition



# Benefit Cost Ratio

Compared with usual care, ZA 12-weekly is able to prevent SRE by 32%.

## ORIGINATOR

For every RM 1.00 spent,  
the cost-saving from  
prevented SRE is  
**RM 1.50**

## GENERIC

For every RM 1.00 spent,  
the cost-saving from  
prevented SRE is  
**RM 2.00**



# Conclusion



The use of bone targeting agents in preventing skeletal-related events among Stage IV solid tumour patients with bone metastases is a **cost-effective strategy**.



The most cost-effective option was 12-weekly intravenous Zoledronic Acid, yielding an ICER of **RM 4,968.87 per QALY gained**



The estimated total financial implications for this strategy with 100% potential patients coverage (n=2,054) was **RM 8.8 million per year**.

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Thank you

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