

Original Research

Evaluation of angiotensin II receptor blockers for drug formulary using objective scoring analytical tool

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ABSTRACT*

Drug selection methods with scores have been developed and used worldwide for formulary purposes. These tools focus on the way in which the products are differentiated from each other within the same therapeutic class. Scoring Analytical Tool (SAT) is designed based on the same principle with score and is able to assist formulary committee members in evaluating drugs either to add or delete in a more structured, consistent and reproducible manner.

Objective: To develop an objective SAT to facilitate evaluation of drug selection for formulary listing purposes.

Methods: A cross-sectional survey was carried out. The proposed SAT was developed to evaluate the drugs according to pre-set criteria and sub-criteria that were matched to the diseases concerned and scores were then assigned based on their relative importance. The main criteria under consideration were safety, quality, cost and efficacy. All these were converted to questionnaires format. Data and information were collected through self-administered questionnaires that were distributed to medical doctors and specialists from the established public hospitals. A convenient sample of 167 doctors (specialists and non-specialists) were taken from various disciplines in the outpatient clinics such as Medical, Nephrology and Cardiology units who prescribed ARBs hypertensive drugs to patients. They were given a duration of 4 weeks to answer the questionnaires at their convenience. One way ANOVA, Kruskal Wallis and post hoc comparison tests were carried out at alpha level 0.05.

Results: Statistical analysis showed that the descending order of ARBs preference was Telmisartan or Irbesartan or Losartan, Valsartan or Candesartan, Olmesartan and lastly Eprosartan. The most cost saving ARBs for hypertension in public hospitals was Irbesartan.

Conclusion: SAT is a tool which can be used to reduce the number of drugs and retained the most therapeutically appropriate drugs in the formulary, to determine most cost saving drugs and has the potential to complement the conventional method of drug selection as it is effective in aiding decision making process through the pre-established criteria

and increasing scientific ground of decisions and transparency.

Keywords: Angiotensin Receptor Antagonists. Cost Savings. Formularies, Hospital. Malaysia.

EVALUACIÓN DE LOS ANTAGONISTAS DE RECEPTORES DE ANGIOTENSINA II PARA LOS FORMULARIOS UTILIZANDO EL INSTRUMENTO DE SCORING ANALYTICAL TOOL

RESUMEN

Se han desarrollado y utilizado alrededor del mundo métodos de selección de medicamentos para inclusión en formularios. Estos instrumentos se basan en el modo en que los productos se diferencian entre sí dentro del mismo grupo terapéutico. El Scoring Analytical Tool (SAT) se diseñó basado en el mismo principio mediante puntos y puede ayudar a los miembros del comité de formulario a evaluar medicamentos o a añadir o eliminar de un modo más estructurado e reproducible.

Objetivo: Desarrollar un SAT objetivo para facilitar la evaluación de la selección de medicamentos para creación de listas de formulario.

Métodos: Se realizó un estudio transversal. Se desarrolló un STA propuesto para evaluar medicamentos de acuerdo a criterios y sub-criterios pre-establecidos que se emparejaron a las enfermedades en cuestión y a los que se dio una puntuación en base a su importancia. Los criterios principales considerados fueron seguridad, calidad, coste y eficacia. Todos estos fueron convertidos en formato cuestionario. La información fue recogida a través de cuestionarios auto-administrados que se distribuyeron a médicos y especialistas de hospitales públicos. Se creó una muestra de conveniencia de 167 médicos (especialistas y no especialistas) extraídos de varias disciplinas en clínicas ambulatorias tales como medicina, nefrología y cardiología, que prescribían antihipertensivos ARAII a pacientes. Se les dio un plazo de 4 semanas para responder la encuesta. Se realizaron testes ANOVA de una vuelta, Kruskal Wallis y comparaciones *post hoc* con un nivel alfa de 0.05.

Resultados: Los análisis estadísticos demostraron que el orden descendente de preferencia de ARAII era Telmisartan o Irbesartan o Losartan, Valsartan o Candesartan, Olmesartan y finalmente Eprosartan.

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El ARAII más ahorrador para hipertensión en hospitales públicos era el Irbersartan.

Conclusión: El SAT es un instrumento que puede usarse para reducir el número de medicamentos y mantener en el formulario los medicamentos terapéuticamente más apropiados, determinar los medicamentos más ahorradores, y tiene el potencial de complementar los métodos convencionales de selección de medicamentos, ya que añade al proceso de toma de decisiones unos criterios pre-establecidos y aumenta la base científica y la transparencia de las decisiones

Palabras clave: Antagonistas de Receptores de Angiotensina. Ahorro de Costo. Formularios, Hospital. Malasia.

INTRODUCTION

A drug formulary is a manual containing clinically oriented summaries of pharmacological information of selected drugs, administrative and regulatory information pertaining to the prescribing and dispensing of drugs.¹ Drug formulary is developed mainly to promote rational prescribing and to limit cost.^{2,3} However, it should be noted here that rational prescribing might even lead to increased drug costs. This is especially true for such cases which are inclusive of those drugs which might be optimum or potential choice for certain patients to control their diseases.^{2,3} Evidence that the introduction of formulary improves the quality of prescribing is limited but few number of cases do show cost savings.²

Development of a drug formulary is a continuous and ongoing process due to constant changes in information about drugs and pharmacological practices. It is an important process that also includes updating and monitoring but it is time consuming. Over recent years many tools have been developed and nowadays, there are many decision making tools available which can help to speed up the processes of evaluation and selection of drug in the formulary such as Comparative Utilisation of Resources Evaluation Model (CURE Model)⁴, System of Objectified Judgment Analysis (SOJA)⁵, and Pharmaceutical Product Drug Differentiation Evaluation Model (PPDEM).⁶ These tools minimise subjective factors such as emotional factors, commercial influence or financial interest in seeing a drug included or be excluded as much as possible and transparent especially on which criteria and weighting decisions are based on. This tool also enables drugs to be assessed in a more consistent and reproducible manner.

SAT is a combination of concepts from both SOJA⁵ and CURE⁴ methods. SAT that is being developed is not exclusive to a small group of professionals but rather to pre-qualified professionals of "sufficient experience." SAT aims to make available to more medical practitioners' of sufficient experience. Other differences of SAT includes the selection of drugs based on cost saving which is not merely on cost comparisons but measures from the ratio of drug cost to the Quality Score. This ratio covers drug

cost as well as all the quality aspects of drugs. In addition, the outcome of the results in each selected criteria was subjected to statistical analysis. It is obvious from the outcome of the results what the decisions are based on.

The group of drugs to be focused on for the development of the scoring tool for evaluation or selection of drugs is Angiotensin II Receptor Blockers (ARBs) hypertensive drugs. The seven ARBs approved by FDA for hypertension were Candesartan, Eprosartan, Irbersartan, Losartan, Olmesartan, Telmisartan and Valsartan). ARBs drugs were chosen for this study because the utilisation rate of ARBs is expected to increase with these evidences supporting beneficial effects that extend beyond blood pressure reduction alone. ARBs are expensive drugs and decision-makers at all levels (national, regional, hospital, primary care) faced with difficult choices about which ARBs drugs to make available to their patients especially those new ARBs drugs which offer marginal improvement over existing therapies. Furthermore, there is no need to include all members of a particular drug class in a drug formulary especially those new drugs which offer only marginal improvements over existing therapies but at substantially increased costs

This paper will discuss and highlight to certain extent in detail the development of the method leading to the application of the evaluation of ARBs for drug formulary using an objective SAT as well as reporting findings which exhibit drug decision making especially in facilitating rational drug selection.

METHODS

The formulary decision criteria for these ARBs drugs were identified based on evidence-based studies and literature review and with reference to both CURE Model⁴ and SOJA⁵ and these formed the basis for the development of a written survey scoring tool or questionnaire. The sources of reference were mainly the Micromedex Healthcare Series drug evaluation database, CPG on hypertension (2008), free Pub Med services on the internet, journals, Medscape Resource Centre, drug information handbooks and package insert.

A questionnaire-based tool SAT was developed to evaluate ARBs drugs objectively according to pre-set criteria and relative weightage. The key relevant criteria identified were quality and cost criteria as these criteria were able to contain drug costs and to retain the most therapeutically appropriate drugs. The quality criteria consisted of three sections i.e. a) general drug information b) efficacy of the drugs c) safety of the drugs. The cost criteria involved only the acquisition cost of the drugs. This was based on the findings by Conlin and colleague that there was no significant difference in blood lowering efficacy between any of the ARBs when used as monotherapy.⁷ As such, the economic evaluation or cost analyses was justified to be reduced to a comparison of drug acquisition cost only as there was no significance in the effect of lowering blood

pressure among the ARBs. A weighting score was assigned to each criteria and sub-criteria according to its importance in the evaluation process. The more important criteria were given a higher score. Finally, individual scores for each drug being assessed were assigned. The total score allocated for both quality and cost scores criteria were 1000 points. The percentage of total score allocated for quality and cost criteria were 70% and 30% respectively. The breakdown of weightage scores for quality and cost criteria is shown in Table 1. The weighting score assigned to quality and cost criteria were arbitrary and CURE Model⁴ and SOJA⁵ were used as a reference as there was no guideline to prioritise the importance of drug criteria. The questionnaire-based scoring tool was subjected to pilot testing. Based on statistical analysis and their comments on the allocation of the scores through justification (written or verbally), the final scoring system was developed and subsequently, refinements were made to the scoring tool.

This step involves the conduct of the cross-sectional survey on a group of specialists and non-specialists. The survey was conducted in six established government hospitals: Serdang Hospital (HSDG), Selayang Hospital (HSLY), Tengku Ampuan Rahimah Hospital (HTAR), Kuala Lumpur Hospital (HKL), National Heart Institute (IJN) and University Malaya Medical Centre (UMMC). These few established hospital were selected in an attempt to reflect or represent the population of secondary, tertiary, specialise and university teaching hospitals in the country. This cross-sectional survey was conducted between February 2009 and April 2009. The study was approved by the Ministry of Health Ethical Committee prior to the execution of the study.

The target population was the specialists and non-specialist in the various disciplines in the outpatient clinics in government hospitals such as Medical, Nephrology and Cardiology units who have been prescribing the Angiotensin II Receptor Blockers (ARBs) hypertensive drugs to patients. The study excluded housemen or trainees and medical students.

The total number of specialists and non-specialists at outpatient clinics in the six established government hospitals were 178. The sample size for each hospital was determined from the Raosoft sample size calculator (which was available online <http://www.raosoft.com/samplesize.html>) by keying the requested parameters i.e. confidence level of 95%, confidence interval of 5% and $p < 0.05$ together with the total number of specialists and non-specialists for each hospital.

Before the questionnaires were distributed to the Head of Department (HOD), specialists and non-specialists, a briefing on the objectives, the importance of the selection criteria and the allocation of the indicative scores were explained to them (Table 1). The specialists were encouraged to include their comments on the allocation of the scores, to recommend a new selection criteria (if any) or to change the indicative scores to their justification.

The SPSS version 14 was used to analyse the data collected. Kolmogorov-Smirnov test was employed for analysing the distribution of data and Levene F test was used for examining the homogeneity of variances. Comparison between ARBs on each type of scores and cost analysis using Mann Whitney U test, independent t-test, Kruskal Wallis or one-way ANOVA as appropriate were conducted. Tukey's test was also used for the results of parametric tests that exhibited significant differences as well as to determine which pair of ARBs showed significant differences. A $p\text{-value} \leq 0.05$ was considered statistically significant.

RESULTS

Responses to the survey questionnaire were obtained from 69 respondents in total (out of 167 participants), representing an overall response rate of 41.3%. The 69 respondents comprised 41 specialists (59.4%) and 28 non-specialists (40.6%), respectively. The breakdown of the specialists was 6 (14.6%) nephrologists, 10 (24.4%) cardiologists and 25 (61.0%) medical specialists.

The differences between the average score for each

Table 1: Weighting score assigned to each sub-criteria

Type of Score	Criteria	Question	Sub-criteria	Assigned score (Max points)
Drug Information Score	General Drug Information	1	Number of double blind comparative studies	30
		2	Year of FDA approval for hypertension	30
		3	FDA approved indications	80
		4	Dosage strengths available	30
		5	Type of fixed combinations	30
Efficacy Score	Efficacy	6	Antihypertensive efficacy	200
		7	Trough to peak ratio	50
		8	Bioavailability	50
Safety Score	Safety	9	Drug interactions	50
		10	Adverse effect	50
		11	Renal effect	50
		12	Cardiovascular effect	50
Cost Score	Cost	13	Drug Acquisition Cost	300
Quality Score	Drug Information, Efficacy and Safety	1 to 12	Sub-criteria from Question 1 to Question 12	700
Final Score	Drug Information, Efficacy, Safety and Cost	1 to 13	Sub-criteria from Question 1 to Question 13	1000

type of scores among the ARBs were shown in Table 2.

Multiple comparisons analysis revealed that there were no statistical significant differences between the Drug Information Score for pair-wise of Eprosartan and Olmesartan ($p=0.75$), Irbesartan and Valsartan ($p=0.60$), Telmisartan and Valsartan ($p=0.34$) as well as Irbesartan and Telmisartan ($p=0.10$). An inspection of the mean ranks for each pair-wise of ARBs suggested that the order of preference based on the Drug Information Score of ARBs in decreasing order were Losartan, Irbesartan or Telmisartan or Valsartan, Candesartan, followed by Olmesartan or Eprosartan. Similarly, there were no statistical differences between Efficacy Score for pair-wise of Candesartan and Losartan ($p=0.69$), Candesartan and Valsartan ($p=0.89$), and Losartan and Valsartan ($p=0.74$). The results also suggested that Telmisartan was the most preferred ARBs with Eprosartan the least preferred for the Efficacy Score.

As for Safety Score, Losartan had the highest average score with Eprosartan reporting the lowest. No statistical differences between the pair-wise of Candesartan and Olmesartan ($p=0.31$), Irbesartan and Telmisartan ($p=0.26$), Irbesartan and Valsartan ($p=0.06$) and Telmisartan and Valsartan ($p=0.43$) were noted. The findings on the Cost Score of ARBs showed that the order of preference in decreasing order were Telmisartan or Candesartan or Irbesartan or Losartan or Olmesartan followed by Valsartan or Eprosartan. With reference to the ANOVA results in Table 2, a post hoc test, Tukey's test for both Quality Score and Final Score which was conducted revealed that there was no statistical significance between Candesartan versus Valsartan ($p_{\text{quality}}=0.12$, $p_{\text{final}}=0.56$), Irbesartan versus Losartan ($p_{\text{quality}}=0.92$, $p_{\text{final}}=0.83$), Irbesartan versus Telmisartan ($p_{\text{quality}}=0.96$, $p_{\text{final}}=0.94$) and Telmisartan versus Losartan ($p_{\text{quality}}=0.92$, $p_{\text{final}}=0.28$). Multiple comparisons test indicated that Eprosartan was the least preferred. From these findings, the decreasing order of preference based on Quality Score and Final Score were Telmisartan or Irbesartan or Losartan, Candesartan or Valsartan, Olmesartan and lastly Eprosartan.

The cutoff point will determine the number of drugs to be retained in the drug formulary. Based on the average scores for each drug, the cutoff point was set at 700 points for Final Score and at 500 points for Quality Score. Eprosartan and Olmesartan were excluded as both of these ARBs scored less than the target cutoff points as depicted in Figure 1. However, if the cutoff point was to be increased to 750 points for Final Score or 550 points for Quality Score, then the ARBs retained would be Telmisartan, Irbesartan and Losartan only.

The result of the ratio of Acquisition Cost to Quality Score based on both British National Formulary (BNF)⁸, and government tender drug acquisition cost of the ARBs were as shown in Table 3 (The main reason BNF drug cost was taken as reference was due to variation of drug cost from public hospitals to private hospitals as well as between pharmacies).

Table 2: Difference between the average score of each type of scores among the ARBs

Type of score	Average score							p-value
	Candesartan	Eprosartan	Irbesartan	Losartan	Olmesartan	Telmisartan	Valsartan	
Drug Information Score		120.0(6.0)**		178.0(22.0)**	120.0(12.0)**	160.0(20.5)**	160.0(34.0)**	0.00 ^{ΔΔ}
Efficacy Score	148.0±20.9*		162.5±20.0*					0.00 ^{***}
Safety Score	230.0(50.0)**	180.0(10.0)**	240.0(40.0)**	230.0(40.0)**	210.0(50.0)**	250.0(50.0)**	230.0(20.0)**	0.00 ^{ΔΔ}
Cost Score	130.0(22.5)**	120.0(10.0)**	140.0(20.0)**	150.0(12.5)**	130.0(20.0)**	140.0(22.5)**	140.0(22.5)**	0.00 ^{ΔΔ}
Quality Score	240.0(60.0)**	180.0(15.0)**	240.0(0.0)**	240.0(60.0)**	240.0(60.0)**	240.0(0.0)**	180.0(0.0)**	0.00 ^{ΔΔ}
Final Score	506.8±61.3*		561.3±46.3	558.9±47.5*	456.3±58.0*	558.6±52.9*	536.8±57.3*	0.00 ^Δ
		420.0(24.5)**						
	734.8±82.5*		796.5±65.0	792.9±66.6*	671.0±74.6*	802.2±76.7*	719.2±80.5*	0.00 ^Δ
		600.0(63.0)**						

* mean ± SD, **medium (IQR) ΔANOVA test $p<0.05$ (excluded Eprosartan)
 ΔΔKruskal Wallis test $p<0.05$ *** independent t-test $p<0.05$ IQR=inter-quartile range

Further analysis showed that Candesartan (9.6 cent/point) and Irbesartan (4.9 cent/point) were ranked the most cost saving based on BNF and tender drug acquisition cost, respectively.

DISCUSSION

The response rate for the survey (41.3%) was as expected. It was found that health surveys targeting physicians historically have had difficulties in obtaining high response rates.^{9,10} The response rates for physician surveys were routinely in the 40-50% range. However, this response rate did not imply that it had a lower survey accuracy but simply indicated that there was a risk of lower accuracy.^{11,12} The main reasons were unwillingness of the physicians to participate in the survey, too

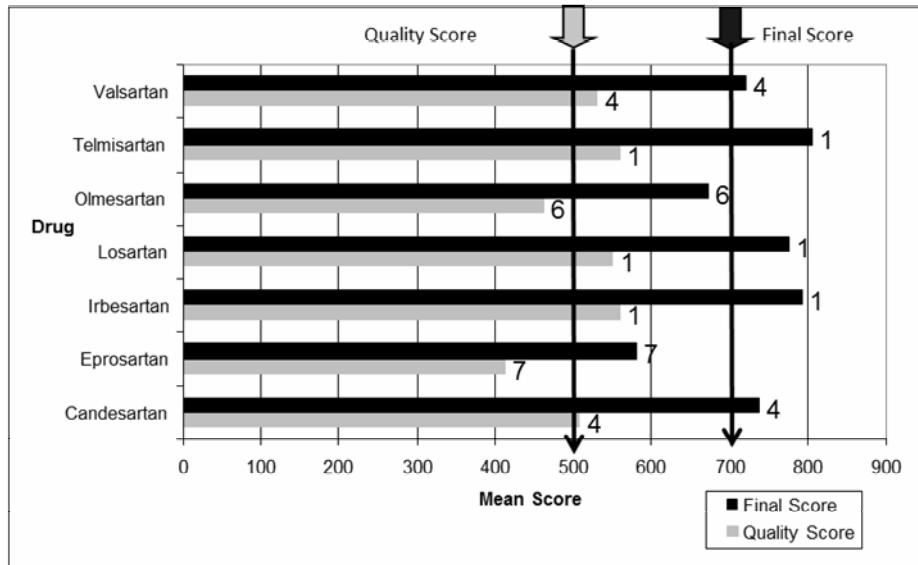


Figure 1: Cutoff point for Quality Score and Final Score of ARBs

busy to complete the questionnaire, too busy with their work or lack of interest in the study area. However, there were non response studies for physician being carried out and found no or minimal amount of response bias. For example, Kellerman and Herold¹³ reviewed that the variability of demographic characteristics on physician responses to surveys and medical specialty type was not associated with response rate. They also suggested that response bias may be less of a concern for physician surveys compared to survey with the general population as most non response studies have found no or minimal amount of response bias. This finding holds true for studies conducted after 2001 as well.¹⁴⁻¹⁶

The results do show that SAT is successful in capturing the order of trending in drug preference and enable one to understand or be clear on which criteria and weighting decisions were made. This was demonstrated in each type of scores. For example, Losartan emerged as the drug of preference for safety criteria. The high average score of Losartan was contributed mainly by its overall safety and tolerability profile^{17,18} and its unique lowering serum uric acid effect.¹⁸⁻²⁰ From the order of drug preference in both Final Score and Quality Score which were Irbesartan or Telmisartan or Losartan, Valsartan or Candesartan, Olmesartan and lastly Eprosartan, it can be seen that SAT can be used as a tool to assist formulary committee

members in evaluating claims made about drugs being considered for addition to the drug formulary. Olmesartan was ranked as second lowest in both Quality Score and Final Score and this trend is as expected as this ARB was the most recently introduced into the market and its long term safety is yet to be established.

SAT has the potential to greatly reduce the number of drugs of the same therapeutic class and subsequently a decrease in hospital inventory and the overall cost of drugs within a particular class. SAT was developed so that it was able to focus on the way in which the drugs were differentiated from each other within the same therapeutic class based on criteria such as efficacy, safety, side effect, patient compliance, outcome data, durations of effects or drug cost. Four of the selected ARBs in the survey using SAT i.e. Telmisartan, Irbesartan, Losartan and Valsartan (excluding Candesartan) were the approved ARBs used in public hospitals in Malaysia. This indicated that SAT could be introduced and used together with our own formularies principle for drugs selection as it could enable drugs to be assessed in a more consistent and reproducible manner.

In this study, cost saving was measured as ratio drug acquisition cost for 28 days treatment to Quality Score. Quality Score was used because it covered clinical efficacy, safety, adverse events, drug interactions, pharmacokinetics and other

Drug	Cost 28 tab ^{ΔΔ} (RM)	Cost 28 tab ^Δ (RM)	AC ^{ΔΔ} /QS (cent/point)	AC ^Δ /QS (cent/point)	p-value ^{***}		p-value ^{****}	
					AC ^{ΔΔ} /QS (cent/point)	AC ^Δ /QS (cent/point)	AC ^{ΔΔ} /QS (cent/point)	AC ^Δ /QS (cent/point)
Irbesartan 150mg	62.85	27.44	11.3±0.9*	4.9±0.4*	0.20	0.20	0.00	0.00
Losartan 50mg	64.00	30.00	11.7 ±1.0*	5.1±0.4*	0.20	0.20		
Telmisartan 40mg	56.70	31.20	10.2 ±0.9*	5.2±0.4*	0.20	0.20		
Valsartan 80mg	82.20	38.24	15.5 ±1.6*	5.9±0.6*	0.20	0.20		
Candesartan 8mg	49.45	NA	9.6 (2.0)**	NA	0.02	NA		
Eprosartan 600mg	71.55	NA	17.6 (1.0)**	NA	0.00	NA		
Olmesartan 20mg	64.75	NA	14.1(2.0)**	NA	0.00	NA		

IQR=inter- quartile range; NA=not available; AC= Acquisition Cost; QS= Quality Score
^Δbased on Government tender drug acquisition cost ^{ΔΔ}based on BNF drug acquisition cost
 * Mean ± SD ** Median (IQR) ***Kolmogorov-Smirnov test of normality p<0.05 ****Kruskal Wallis test p<0.05

additional clinical benefits. In Malaysia, the most cost saving ARBs in public hospitals was Irbesartan (4.9 cent/point). The least preference ARBs was Valsartan (5.9 cent/point) as reflected by its high cost per score point. This clearly shows that SAT is a useful tool for selection of drug which are both most cost saving and therapeutic appropriate.

SAT can be used to decide the determining factor for selection of drugs of similar therapeutic equivalent. The World Health Organization (WHO) described broad criteria to be considered in making formulary decisions but did not attach relative importance to the individual criteria.²¹ For instance, both Candesartan and Valsartan were indicated for both hypertension and heart failure. These two ARBs have shown a reduction in all-cause mortality, cardiovascular death and heart failure hospitalisations in patients with congestive heart failure and left ventricular ejection fraction.²²⁻²⁴ In the survey, the result showed that Quality Score of Valsartan was comparable to Candesartan. In such situation, the drug acquisition cost became the determining factor for selection and Candesartan with the lower drug acquisition cost than Valsartan should be considered or preferred.

At this point of time, SAT can be recommended as an aid to drug formulary in decision making. This is because SAT is objective where evaluation and selection of drug is concerned as the outcome of the results was subjected to statistical analysis and at the same time with the experience from the healthcare professional who are actually prescribing such drugs. It is also clear from the outcome of the results, one can know what the decision are based on. This can form a basis for discussion within the Drug and Therapeutic Committee. Secondly, SAT can be introduced at hospital level especially to the Drug and Therapeutic Committee in the hospitals. One way is by formatting the interactive SAT into a spread sheet version and then making it available on the hospital website to be used by relevant personnel.

In this study, some limitations encountered included potential for bias in response especially for those

ARBs whom the doctors were not familiar and had to base on the notes or literature review provided. Another area was shortage of specialists/medical officers with many years of experience on these ARBs and this was a pre-requisite to be eligible as competent participants were not quantified. Other limitations included non-availability of established specialist panel to give consistent scores, and thus information and selection biasness which in reality would always exist. SAT need to be further fine-tuned and a larger-scale study need to be carried out before generalization can be applied.

SAT can be successfully exploited as a tool to evaluate any drugs objectively according to pre-set criteria and relative weightage. All these have been shown through the trending and statistical analysis. There was an admission that it was impossible to be absolutely objective but it could be confidently mentioned that the evaluation process had indeed been simplified but with time and further fine tuning the tool can achieve near to ideal level.

CONCLUSIONS

In short, SAT can be used to facilitate rational drug evaluation, reduce drugs inventory, retain the most therapeutically appropriate and cost saving drugs in the drug formulary which is beneficial to both formulary and healthcare professionals. This study concluded that SAT is able to provide framework for formulary decision making but use in a generalized manner still require further test.

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CONFLICT OF INTEREST

Nothing to declare.

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