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# The use of special approval medicines among pediatric patients in a tertiary care hospital: A reality check

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ABSTRACT

*Background:* Special approval medicines (SAMs) are medicines used with approval from the Director General of Health Malaysia when the therapeutic options within regulatory and formulary boundaries appear unsuitable or ineffective to treat the patients.
*Objectives:* To examine and characterize the use of SAMs among children in a Malaysian tertiary care hospital.
*Methods:* The named-patient basis SAM application forms, cover letter, pharmacist review summary and patient monitoring forms available at the Pharmacy Department between 1st January 2019 and 31st December 2020 were reviewed. Unprocessed, unapproved and stock-basis applications were excluded. The outcome measures were categories, scope, off-label use and cost of SAM. Per-patient data were analyzed descriptively.
*Results:* Overall, 1010 patients (mean age of 8.7 ± 5.6 years) were involved in 328 SAMs applications. The most common SAMs pharmacological groups were nervous system ($n$ = 371, 36.7%) and antineoplastic and immunomodulating agents ($n$ = 332, 32.9%). Top three SAMs were melatonin (11.5%), scopolamine (7.6%) and cholecalciferol (7.1%). A total of 837 (82.9%) and 513 (50.8%) patients were involved in the SAMs applications for non-formulary and unregistered medicines, respectively. Unregistered, non-formulary medicines were applied for 47.3% ($n$ = 478) of the patients. The majority of the scope for SAMs (64.7%) were to substitute the available alternatives in the national formulary which were ineffective or sub-optimal for the patients. Among the 262 patients with repeat applications, 93.8% reported disease or symptom improvement while 1.9% experienced side effects. Up to 17% of SAMs analyzed in this study were used for off-label indications. The total cost of the SAMs was RM8,748,358.38 (USD 2,090,418.86).
*Conclusion:* The use of SAMs among children in this hospital involved unregistered, non-formulary medicines used to substitute the available alternatives in the formulary. A concerted effort is warranted in exploring supplementary mechanisms to enhance the medicine registration process and formulary system towards facilitating enhanced provision of treatment for children.

## 1. Introduction

In most countries, the choice of medicines used to treat a disease is often 'controlled' by the registration status of the medicine and formulary system. However, the use of unregistered and non-formulary medicines are sometimes the cornerstone in the management of certain diseases[1,2] or population.[3,4] Furthermore, off-label use of registered, unregistered or non-formulary medicines is another spectrum of concern, especially in pediatric patients.[5] Pediatric patients are prescribed with an average of 2 to 5 medicines per prescription,[6,7] which may increase up to 7 and 12 medicines per prescription for terminally-ill patients[8] and patients in tertiary care centres,[4] respectively. When treating pediatric patients, prescribers tend to use therapeutic options outside regulatory and formulary boundaries as the existing alternative is unsuitable or ineffective to principally treat their patients.[9,10] The problems with access to and supply of unregistered or non-formulary medicines is potentially a barrier in providing optimal care for patients.[11,12]

It was reported that 22% of pediatric patients admitted for highly specialised inpatient care were prescribed with unregistered medicines.[3] Various mechanisms exist in different countries to allow the importation and use of unregistered medicines for patient's use. In Singapore, the Health Sciences Authority (HSA) allows the importation or supply of unregistered medicines for patient's use as named-patient or buffer stock application via the Special Access Route (SAR).[13] Similarly in Australia, the Special Access Scheme (SAS) allows for the importation and supply of an unregistered medicine for an individual patient under the supervision of a medical practitioner, on a case-by-case basis.[14] On the other hand, a 'single permit for import of drug' can be applied from the Ministry of Public Health of the People's Republic of China for import of medicines without import registration certificates.[15] Although some variations exist in these mechanisms, the

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ultimate goal remains unanimous to ensure safety, efficacy and quality of the therapeutic options bypassing the medicine registration regulatory pathways.

The use of non-formulary medicines have been reported worldwide in previous studies[16,17] whereby up to 20% of hospitalised patients were prescribed non-formulary medicines.[18] In children, non-formulary medicines accounted for 13.4% of the total prescriptions, mostly for patients in the general pediatric wards.[4] Non-formulary medicines were prescribed when conventional therapies have failed[2] or patients developed adverse reactions towards medicines within the formulary.[16] However, the provision of non-formulary medicines in the hospital setting has been shown to incur additional pharmacy cost.[19]

In some situations, registered and formulary medicines are used for unapproved indications, commonly known as unlicensed or off-label use of medicines. The use of unlicensed or off-label medicines is common in the pediatric population, especially in oncology and critical care settings.[4,5] This is attributable to the greatly limited availability in the number of pharmaceutical dosage forms and the lack of scientific evidence for choices of medicines in the pediatric population.[4] Furthermore, the lack of clinical trials in the pediatric settings as a result of the high heterogeneity in pharmacokinetic parameters as well as the ethical and legal issues for research have also contributed to the unlicensed and off-label use of medicines among this group of patients.[20,21] Consequently, unlicensed and off-label medicines are used as first-line agents to treat pediatric patients.

In Malaysia, the National Pharmaceutical Regulatory Agency (NPRA) is a regulatory body which is responsible to register medicines which has fulfilled the registration requirements determined by the Drug Control Authority (DCA). In line with the objective of the Malaysian National Medicines Policy (MNMP),[22] the Ministry of Health Medicines Formulary (MOHMF) serves as a reference to medicine prescribing in the Ministry of Health (MOH) facilities by emphasizing on the priority of using registered medicines to promote equitable access to safe, effective and good quality medicines. However, the usage of medicines outside the MOHMF (hereinafter referred to as non-formulary medicines) or unregistered medicines are allowed, in justified circumstances, with special approval from the Director General of Health Malaysia, Senior Director of Pharmaceutical Services, Director of Pharmacy Practice and Development, Hospital Directors or Family Medicine Specialists (FMS) in-charge of Health Clinics. This group of medicines are known as Special Approval Medicines (SAMs). Generally, SAMs in Malaysia comprise of non-formulary medicines, medicines within the MOHMF used for off-label indications, and unregistered medicines. Overall, the approval for and total cost of SAM in MOH facilities showed a three-fold increase from the year 2016 to 2020.[23] Most of the approved SAMs from the year 2016 to 2020 were non-formulary registered medicines, with about 41% in the year 2020 attributed to unregistered medicines.[23]

Although the use of unregistered, non-formulary and off-label medicines in pediatric patients appears inevitable, it was reported to be inappropriate in some cases,[24] had a potential for interactions[4] and significantly higher risk of adverse drug reactions (ADR),[25] urging the need to examine the use of these medicines in hospital settings. To the best of our knowledge, there are no studies examining the use of SAM in Malaysia, leading to scarcity of information on the use of SAM particularly in pediatric patients. Hence, this study was conducted to characterize the use of and identify the scope of SAM at a tertiary care children hospital in Malaysia. The data will be of paramount importance to healthcare policy makers for decision-making in the inclusion of medicines in the MOHMF in the future and to explore alternative mechanisms enabling access and supply of SAM in the country.

## 2. Methods

### 2.1. Ethical consideration

The study was approved by the ethics committee for Ministry of Health (MOH) facilities in Malaysia, Medical Research and Ethics Committee (MREC) (NMRR-21-738-59630). Approval to conduct the study was obtained from the hospital director and the head of department. The patient identifiers were kept confidential. The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[26] recommendations.

### 2.2. Operational definitions

a. **Special approval medicine (SAMs)** are medicines used in the MOH facilities with special approval from the Director General of Health Malaysia, Senior Director of Pharmaceutical Services, Director of Pharmacy Practice and Development, Hospital Directors or FMS in-charge of Health Clinics. These medicines include:

i. Registered, non-formulary medicines
ii. Registered, formulary medicines used for indications outside those approved by the DCA or MOHMF
iii. Unregistered, formulary medicines
iv. Unregistered, non-formulary medicines.

b. A **registered medicine** is a medicine that is approved by the DCA for sale or use in Malaysia.[27]

### 2.3. Study design and setting

The conceptualisation of the study was done through mapping of key terms, definitions and constructs of SAM application (Fig. 1). The cross-sectional retrospective study was conducted in a tertiary care hospital in the central region of Peninsular Malaysia. The 600-bedded hospital functions as the national referral centre and Centre of Excellence for women's and children's disease.

### 2.4. Eligibility criteria

Named-patient basis SAM applications for patients below 19 years old, received by the Pharmacy Department between 1st January 2019 and 31st December 2020 were included. Additionally, SAM applications for patients above 18 years old who were still under the care of pediatricians were also included. Unprocessed, unapproved and stock-basis SAM applications was excluded from the study.

### 2.5. Sample size estimation

The hospital formulary is a subset of the MOHMF. The total number of medicines available in the hospital formulary was 1219 items (according to the list updated on the 28th May 2020). Out of this, a total of 161 medicines were SAMs. The Pharmacy Department received an average of 150 SAM applications per year. Therefore, the estimated number of SAMs application during the 2-year study duration was 300.

### 2.6. Data collection

The study source documents were the SAM application forms, cover letter provided by the applicant, pharmacist review summary, patients monitoring forms and SAM approval documents. A structured and piloted data collection form was used to collect patients' demographic data, SAM details, SAM application details, cost of SAM and category as well as the scope of use of SAM.

The SAMs were classified according to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification. In the absence of exact WHO ATC classification for a particular SAM, the pharmacological grouping was made based on the routes of administration with clearly different therapeutic uses which were verified in discussion with the respective pediatric specialists. All SAMs except unregistered and non-formulary medicines were examined for its off-label use. A SAM was

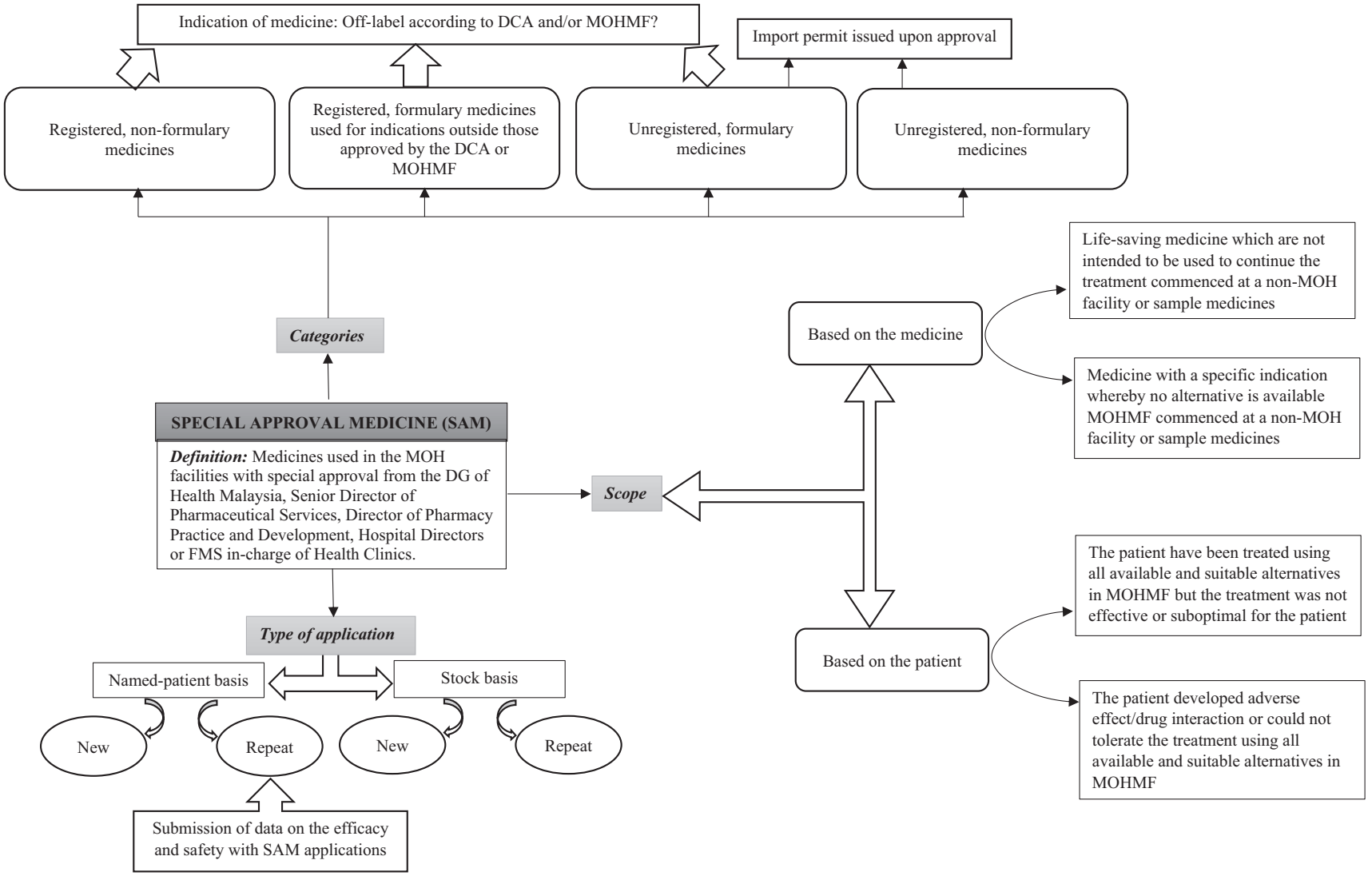


**Fig. 1.** Conceptual framework of the study. DCA = Drug Control Authority; DG = Director General; FMS = Family Medicine Specialist; MOHMF = Ministry of Health Medicines Formulary.

**Table 1**
List of special approval medicines.

| Drug name | Strength/concentration | Dosage form |
|---|---|---|
| Abacavir | 300 mg and 20 mg/ml | Tablet and Oral solution |
| Blinatumomab | 35μg/3 ml | Injection |
| Cholecalciferol | 1000iu and 5000iu | Tablet and Capsule |
| Cladribine | 10 mg/10 ml | Injection |
| Clofarabine | 20 mg/20 ml | Injection |
| *Clostridium Botulinum* Toxin Type A | 100 IU and 500 IU | Injection |
| Coenzyme Q10 | 30 mg | Softgel capsule |
| Darunavir | 600 mg | Tablet |
| Dasatinib | 50 mg | Tablet |
| Defibrotide | 200 mg | Injection |
| Deflazacort | 30 mg | Tablet |
| Diazoxide | 100 mg | Capsule |
| Dibutyl Squarate Liquid (SADBE) | 5 g | Topical liquid* |
| Doxycycline | 100 mg | Injection |
| Dupilumab | 300 mg | Pre-filled syringe |
| Emicizumab | 150 mg/ml | Injection |
| Entecavir | 0.5 mg | Tablet |
| Epinephrine | 0.15 mg | Injection |
| Etoposide | 50 mg | Capsule |
| Everolimus | 10 mg | Tablet |
| Foscarnet | 24 mg/ml | Injection |
| Gabapentin | 300 mg | Capsule |
| Gemcitabine | 1000 mg | Injection |
| Glibenclamide | 5 mg | Tablet |
| Glycopyrronium bromide | 1 mg/5 ml | Syrup** |
| Gonadorelin | 100μg | Injection |
| Imatinib | 100 mg | Tablet |
| Interferon Beta 1a | 22μg | Injection |
| Iron (III)-hydroxide Polymaltose Complex | 100 mg | Chewable tablet |
| Lomustine | 10 mg, 40 mg | Capsule |
| Macrogol | 10 g | Powder for oral solution |
| Melatonin | 3 mg | Capsule |
| Melphalan | 50 mg/10 ml | Injection |
| Methadone | 5 mg/ml | Syrup** |
| Mexiletine | 100 mg | Capsule |
| Midazolam | 10 mg/ml | Buccal Liquid |
| Mitotane | 500 mg | Tablet |
| Mycophenolate mofetil | 250 mg and 1 g/5 ml | Capsule and Oral suspension |
| Nelarabine | 250 mg/50 ml | Injection |
| Nivolumab | 100 mg/10 ml | Injection |
| Onasemnogene abeparvovec | $2 \times 10^{13}$ vector genomes/ml | Injection |
| Oxaliplatin | 50 mg/10 ml | Injection |
| Oxcarbazepine | 300 mg | Tablet |
| Oxymetholone | 50 mg | Tablet |
| Paclitaxel | 300 mg/50 ml | Injection |
| Peglyated L-Asparaginase | 3750/5 ml | Injection |
| Perampanel | 2 mg and 4 mg | Tablet |
| Ponatinib | 15 mg | Tablet |
| Protein C concentrate human | 500 IU | Injection |
| Pyrimethamine | 25 mg | Tablet |
| Recombinant Factor VIIa | 1 mg | Injection |
| Risdiplam | 60 mg/80 ml | Oral solution |
| Rufinamide | 200 mg | Tablet |
| Rurioctocog alfa pegol | 250 IU | Injection |
| Scopolamine | 1.5 mg | Transdermal patch |
| Sildenafil | 50 mg | Tablet |
| Sirolimus | 1 mg | Tablet |
| Stiripentol | 250 mg | Capsule and Powder for oral suspension |
| Sulfadiazine | 500 mg | Tablet |
| Sulthiame | 200 mg | Tablet |
| Tacrolimus | 0.5 mg and 1 mg | Capsule |
| Tamoxifen | 20 mg | Tablet |
| Thiotepa | 100 mg | Injection |
| Timolol maleate | 0.5% | Eye drop |
| Topotecan | 1 mg and 4 mg | Injection |
| Triptorelin | 11.25 mg | Injection |
| Valaciclovir | 500 mg | Tablet |
| Valganciclovir | 5 g/100 ml | Syrup |
| Vinblastine | 10 mg | Injection |
| Vindesine | 5 mg | Injection |
| Vinorelbine | 50 mg/5 ml | Injection |
| Zinc + Vitamin C | 10 mg + 100 mg/5 ml | Oral solution |
| Zinc gluconate | 50 mg | Tablet |
| Zonisamide | 100 mg | Tablet |

* Dibutyl Squarate Liquid (SADBE) 5 g liquid is further diluted to various concentrations, from 2%, 1%, 0.5%, 0.1%, 0.01%, and lastly 0.001% in acetone by in-house non-sterile production unit.

** Prepared by in-house non-sterile production unit.

**Table 2**
Profile of patients with SAM applications.

| Characteristics | Number of patients (%) |
|---|---|
| Total (*n*) | 1010 |
| Gender | |
| Male | 552 (54.7) |
| Female | 458 (45.3) |
| Ethnicity | |
| Malay | 736 (72.9) |
| Chinese | 163 (16.1) |
| Indian | 82 (8.1) |
| Others | 29 (2.9) |
| Age | |
| Neonate (birth to 1 month) | 20 (2.0) |
| Infant (>1 month – 1 year) | 60 (5.9) |
| Children (>1–12 years) | 641 (63.5) |
| Adolescent (>12–18 years) | 262 (25.9) |
| Adult (>18 years) | 27 (2.7) |
| Mean age (years ±SD) | 8.7 ± 5.6 |
| Mean weight (kg ± SD) | 23.87 ± 13.73 |
| Mean body surface area ($m^2$ ± SD) | 0.88 ± 0.18 |
| Applicant's department/sub-speciality | |
| Pediatric Neurology | 343 (34.0%) |
| Pediatric Oncology | 235 (23.3%) |
| Pediatric Dermatology | 162 (16.0%) |
| Pediatric Nephrology | 96 (9.5%) |
| Pediatric Gastrology | 40 (4.0%) |
| Pediatric Palliative Care | 38 (3.8%) |
| Pediatric Endocrinology | 26 (2.5%) |
| Ophthalmology | 25 (2.4%) |
| Neonatology | 15 (1.5%) |
| Pediatric Infectious Disease | 13 (1.3%) |
| Pediatric Surgery | 4 (0.4%) |
| Pediatric Cardiology | 4 (0.4%) |
| Otorhinolaryngology | 3 (0.3%) |
| Radiology | 3 (0.3%) |
| Urology | 3 (0.3%) |

SAM = Special Approval Medicine.

considered used in an off-label manner if the indication of the medicine were outside those approved by the DCA or MOHMF. The off-label categories were classified as:

i. Off-label DCA: SAM used outside the indication approved by the DCA
ii. Off-label MOHMF: SAM used outside the indication listed in the MOHMF
iii. Off-label DCA and MOHMF: SAM used outside the indication approved by the DCA and listed in the MOHMF

The determination of the scope of use of SAM was derived by critical reviewing of the SAM application process, the indication for SAM and rationale for the SAM application. The classification of the scope of use of SAM is as stated below:

i. Based on the medicine:

- Life-saving medicine which are not intended to be used to continue the treatment commenced at a non-MOH facility or sample medicines.

**Table 3**
Per-patient data on SAMs based on the WHO ATC classification.

| ATC classification<br>*Top 3 prescribed medicines** | *n* (%) | Number of SAM applications (%) | Types of SAM applications (new/repeat) | Cost [MYR (USD)] |
|---|---|---|---|---|
| Nervous system | **371 (36.7)** | **44 (13.4)** | **26/18** | **1, 506, 349.32 (359, 940.21)** |
| *Melatonin* | *116 (11.5)* | | | |
| *Scopolamine* | *77 (7.6)* | | | |
| *Oxcarbazepine* | *56 (5.5)* | | | |
| Antineoplastic and immunomodulating agents | **332 (32.9)** | **202 (61.6)** | **182/20** | **4, 943, 015.09 (1, 181, 127.03)** |
| *Sirolimus* | *68 (6.7)* | | | |
| *Peglyated L-Asparaginase* | *48 (4.8)* | | | |
| *Vindesine* | *35 (3.5)* | | | |
| Alimentary tract and metabolism | **153 (15.1)** | **18 (5.5)** | **17/1** | **80, 622.30 (19, 264.59)** |
| *Cholecalciferol* | *72 (7.1)* | | | |
| *Macrogol* | *39 (3.9)* | | | |
| *Zinc + Vitamin C* | *25 (2.5)* | | | |
| Blood and blood forming organs | **47 (4.6)** | **20 (6.1)** | **15/5** | **1, 755, 239.38 (419, 412.17)** |
| *Iron (III) hydroxide polymaltose complex* | *30 (3.0)* | | | |
| *Defibrotide* | *9 (0.9)* | | | |
| *Rurioctocog alfa pegol* | *4 (0.4)* | | | |
| Dermatologicals | **33 (3.3)** | **5 (1.5)** | **4/1** | **217, 986.20 (52, 087.52)** |
| *Timolol maleate* | 29 (2.9) | | | |
| *Dupilumab* | 4 (0.4) | | | |
| Cardiovascular system | **17 (1.7)** | **5 (1.5)** | **4/1** | **12, 312.93 (2, 737.29)** |
| *Epinephrine* | *12 (1.2)* | | | |
| *Co-enzyme Q10* | *4 (0.4)* | | | |
| *Mexiletine* | *1 (0.1)* | | | |
| Antiinfectives for systemic use | **17 (1.7)** | **16 (4.9)** | **11/5** | **180, 076.30 (43, 029.00)** |
| *Abacavir* | *5 (0.5)* | | | |
| *Valganciclovir* | *4 (0.4)* | | | |
| *Darunavir* | *2 (0.2)* | | | |
| Musculo-skeletal system | 13 (1.3) | 9 (2.7) | 9/0 | 20, 515.44 (4, 902.14) |
| *Clostridium Botulinum Toxin Type A* | *7 (0.7)* | | | |
| *Risdiplam* | *3 (0.3)* | | | |
| *Onasemnogene abeparvovec* | *3 (0.3)* | | | |
| Various | **8 (0.8)** | **4 (1.2)** | **3/1** | **6, 227.74 (1, 488.11)** |
| *Gonadorelin* | *5 (0.5)* | | | |
| *Diazoxide* | *3 (0.30)* | | | |
| Genito urinary system and sex hormones | **17 (1.7)** | **3 (0.9)** | **2/1** | **22, 645.28 (5, 034.52)** |
| *Sildenafil* | *15 (1.5)* | | | |
| *Tamoxifen* | *2 (0.2)* | | | |
| Antiparasitic products, insecticides and repellents | **1 (0.1)** | **1 (0.3)** | **1/0** | **264.60 (63.23)** |
| *Pyrimethamine* | *1 (0.1)* | | | |
| Systemic hormonal preparations, excluding sex hormones and insulins | **1 (0.1)** | **1 (0.3)** | **1/0** | **3, 103.80 (741.65)** |
| *Deflazacort* | *1 (0.1)* | | | |
| TOTAL | **1010** | **328** | **275/53** | **8, 748, 358.38 (2, 090, 408.87)** |

ATC = Anatomical Therapeutic Chemical; SAMs = Special Approval Medicines; WHO = World Health Organization.
* Only for groups with >2 medicines per ATC classification.

- Medicine with a specific indication whereby no alternative is available in MOHMF.

ii. Based on the patient:

- The patient have been treated using all available and suitable alternatives in MOHMF but the treatment was ineffective or suboptimal for the patient.
- The patient developed adverse effect/drug interaction or could not tolerate the treatment using all available and suitable alternatives in MOHMF.

Two researchers reviewed the source documents to determine the classification of the scope of use of SAM. Two other researchers reviewed and validated the classifications. Discrepancies were resolved through discussions and consensus among the researchers. The patients monitoring forms accompanying the repeat SAM applications were further examined for occurrence of side effects and reporting of disease or symptom improvement.

The cost incurred in purchasing SAMs were primarily funded by the MOH. For cost calculation, the unit cost for each medicine was calculated by dividing the pack price by the size to determine cost per tablet or capsule. The cost of any oral liquids was based on the number of bottles needed for the requested duration (up to 12 months). The cost of parenteral medicines was based on the number of ampules or vials required to administer the prescribed dose for the requested duration. The total cost of SAM was calculated by multiplying unit cost with the quantity of medicine required for the requested duration. The unit cost of the medicine was based on the price quotation (lowest quoted price) enclosed with the SAM application form. The quantity of medicine required was extracted from the SAM application form. Manual calculations of quantity of SAM was determined based on the dose, dosing frequency, duration of treatment and shelf-life of medicines (for diluted or reconstituted medicines). The manual calculations of the quantity of SAM was randomly checked by the researchers. Discrepancies were resolved through a consensus discussion between the researchers. The SAM purchased by the patients (out-of-pocket) and borne by other funding sources besides MOH were excluded from cost calculation. Costs were expressed in 2022 Malaysian Ringgit (MYR) and United States Dollar (USD).

### *2.7. Statistical analysis*

Descriptive analysis of per-patient data was conducted using the Statistical Package for the Social Sciences (SPSS) version 24. Continuous

**Table 4**
Category and scope of use of SAMs.

| Category of SAMs | n (%) |
|---|---|
| Registered, non-formulary medicines | 359 (35.5) |
| Registered, formulary medicines used for indications outside those approved by the DCA or MOHMF | 138 (13.7) |
| Unregistered, formulary medicines | 35 (3.5) |
| Unregistered, non-formulary medicines | 478 (47.3) |
| [a]Scope of SAMs | n (%) |
| Life-saving medicine which are not intended to be used to continue the treatment commenced at a non-MOH facility or sample medicines | 22 (2.2) |
| Medicine with a specific indication whereby no alternative is available MOHMF | 363 (35.9) |
| The patient have been treated using all available and suitable alternatives in MOHMF but the treatment was not effective or suboptimal for the patient | 653 (64.7) |
| The patient developed adverse effect/drug interaction or could not tolerate the treatment using all available and suitable alternatives in MOHMF | 282 (27.9) |

DCA = Drug Control Authority; MOH = Ministry of Health; MOHMF = Ministry of Health Medicines Formulary; SAMs = Special Approval Medicines.
[a] Number of patients fulfilled more than one scope of use of SAM = 310.

variables were summarized using mean (standard deviation) or median (interquartile range) depending on the data normality. Categorical variables were represented using frequencies and percentages.

## 3. Results

In total, 328 applications corresponding to 74 types of SAMs (Table 1) for 1010 patients with the mean age of 8.7 ± 5.6 years were analyzed (Table 2). As the per-patient data was used for analysis, the denominator for percentage calculation was the total number of patients i.e. 1010. The most common SAM dosage forms were tablet or capsule ($n$ = 556, 55%), injectable ($n$ = 215, 21.3%) and liquid oral formulations ($n$ = 97, 9.6%). The profile of SAM by Anatomical Therapeutic Chemical (ATC) classification system is shown in Table 3. The most common pharmacological group was nervous system ($n$ = 371, 36.7%) followed by antineoplastic and immunomodulating agents ($n$ = 332, 32.9%). The top three SAMs were melatonin ($n$ = 116, 11.5%), scopolamine ($n$ = 77, 7.6%) and cholecalciferol ($n$ = 72, 7.1%).

The SAM used for off-label indications were analyzed for 532 (52.7%) patients. The off-label status per DCA, MOHMF as well as DCA and MOHMF were 16.7%, 6.8% and 4.9%, respectively. The category and scope of SAM is shown in Table 4. Unregistered, non-formulary medicines were applied for 47.3% ($n$ = 478) of the patients while unregistered, formulary medicines were applied for 3.5% ($n$ = 35) of the patients. This resulted in the overall SAM applications for unregistered medicines for 513 patients (50.8%). On the other hand, registered and unregistered non-formulary medicines were applied for 359 (35.5%) and 478 patients (47.3%), respectively. In total, 837 patients (82.9%) were involved in the SAM applications for non-formulary medicines. The majority of the SAMs (64.7%) were applied to substitute the available alternatives in MOHMF which were ineffective or sub-optimal for the patients (Table 4).

The proportion of new and repeat SAM applications were 83.8% and 16.2%, respectively. Among the 262 patients with repeat applications, 93.8% reported disease or symptom improvement while 1.9% experienced side effects. The total cost of SAMs was MYR 8,748,358.38 (USD 2,090,418.86) (Table 3).

## 4. Discussion

This study examined the use and characterized the scope of SAMs in a Malaysian tertiary care children hospital. The findings of the study revealed that drugs acting on the nervous system as well as the antineoplastic and immunomodulating agents were the most commonly used SAMs in the study population. Despite the efforts taken to diversify the treatment of cancer[28] and neurological disorders in children,[29] approved or licensed treatment options for these diseases remains inadequate.[30]

Up to 17% of SAMs analyzed in this study were used for off-label indications. This data is almost similar to the proportions of off-label prescriptions due to indication (about 20%) that were reported by studies on off-label use of medicines in pediatric patients in various healthcare setting.[31] Using SAM for off-label indication calls for heightened patient autonomy and poses additional responsibilities on the prescribers. Although obtaining informed consent from the patient for off-label use is recommended in Malaysia,[32] other approaches have been suggested in the literature[33] to help prescribers navigate the medical-legal landscape when engaged with off-label prescribing.

In the current study, 82.9% and 50.8% of the patients were involved in the SAM applications for non-formulary and unregistered medicines, respectively. This is parallel to the national trend in the SAM applications for non-formulary and unregistered medicines of about 83.7% and 40.6%, respectively.[23] A high proportion of SAM applications for non-formulary medicines may signal the need to develop a national pediatric formulary encompassing best available evidence from registration data, investigator-initiated research, clinical experience and consensus.[34] Besides developing a new pediatric formulary, extension of an existing pediatric formulary with the addition of country-specific information to address country-specific needs have also shown to be successful.[35]

About 65% of the SAM applications were submitted to substitute the alternatives in the formulary which were ineffective or sub-optimal for the patients. This finding contradicts data reported by another study conducted in Spain[18] whereby the most common cause of non-formulary prescription was unavailability of a formulary therapeutic alternative. Side effects towards SAM were reported in about 2% of the patients with repeat applications. An analysis of ADR reports till the year 2019 at the same study site showed that about 8% of the ADR reports involved SAMs[36]. Given the potential for ADR in pediatric patients with SAM, the development of ADR reporting forms suitable for reporting cases related to the use of SAM is warranted.

To the best of our knowledge, this was the first study conducted to examine the use of SAMs at a tertiary care children hospital in Malaysia. The strength of the study lies in the generation of evidence using real world data. This study had signposted that the Malaysian regulatory and formulary boundary could be reengineered to include effective and safe alternatives for children. This study, however, is subject to several limitations. The cost-saving strategies employed at the study site was not taken into account in the drug cost calculation in this study. The occurrence of side effects and reporting of disease or symptom improvement was obtained from the study's source documents and lacks verification against patient's progress notes or adverse drug reaction report.

To obtain valuable clinical relevance, future research should identify the effectiveness and risks of SAM in children using “real-world approach” of effectiveness studies. This could be achieved by conducting Hypothesis Evaluating Treatment Effectiveness (HETE) studies[37] involving the SAMs profiled in this study. Firstly, the most commonly used SAM with the highest cost implication need to be identified. Following this, the critical clinical parameters and cutoffs that will define sufficient efficacy and unacceptable safety for the identified SAM should be established. Once the mapping of SAM with its relevant efficacy and safety parameters are established, structured data collection can be implemented as a routine practice to evaluate whether a treatment effect observed under controlled environment gives the same result in the real world. These results may lead to real world evidence-based treatment recommendations that can be implemented to benefit healthcare provision.

## 5. Conclusion

The SAMs in the tertiary care children hospital in Malaysia involved unregistered, non-formulary medicines used as a substitute for the available

alternatives in MOHMF. A concerted effort is warranted in exploring supplementary mechanisms to reconstruct the medicine registration process and formulary system towards facilitating enhanced provision of treatment for pediatric population.

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## CRediT authorship contribution statement

**Shamala Balan:** Conceptualization, Formal analysis, Writing – review & editing, Supervision, Project administration. **Koo Kaitian:** Methodology, Data curation. **Muhamad Danial Muhamad Hamdan:** Investigation, Writing – original draft. **Lee Su Vin:** Investigation, Writing – original draft.

## Declaration of Competing Interest

The authors declare no competing interests.

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## References

1. Hillock NT, Paradiso L, Turnidge J, Karnon J, Merlin TL. Clinical indications treated with unregistered antimicrobials: regulatory challenges of antimicrobial resistance and access to effective treatment for patients. Aust Health Rev 2020;44(2):263–269. https://doi.org/10.1071/AH18240.
2. Inglis JM, Caughey GE, Shakib S. Use of non-formulary high-cost medicines in an Australian public hospital. Int J Clin Pharmacol 2019;41(4):920–931.
3. Kooblal Y. Unregistered and off-label medicine use in highly specialised paediatrics at Tygerberg HospitalPublished online. 2016.
4. Tramontina MY, Heineck I, Dos Santos L. Use of non-formulary drugs in children at a Brazilian teaching hospital: a descriptive study. Pharm Pract (Granada) 2013;11(1):17.
5. Balan S, Hassali MAA, Mak VSL. Two decades of off-label prescribing in children: a literature review. World J Pediatr 2018;14(6):528–540.
6. Aldabagh A, Farha RA, Karout S, Itani R, Hammour KA, Alefishat E. Evaluation of drug use pattern in pediatric outpatient clinics in a tertiary teaching hospital using WHO drug-prescribing indicators. J Multidiscip Healthc 2022;15:1143.
7. Thiruthopu NS, Mateti UV, Bairi R, Sivva D, Martha S. Drug utilization pattern in south Indian pediatric population: a prospective study. Perspect Clin Res 2014;5(4):178.
8. Efraim J, Munisi C, Magige A, et al. Drug utilization pattern and adverse drug reactions of chemotherapy in pediatric patients at Muhimbili National Hospital, Tanzania. F1000Research 2022;11(396):396.
9. Flotats-Bastardas M, Hahn A. New therapeutics options for pediatric neuromuscular disorders. Front Pediatr 2020:8. https://doi.org/10.3389/fped.2020.583877.
10. Rinaldi VE, Di Cara G, Mencaroni E, Verrotti A. Therapeutic options for childhood absence epilepsy. Pediatr Reports 2021;13(4). https://doi.org/10.3390/pediatric13040078.
11. Nohavicka L, Patel B, Chadwick A, Bluebond-Langner M. 61 medication access and supply issues as a barrier to good symptom management: how big is the problem? Arch Dis Child 2021;106(suppl 3). https://doi.org/10.1136/archdischild-2021-gosh.61.A23LP-A23.
12. Elahi E, Siddiqui A. A call for revamping the policy on import process of anticancer drugs in Pakistan. J Pak Med Assoc 2021;71(10):2483.
13. Health Sciences Authority. Import and supply of unregistered therapeutic products for patient's use. Accessed January 19, 2022: https://www.hsa.gov.sg/therapeutic-products/register/special-access-routes/import-for-patients 2022.
14. Donovan P. Access to unregistered drugs in Australia. Aust Prescr 2017;40(5):194–196. https://doi.org/10.18773/austprescr.2017.062.
15. Ministry of Commerce People"s Republic of China. Provisions governing the import of drugs. Accessed January 19, 2022: http://english.mofcom.gov.cn/article/lawsdata/chineselaw/200211/20021100050734.shtml 2022.
16. Her QL, Amato MG, Seger DL, et al. Review of nonformulary medication approvals in an academic medical center. Jt Comm J Qual Patient Saf 2017;43(2):89–96.
17. Barceló-Vidal J, Fernández-Sala X, Grau S, et al. Impact of non-formulary drugs on pharmacological prescription in hospitalised patients. Eur J Hosp Pharm 2021;28(2):e92–e96. https://doi.org/10.1136/ejhpharm-2020-002204.
18. Rodriguez-Carrero R, Iglesias T, Puente P. Non-formulary drugs: situation analysis. Eur J Hosp Pharm Sci Pract 2012;19(2):203.
19. Sweet BV, Stevenson JG. Pharmacy costs associated with nonformulary drug requests. Am J Heal Pharm 2001;58(18):1746–1752.
20. Napoleone E. Children and ADRs (adverse drug reactions). Ital J Pediatr 2010;36(1):1–5.
21. Santos DB, Clavenna A, Bonati M, Coelho HLL. Off-label and unlicensed drug utilization in hospitalized children in Fortaleza, Brazil. Eur J Clin Pharmacol 2008;64(11):1111–1118.
22. Pharmaceutical, Services P, Malaysia Moh. *Malaysian National Medicines Policy3rd ed.* . 2017-2021.Accessed February 22, 2021: https://www.pharmacy.gov.my/v2/sites/default/files/articles-upload/mnmp-term-3.pdf.
23. Pharmaceutical Services Programme MOH. Pharmacy Programme Statistics Report 2020. https://www.pharmacy.gov.my/v2/sites/default/files/document-upload/statistics-report-pharmaceutical-services-programme-2020.pdf 2020.
24. Her QL, Amato MG, Seger DL, et al. The frequency of inappropriate nonformulary medication alert overrides in the inpatient setting. J Am Med Inform Assoc 2016;23(5):924–933.
25. Pratico AD, Longo L, Mansueto S, et al. Off-label use of drugs and adverse drug reactions in pediatric units: a prospective, multicenter study. Curr Drug Saf 2018;13(3):200–207.
26. Vandenbroucke JP, Von Elm E, Altman DG, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. PLoS Med 2007;4(10), e297.
27. National Pharmaceutical Regulatory Agency. FAQ: Product registration. https://npra.gov.my/index.php/en/component/content/article/37-faq/623-product-registration?Itemid=437#:~:text=A February 22, 2021.registered drug is a,on its label or package.
28. Barone A, Casey D, McKee AE, Reaman G. Cancer drugs approved for use in children: impact of legislative initiatives and future opportunities. Pediatr Blood Cancer 2019;66(8), e27809. https://doi.org/10.1002/pbc.27809.
29. Mueller S, Jain P, Liang WS, et al. A pilot precision medicine trial for children with diffuse intrinsic pontine glioma—PNOC003: a report from the Pacific pediatric neuro-oncology consortium. Int J Cancer 2019;145(7):1889–1901.
30. Manjesh PS, Shetty YC, Chinnaswamy G, Patankar PS. Prescription pattern of drugs in pediatric cancer patients in a tertiary care hospital: an observational study. Oncol J India 2021;5(2):76.
31. Allen HC, Garbe MC, Lees J, et al. Off-label medication use in children, more common than we think: a systematic review of the literature. J Okla State Med Assoc 2018;111(8):776–783 https://pubmed.ncbi.nlm.nih.gov/31379392.
32. Pharmaceutical Services Programme M of HM. Consent form for treatment using medicine with unregistered indication (off label). https://www.pharmacy.gov.my/v2/sites/default/files/document-upload/consent-form-updated-28-august.pdf June 14, 2022.
33. Syed SA, Dixson BA, Constantino E, Regan J. The law and practice of off-label prescribing and physician promotion. J Am Acad Psychiatry Law Online November 24, 2020. https://doi.org/10.29158/JAAPL.200049-20.JAAPL.200049–20.
34. van der Zanden TM, de Wildt SN, Liem Y, Offringa M, de Hoog M. Developing a paediatric drug formulary for the Netherlands. Arch Dis Child 2017;102(4):357–361.
35. Van der Zanden T, Neubert A, Zahn J, et al. P101 extending the Dutch Paediatric formulary across Europe: successful development of country specific, parallel, paediatric drug formulariesPublished online. . 2019.
36. Balan S, Koo K, Omar AI, Gan RY. Analysis of adverse drug reactions reported in a tertiary care children hospital. Res Soc Adm Pharm RSAP 2022:S1551–S7411.
37. Berger ML, Sox H, Willke RJ, et al. Good practices for real-world data studies of treatment and/or comparative effectiveness: recommendations from the joint ISPOR-ISPE special task force on real-world evidence in health care decision making. Value Health 2017;20(8):1003–1008.