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AN ALGORITHMS FOR THE OPERATIONAL ASSESSMENT OF ADVERSE DRUG REACTIONS

Algorithm for the operational assessment of adverse drug reactions มีรายละเอียดดังต่อไปนี้
Algorithm ประกอบด้วย 6 axis คือ

Axis I : Previous general experience with the drug

จุดประสงค์ของข้อนี้เพื่อดูว่ายาที่ผู้ป่วยได้รับนั้นเคยมีรายงานและเป็นที่ยอมรับแล้วว่าเป็นสาเหตุของการเกิดผื่นแพ้ยาได้

Axis 2 : Alternative etiologic candidates

จุดประสงค์ของข้อนี้คือเพื่อหาสาเหตุของการเกิดผื่นในผู้ป่วยว่า อาจเกิดจากสาเหตุอื่นที่ไม่ใช่การแพ้ยาได้หรือไม่ เช่น เกิดจาก Underlying clinical conditions, diagnostic or therapeutic interventions เป็นต้น

Axis 3 : Timing of events

จุดประสงค์ของข้อนี้คือการพิจารณาความเหมาะสมและความเป็นไปได้ว่าระยะเวลาตั้งแต่การได้รับยาจนถึงการเกิดผื่นในผู้ป่วยนั้นอยู่ในช่วงเวลาที่เหมาะสมเป็นไปได้หรือไม่

Axis 4 : Drug levels and evidence of overdose

จุดประสงค์ของข้อนี้เพื่อช่วยตัดสินใจว่า อาการแสดงทางคลินิกของผู้ป่วยนั้นเกิดจากการได้รับยาเกินขนาดหรือไม่

Axis 5 : Dechallenge ข้อนี้ยังแบ่งย่อยออกเป็น 3 ส่วนดังนี้

5A : Difficult assessments หมายถึงในกรณีที่ clinical manifestations that are difficult or impossible to assess because they are either irreversible or transient and episodic และยังรวมถึงกรณีที่เมื่อหยุดยาแล้วผื่นในผู้ป่วยก็ยังไม่ดีขึ้นหรือยังไม่หายหลังจากหยุดยาที่คิดว่าเป็นสาเหตุแล้ว

5B : Absence of dechallenge หมายถึงในกรณีที่ผื่นหรืออาการแสดงทางคลินิกของผู้ป่วยมีการเปลี่ยนแปลงในทางที่ดีขึ้นแม้ว่ายังไม่ได้หยุดยาที่คิดว่าเป็นสาเหตุซึ่งในกรณีนี้ผู้ป่วยอาจเกิดจากความทนต่อยาหรือได้รับการรักษาอื่นๆที่สามารถช่วยลดความรุนแรงของลักษณะอาการทางคลินิก

5C : Improvement after dechallenge หมายถึงในกรณีที่อาการแสดงทางคลินิกของผู้ป่วยดีขึ้นหลังจากที่ได้หยุดยาที่คิดว่าเป็นสาเหตุแล้วซึ่งอาจจะเกิดจาก coincidental improvement in a good alternative etiologic candidate

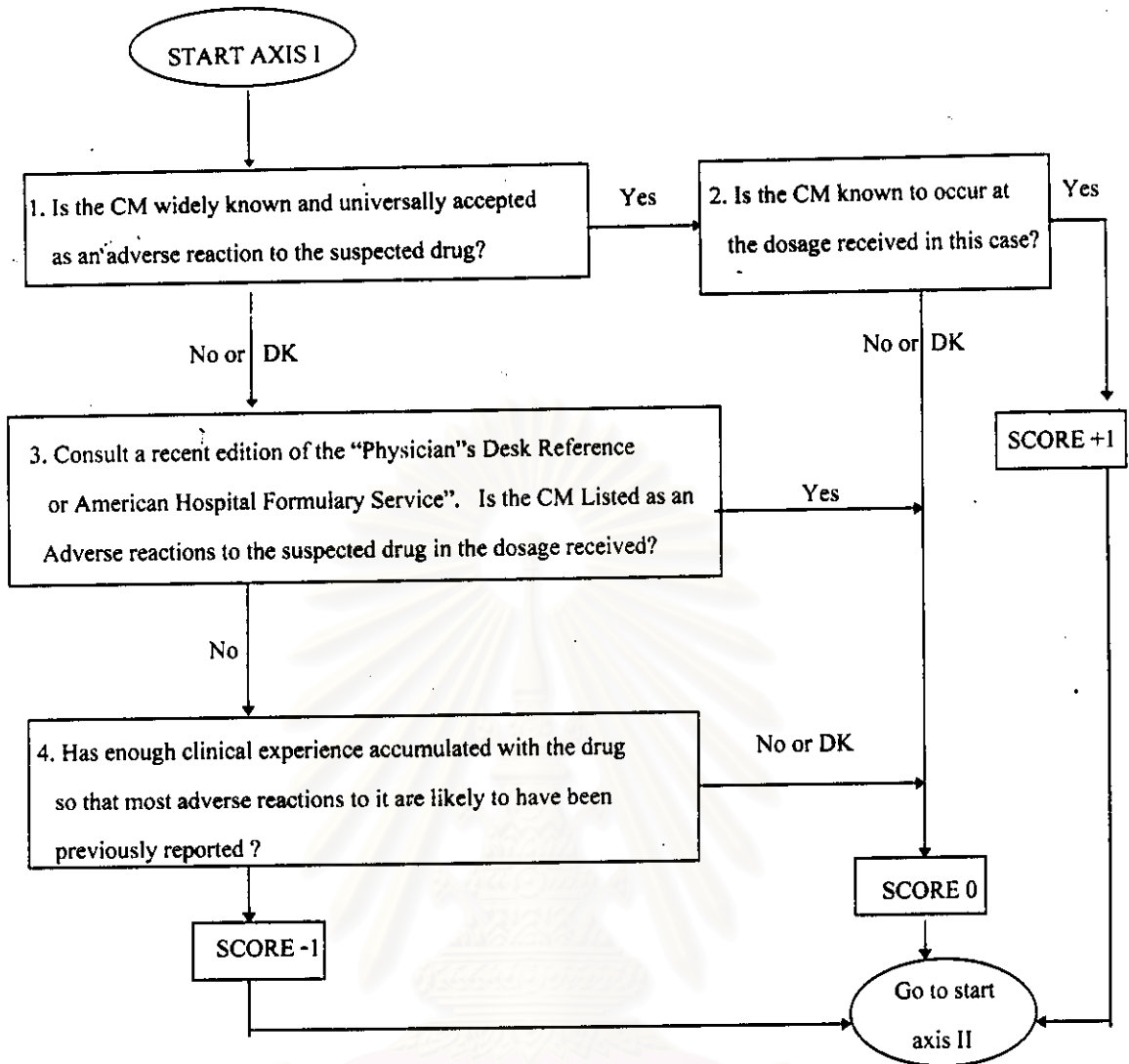
Axis 6 : Rechallenge

ข้อนี้เป็นการให้ผู้ป่วยได้รับยาที่คิดว่าเป็นสาเหตุเข้าไปอีกครั้งหนึ่งแล้วดูว่าเกิดผื่นขึ้นอีกครั้งหรือไม่ ซึ่งหากเกิดผื่นขึ้นใหม่ต้องพิจารณาด้วยว่ามีสาเหตุอื่นๆที่เป็นไปได้ร่วมอยู่หรือไม่ เช่น new clinical conditions or recent interventions เป็นต้น

โดยในแต่ละ Axis จะให้คะแนน +1, 0, -1 (ยกเว้น Axis 2, Axis 3 ที่จะมีคะแนน +2, +1, 0, -1, -2) โดยขั้นตอนการให้คะแนนในแต่ละ Axis ดังแสดงในแผนภูมิต่อไปนี้



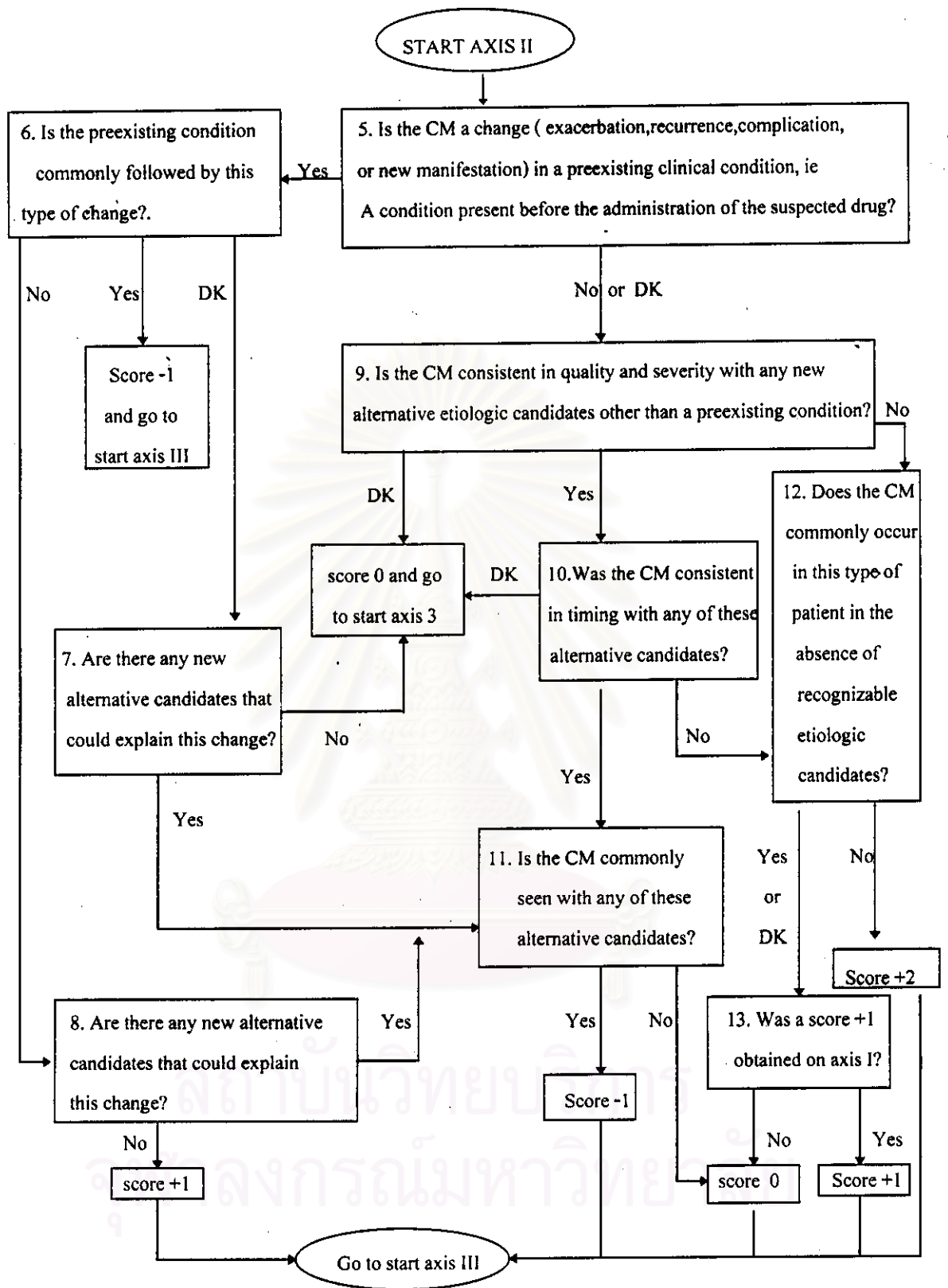
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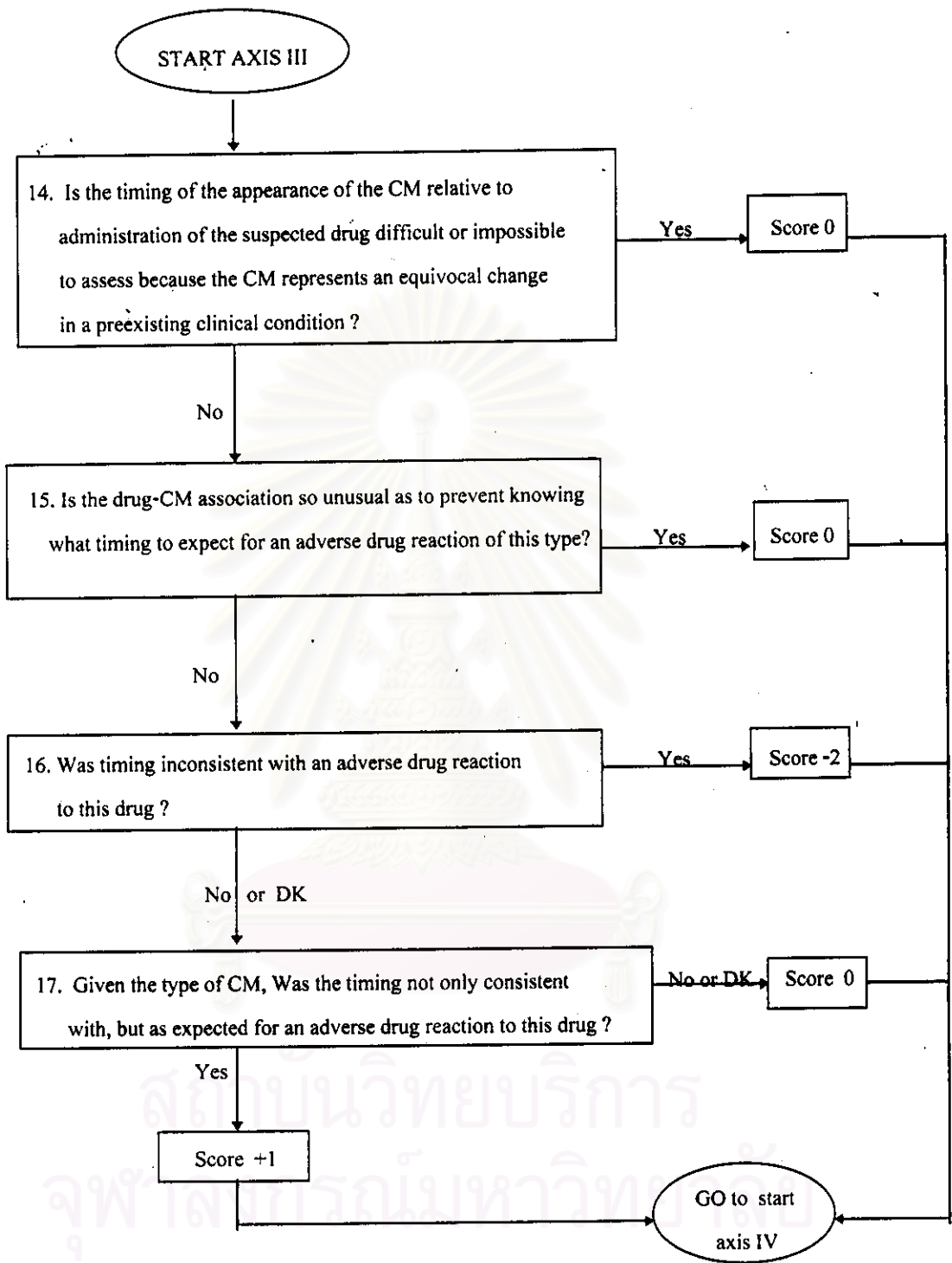


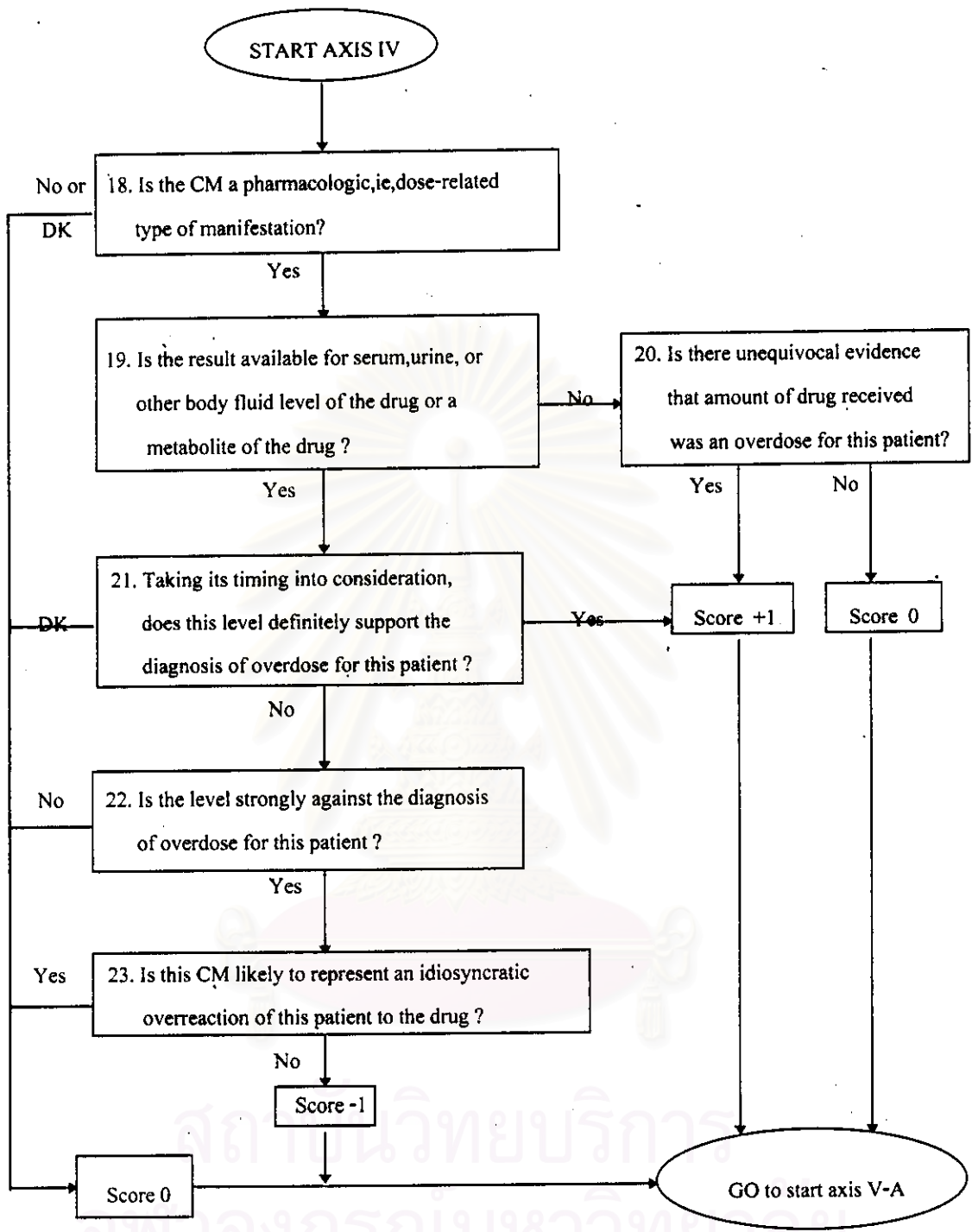
Consult "MARTINDALE The Extra Pharmacopoeia twenty-nine edition" in this project.

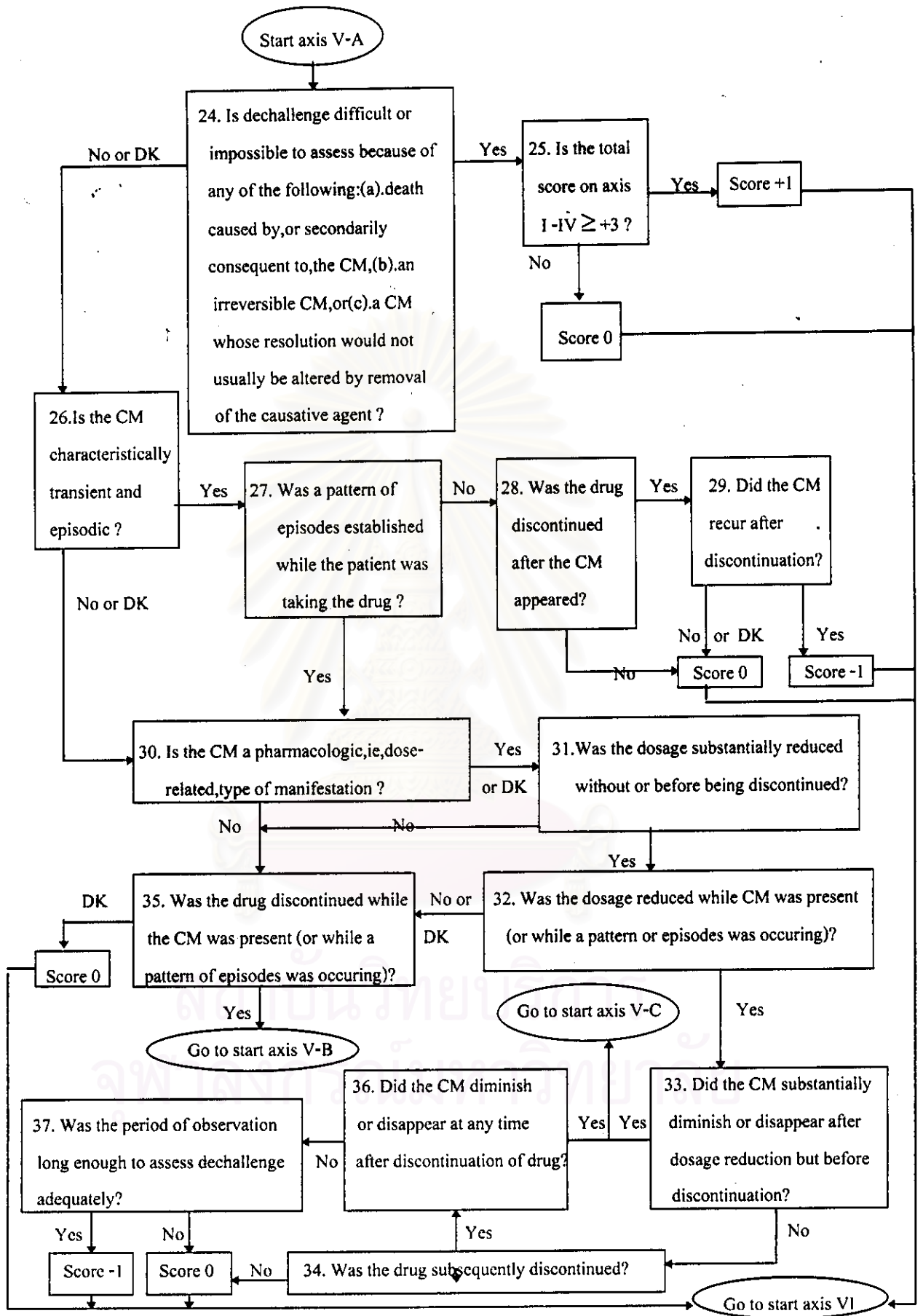
DK = DO NOT KNOW , CM = CLINICAL MANIFESTATION

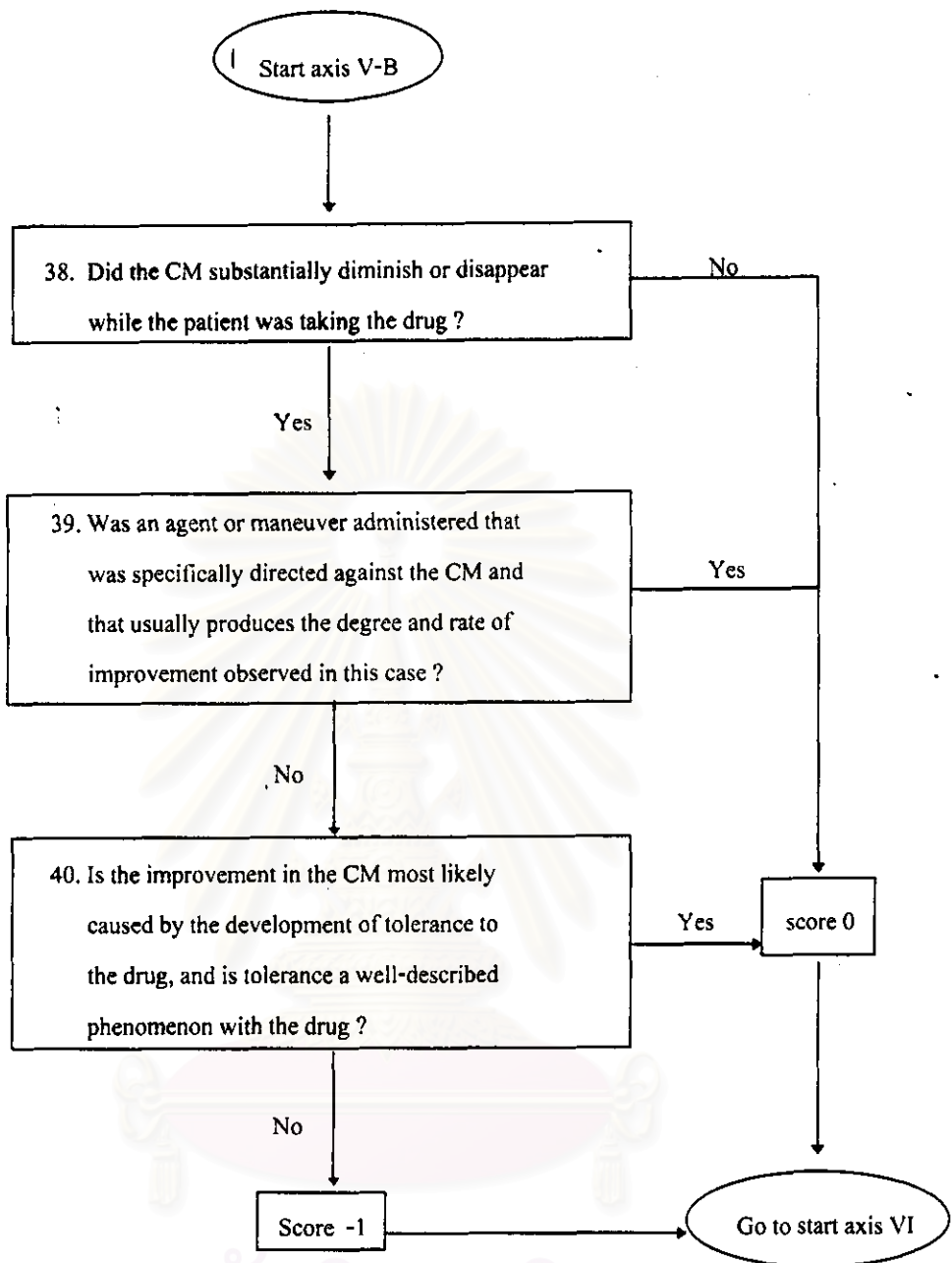
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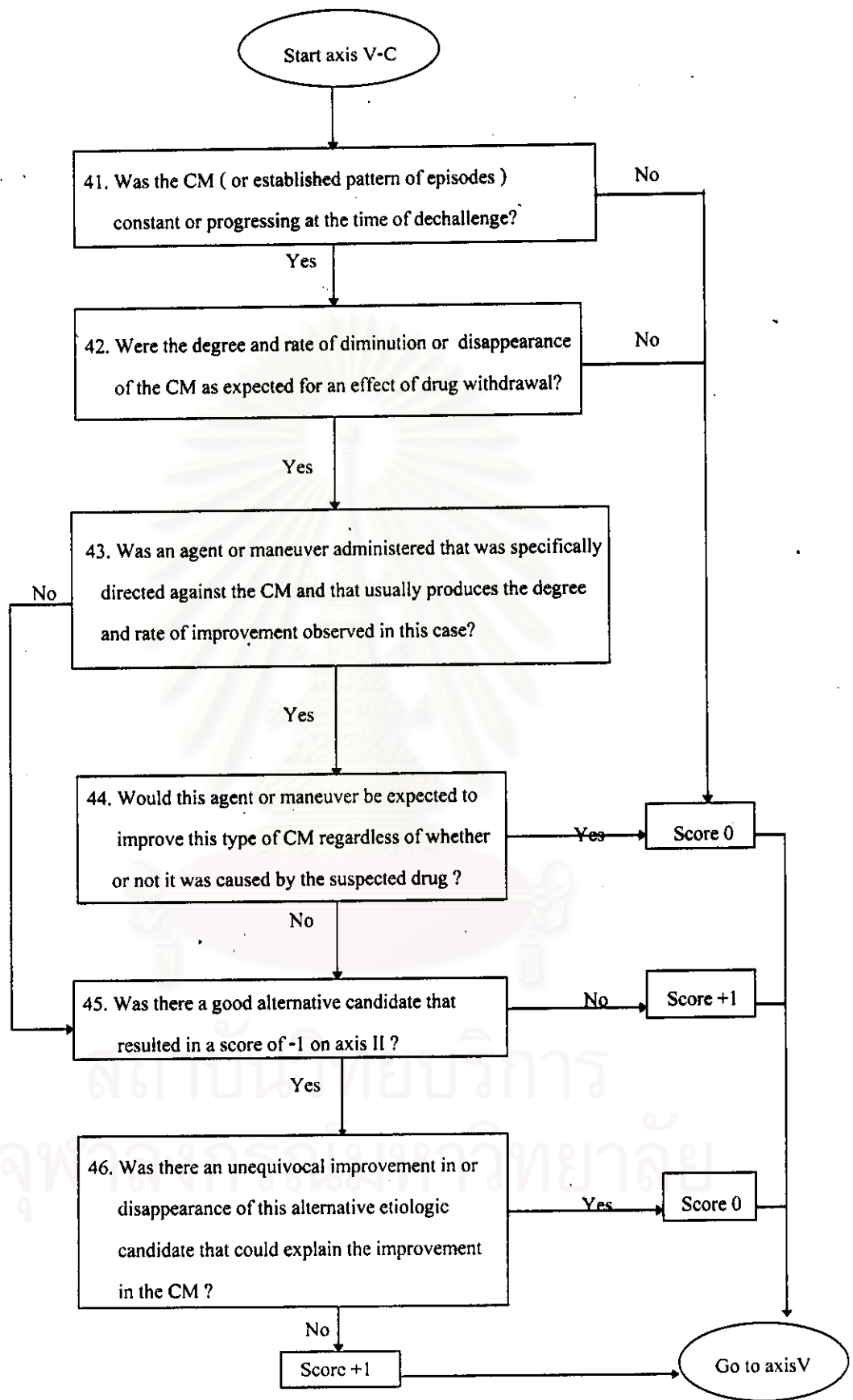


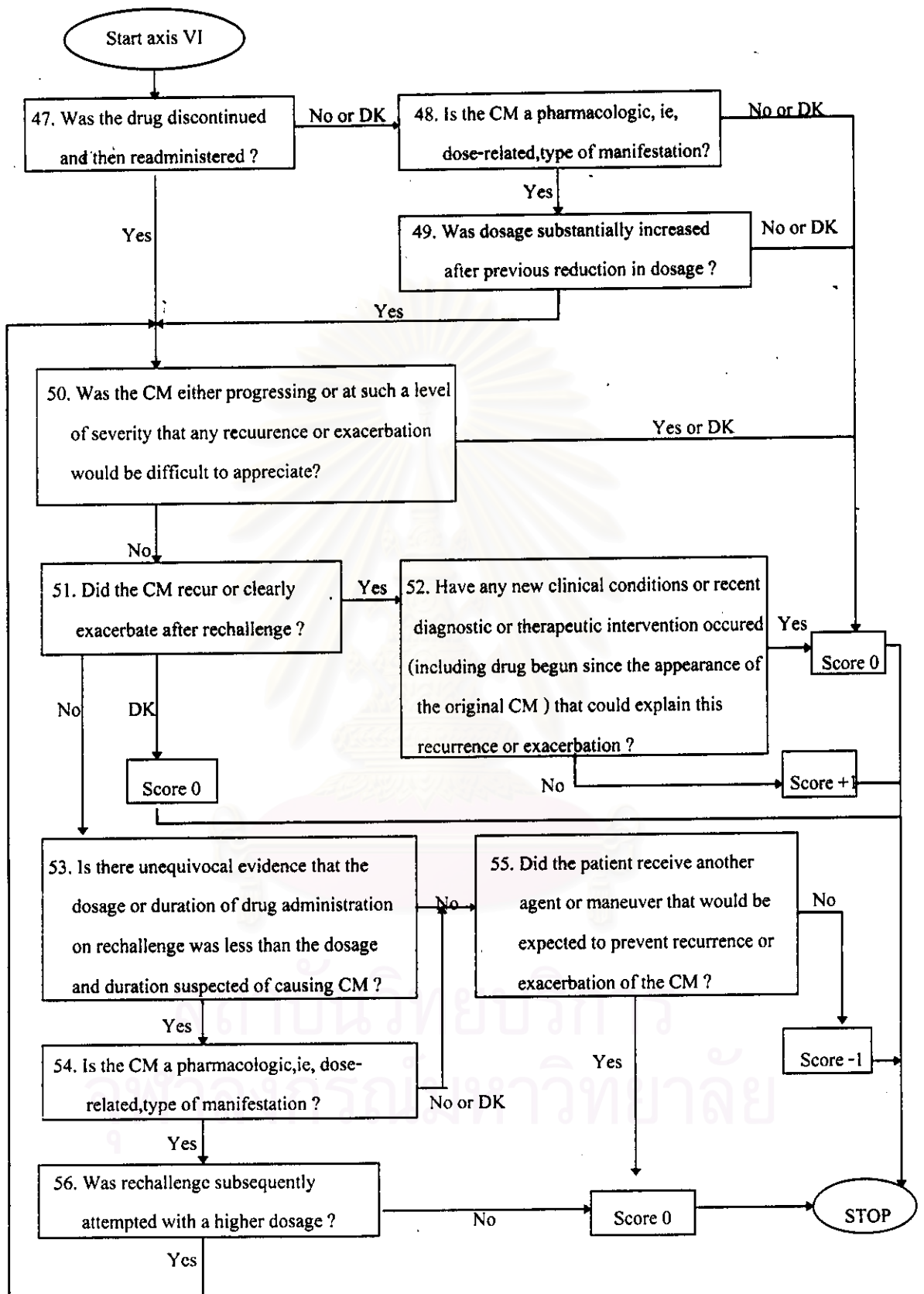






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OUTLINE OF SCORING STRATEGY

Score	+1	0	-1
Axis 1	CM well accepted as ADR to suspected drug	CM is not well known or drug is new	CM previously unreported as ADR to well-known drug
Axis 2	(a).No good alternative candidate(score +2); or (b).Otherwise unexplained exacerbation or recurrence of underlying illness (score +1)	Candidate(s) exist, but no good ones	Good alternative candidate
Axis 3	Timing as expected for ADR for this drug-CM pair	Timing equivocal or nonassessable	Timing inconsistent for ADR for this drug-CM pair (score -2)
Axis 4	Drug level or other data provide unequivocal evidence of overdose	Unobtained, unknown, or equivocal level or other evidence of overdose	Drug level strongly against overdose
Axis 5	(a).CM improves suitably after dechallenge ; or (b).Nature of CM prevent assessment of dechallenge for otherwise likely ADR	(a).CM improved,but degree or rate are unexpected ; or (b).CM is treated by auxiliary maneuver	(a).CM improves without dechallenge ; or (b).Potentially reversible CM fails to improve after dechallenge
Axis 6	CM unequivocally recurs or exacerbates on rechallenge	(a).No rechallenge attempted ; or (b).Response of CM obscured by auxiliary maneuver	CM fails to recur or exacerbate on rechallenge

CM = indicates clinical manifestation

ADR = adverse drug reaction

AXIS 1 2 3 4 5 6 TOTAL
 SCORE + + + + + =

SCORING TRANSFORMATION

NUMERICAL SCORE	ORDINAL CATEGORY
+7,-6	DEFINITE
+5,-4	PROBABLE
+3,+2,+1,0	POSSIBLE
< 0	UNLIKELY

ซึ่งจากการใช้ algorithm นั้นจะสามารถช่วยสรุปยาที่เป็นสาเหตุของการแพ้ยาได้ ดังที่ได้
 บรรยายไว้ข้างต้นแล้ว ส่วนในกรณีที่ผู้ป่วยได้ยาหลายชนิด (multiple drugs) ก็อาศัยการให้
 คะแนนยาแต่ละชนิดที่ผู้ป่วยได้รับตาม algorithm ยาชนิดใดได้คะแนนมากที่สุดก็น่าจะเป็นยาที่เป็น
 สาเหตุการแพ้ยามากที่สุดในผู้ป่วยแต่ละคน โดยโครงการวิจัยนี้ก็จะใช้ algorithm ในการตัดสินใจ
 ผู้ป่วยแพ้ยาหรือไม่ และ ยาใดน่าจะเป็นสาเหตุมากที่สุด

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ขั้นตอนการตอบคำถามใน algorithm

I. Previous general experience with the drug

1. Is the CM widely known and universally accepted as an ADR to the suspected drug ?
 - yes go to question 2
 - no or DK go to question 3
2. Is the CM known to occur at the dosage received in this case ?
 - yes score +1 in Axis 1 box and go to question 5
 - no or DK score 0 in Axis 1 box and go to question 5
3. Consult a recent edition of the Physicians' Desk Reference or American Hospital Formulary Service (Use "Martindale The Extrapharmacopoeia twenty-nine edition" in this project). Is the CM listed as an ADR to the suspected drug in the dosage received ?
 - yes score 0 in Axis 1 box and go to question 5
 - no go to question 4
4. Has enough clinical experience accumulated with the drug so that most ADRs to it are very likely to have been previously reported ?
 - yes score -1 in Axis 1 box and go to question 5
 - no or DK score 0 in Axis 1 box and go to question 5

II. Alternative etiologic candidates

5. Is the CM a change (exacerbation, recurrence, complication, or new manifestation) in a preexisting clinical condition, ie, a condition present before the administration of the suspected drug ?
 - yes go to question 6
 - no or DK go to question 9
6. Is the preexisting condition commonly followed by this type of change ?
 - yes score -1 in Axis 2 box and go to question 14
 - DK go to question 7
 - no go to question 8

7. Are there any new alternative candidates (illnesses developing after the suspected drug was begun or recent diagnostic or therapeutic interventions apart from the suspected drug or other drugs) that could explain this change ?

- yes go to question 11
- no score 0 in Axis 2 box and go to question 14

8. Are there any new alternative candidates (illnesses developing after the suspected drug was begun or recent diagnostic or therapeutic interventions apart from the suspected drug or other drugs) that could explain this change ?

- yes go to question 11
- no score +1 in Axis 2 box and go to question 14

9. Is the CM consistent in quality and severity with any new alternative etiologic candidates other than a preexistence condition, ie, illnesses developing after the suspected drug was begun or recent diagnostic or therapeutic interventions apart from the suspected drug or other drugs?

- yes go to question 10
- DK score 0 in Axis 2 box and go to question 14
- no go to question 12

10. Was the CM consistent in timing with any of these alternative candidates ?

- yes go to question 11
- DK score 0 in Axis 2 box and go to question 14
- no go to question 12

11. Is the CM commonly seen with any of these alternative candidates ?

- yes score -1 in Axis 2 box and go to question 14
- no score 0 in Axis 2 box and go to question 14

12. Does the CM commonly occur in this type of patient in the absence of recognizable etiologic candidates ? (Examples of such phenomena include headache, fatigue, and anxiety.)

- yes or DK go to question 13
- no score +2 in Axis 2 box and go to question 14

13. Was a score of +1 obtained on Axis 1 ?

- yes score +1 in Axis 2 box and go to question 14
- no score 0 in Axis 2 box and go to question 14

III. Timing of events

14. Is the timing of the appearance of the CM relative to administration of the suspected drug difficult or impossible to assess because the CM represents an equivocal change in the preexisting clinical condition ?

- yes score 0 in Axis 3 box and go to question 18
- no go to question 15

15. Is the drug-CM association so unusual as to prevent knowing what timing to expect for an ADR of this type ?

- yes score 0 in Axis 3 box and go to question 18
- no go to question 16

16. Was the timing inconsistent with an ADR to this drug ?

- yes score -2 in Axis 3 box and go to question 18
- no or DK go to question 17

17. Given the type of CM, was the timing not only consistent with, but as expected for ADR to this drug ?

- yes score +1 in Axis 3 box and go to question 18
- no or DK score 0 in Axis 3 box and go to question 18

IV. Drug levels and evidence of overdose

18. Is the CM a pharmacologic, ie, dose-related, type of manifestation ?

- yes go to question 19
- no or DK score 0 in Axis 4 box and go to question 24

19. Is the result available for serum, urine, or other body fluid level of the drug or a metabolite of the drug ?

- yes go to question 19
- no go to question 20

20. Is there unequivocal evidence that the amount of drug received was an overdose for this patient, eg, a blood glucose level of 30 mg/dl in a patient receiving insulin or discovery of an empty pill bottle of a newly filled prescription for the suspected drug ?

- yes score +1 in Axis 4 box and go to question 24

- no score 0 in Axis 4 box and go to question 24

21. Taking its timing into consideration, does this level definitely support the diagnosis of an overdose for this patient ?

- yes score +1 in Axis 4 box and go to question 24
- no go to question 22
- DK score 0 in Axis 4 box and go to question 24

22. Is the level strongly against the diagnosis of overdose for this patient ?

- yes go to question 23
- no score 0 in Axis 4 box and go to question 24

23. Is this CM likely to represent an idiosyncratic overreaction of this patient to the drug ?

- yes score 0 in Axis 4 box and go to question 24
- no score -1 in Axis 4 box and go to question 24

V. Dechallenge

24. Is dechallenge difficult or impossible to assess because of any of the following ?

- Death caused by, or secondarily consequent to the CM.
- An irreversible CM, eg, optic atrophy, aplastic anemia, loss of a limb.
- A CM whose resolution would not usually be altered by removal of the causative agent, eg, stroke, myocardial infarction (since, in these examples, the resolution of the organ damage would be expected to be independent of drug withdrawal.)

- yes go to question 25
- no go to question 26

25. Is the total score on Axis 1 through 4 $\geq +3$?

- yes score +1 in Axis 5 box and go to question 47
- no score 0 in Axis 5 box and go to question 47

26. Is the CM characteristically transient and episodic, eg, seizures, syncope, classic angina pectoris ? "Characteristically transient and episodic" means that the phenomenon, by its very nature, almost always resolves quickly and spontaneously. CMs that eventually show themselves as self-limited or that gradually subside on their own (eg, dyspnea, gastrointestinal bleeding,

ataxia) would thus not qualify as characteristically transient and episodic and should receive a "No" response.

- yes go to question 27
- no or DK go to question 30

27. Was a pattern of episodes established while the patient was taking the drug ?

- yes go to question 30
- no score 0 in Axis 5 box and go to question 47

28. Was the drug discontinued after the CM appeared ?

- yes go to question 29
- no score 0 in Axis 5 box and go to question 47

29. Did the CM recur after discontinuation ?

- yes score -1 in Axis 5 box and go to question 47
- no or DK score 0 in Axis 5 box and go to question 47

30. Is the CM a pharmacologic, ie, dose-related, type of manifestation ?

- yes or DK go to question 31
- no go to question 35

31. Was the dosage substantially reduced without or before being discontinued ?

- yes go to question 32
- no go to question 35

32. Was the dosage reduced while the CM was present (or while a pattern of episodes was occurring) ?

- yes go to question 33
- no or DK go to question 35

33. Did the CM substantially diminish or disappear after dosage reduction but before complete discontinuation ?

- yes go to question 41
- no go to question 34

34. Was the drug subsequently discontinued ?

- yes go to question 36
- no score 0 in Axis 5 box and go to question 47

35. Was the drug discontinued while the CM was present (or while a pattern of episodes was occurring)?

- yes go to question 36
- DK score 0 in Axis 5 box and go to question 47
- no go to question 38

36. Did the CM diminish or disappear at any time after discontinuation of the drug use ?

- yes go to question 41
- no go to question 37

37. Was the period of observation long enough to be sure that the CM would not subsequently diminish or disappear in a time compatible with an effect of drug withdrawal ?

- yes score -1 in Axis 5 box and go to question 47
- no score 0 in Axis 5 box and go to question 47

38. Did the CM substantially diminish or disappear while the patient was taking the drug?

- yes go to question 39
- no score 0 in Axis 5 box and go to question 47

39. Was an agent or maneuver administered that was specifically directed against the CM and that usually produces the degree and rate of improvement observed in this case ? (A nonspecific therapeutic measure would not qualify for "Yes" response to this question. Thus, the administration of intravenous fluids would result in a "No" response if the CM were coma caused by a drug overdose but a "Yes" response if the CM were dehydration.)

- yes score 0 in Axis 5 box and go to question 47
- no go to question 40

40. Is the improvement in the CM most likely caused by the development of tolerance to the drug, and is tolerance a well-described phenomenon with the drug ?

- yes score 0 in Axis 5 box and go to question 47
- no score -1 in Axis 5 box and go to question 47

41. Was the CM (or the established pattern of episodes) constant or progressing at the time of dechallenge?

- yes go to question 42
- no score 0 in Axis 5 box and go to question 47

42. Were the degree and rate of diminution or disappearance of the CM as expected for an effect of drug withdrawal?

- yes go to question 43
- no score 0 in Axis 5 box and go to question 47

43. Was an agent or maneuver administered that was specifically directed against the CM and that usually produces the degree and rate of improvement observed in this case ? (A nonspecific therapeutic measure would not qualify for a “Yes” response to this question. Thus, the administration of intravenous fluid would result in a “No” response if the CM were coma caused by a drug overdose but a “Yes” response if the CM were dehydration.)

- yes go to question 44
- no go to question 45

44. Would this agent or maneuver be expected to improve this type of CM regardless of whether or not it was caused by the suspected drug? (The administration of a narcotic antagonist to a patient with a CM of coma caused by morphine overdose would result in a “No” response, because the narcotic antagonist will only improve coma if it is caused by a narcotic.)

- yes score 0 in Axis 5 box and go to question 47
- no go to question 45

45. Was there a good alternative etiologic candidate that resulted in a score of -1 on Axis 2?

- yes go to question 46
- no score +1 in Axis 5 box and go to question 47

46. Was there an unequivocal improvement in or disappearance of this alternative etiologic candidate that could explain the improvement in the CM?

- yes score 0 in Axis 5 box and go to question 47
- no score +1 in Axis 5 box and go to question 47

VI. Rechallenge

47. Was the drug discontinued and then readministered ?

- yes go to question 50
- no go to question 48

48. Is the CM a pharmacologic, ie, dose-related, type of manifestation ?

- yes go to question 49
- no score 0 in Axis 6 box and go to question 57

49. Was the dosage substantially increased after previous reduction in dosage?

- yes go to question 50
- no or DK score 0 in Axis 6 box and go to question 57

50. Was the CM either progressing or at such a level of severity that any recurrence or exacerbation would be difficult to appreciate?

- yes score 0 in Axis 6 box and go to question 57
- no go to question 51

51. Did the CM recur or clearly exacerbate after rechallenge?

- yes go to question 52
- no go to question 53
- DK score 0 in Axis 6 box and go to question 57

52. Have any new clinical conditions or recent diagnostic or therapeutic interventions occurred (including drugs begun since the appearance of the original CM) that could explain this recurrence or exacerbation?

- yes score 0 in Axis 6 box and go to question 57
- no score +1 in Axis 6 box and go to question 57

53. Is there unequivocal evidence that the dosage or duration of drug administration on rechallenge was less than the dosage and duration suspected of causing the original CM?

- yes go to question 54
- no go to question 55

54. Is the original CM a pharmacologic, ie, dose-related, type of manifestation?

- yes go to question 56
- no go to question 55

55. Did the patient receive another agent or maneuver that would be expected to prevent recurrence or exacerbation of the CM ?

- yes score 0 in Axis 6 box and go to question 57
- no score -1 in Axis 6 box and go to question 57

56. Was rechallenge subsequently attempted with a higher dosage ?

- yes go back to question 50
- no score 0 in Axis 6 box and go to question 57

57. Stop reading the questionjaire, add up the scores in the six axis boxes on the cover sheet, and place the sum in the box marked "Total".



สถาบันวิทยบริการ
จุฬาลงกรณ์มหาวิทยาลัย

แบบฟอร์มข้อมูลผู้ป่วยในการศึกษาอุบัติการณ์ผื่นแพ้ยาในผู้ป่วยติดเชื้อเอชไอวี

เลขที่

1. วันที่
2. HN.
3. ชื่อ-นามสกุล
4. เพศ
5. อายุ ปี
6. ผู้ป่วย 1.) นอก 2.) ใน แผนก
7. ระยะของโรคติดเชื้อ HIV 1.) ASYMPTOMATIC HIV
..... 2.) SYMPTOMATIC HIV (AIDS-related complex)
..... 3.) AIDS
8. ลักษณะอาการทางคลินิกของผื่นแพ้ยา
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9. อาการร่วมอื่นๆ ของผื่นแพ้ยา
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10. ผลการตรวจร่างกายทางด้านผิวหนัง
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11. ผลการตรวจร่างกายทางระบบอื่นๆ

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12. DIAGNOSIS (TYPE OF DRUG ERUPTION)

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13. ผลการตรวจทางห้องปฏิบัติการ

CBC : Hb g% Hct % Wbc /mm³ Plt...../mm³
N % L % M % E % B %
UA : Sp gr prot glu Rbc Wbc
BUN mg/dl Cr mg/dl
LFT : Alb Glob TB DB SGOT SGPT..... AP
CD4+ CELL COUNNT /mm³

14. ยาที่สงสัยว่าน่าจะเป็นสาเหตุของผื่นแพ้ยา

- 1.) ได้ยามานาน
- 2.) ได้ยามานาน
- 3.) ได้ยามานาน

15. ผลการทำ ORAL RECHALLENGE TEST ด้วยยาที่สงสัยว่าน่าจะเป็นสาเหตุของผื่นแพ้ยา

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สถาบันวิทยบริการ
จุฬาลงกรณ์มหาวิทยาลัย

ประวัติผู้วิจัย

นายแพทย์ วิรัช รุจิแสงวิทยา เกิดเมื่อวันที่ 20 เมษายน พ.ศ. 2515 ที่กรุงเทพมหานคร สำเร็จการศึกษาแพทยศาสตรบัณฑิต จากคณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย เมื่อปี พ.ศ. 2539 ได้เข้าทำงานในตำแหน่งแพทย์ใช้ทุนที่โรงพยาบาลเจ้าพระยาอภัยภูเบศร จังหวัดปราจีนบุรี เป็นเวลา 1 ปี หลังจากนั้นได้ลาออกมาเพื่อเข้าศึกษาคณะระดับปริญญาโท สาขาวิชาอายุรศาสตร์ (ตจวิทยา) ที่ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย เมื่อวันที่ 1 มิถุนายน พ.ศ. 2540



สถาบันวิทยบริการ
จุฬาลงกรณ์มหาวิทยาลัย