CHAPTER V

SAFETY INDICATORS OF THE SMP FROM MODIFIED DELPHI METHOD

During September 7, 2004 to August 14, 2005, information regarding safety indicators of the SMP was obtained by means of a three-round modified Delphi method. The most reliable consensus based on opinion of a group of experts was performed. The experts were given a series of intensive rating questionnaires and asked to rate each item of safety indicators and give an elaborate feedback comments/opinion on each item. All expert identities were kept anonymous. Finally, 19 safety indicators of the SMP system were identified.

5.1 Conceptual Framework for Identifying Safety Indicators

A conceptual model used in this study was to help focus on identifying various safety indicators (Figure 5.1). Elements from the Total Quality Management model (TQM), i.e., structure, process and outcome were applied to help the Delphi experts to easily understand all elements and issues intertwining in the SMP system. Regarding the structure element based on the TQM model, **structure** components of the SMP system included 1) policy, laws, regulation and guideline related to the SMP, 2) organizations of the Thai FDA, drug company and hospital, 3) personnel in the Thai FDA, drug company and hospital/ health care facility, and 4) information system in the SMP.

Based on the process element provided by the TQM, major **process** components of the SMP acted as the connectors between structures and outcomes of the SMP. These process elements include evaluation process for new drug application to the SMP, risk (ADRs) management system, and evaluation process for releasing new drug from the SMP.

Finally, the **outcome** components were the results of both structure and process components. These outcomes were divided into three groups namely, administrative, safety and regulatory outcomes (Figure 5.1).

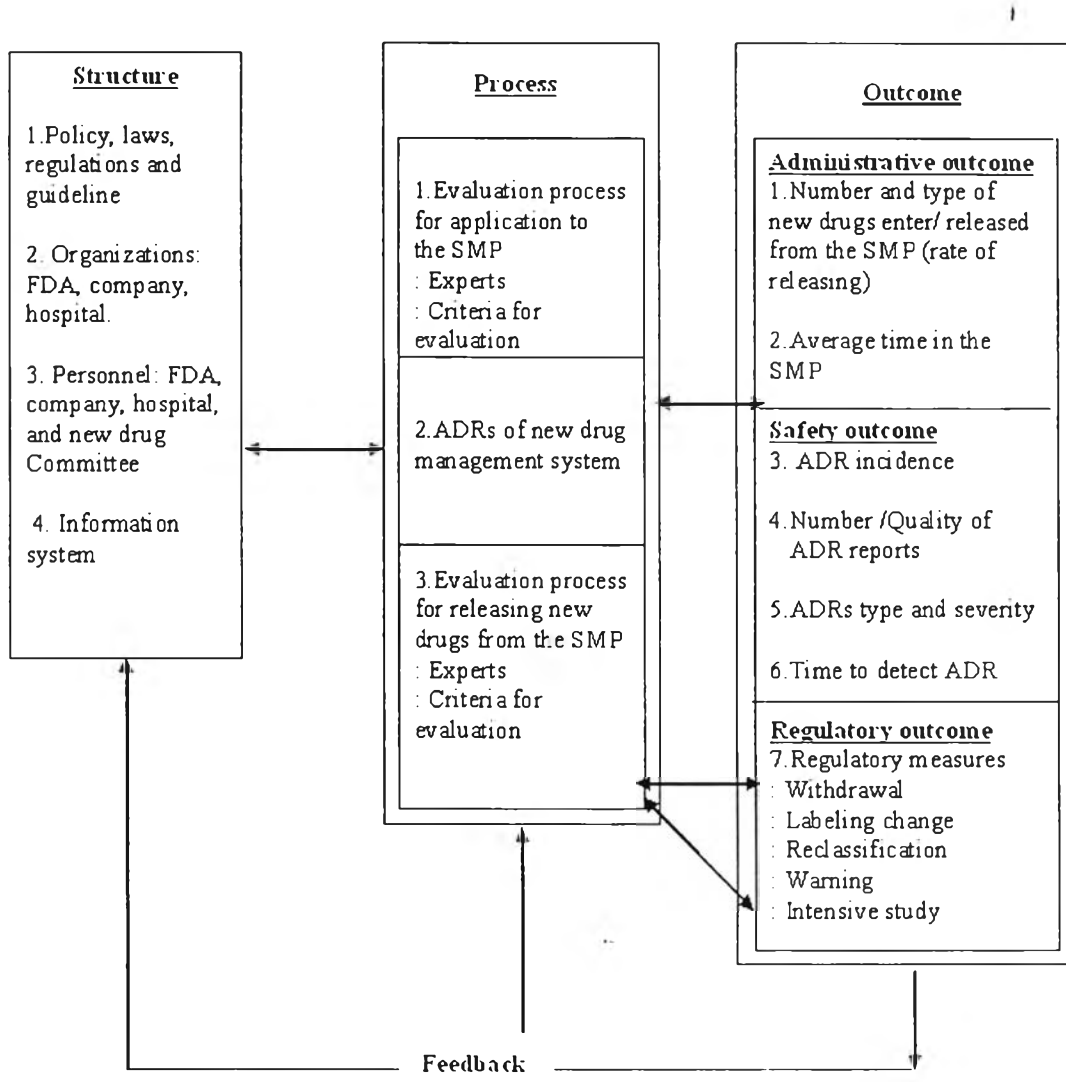

Figure 5.1 Conceptual Framework for Identifying Safety Indicators

5.2 The Modified Delphi Procedure

Delphi Panel

Forty-five persons were asked by telephone or in person contact to join expert panel in the study. These experts were from all kinds of stakeholders dealing with the SMP. These include Thai FDA officers involving in the establishment of the SMP and also those in the ongoing execution of the system, individuals from pharmaceutical companies, officers from Department of Medical Sciences, Academicians from shool of Pharmacy and Medicine and health care professionals from various hospitals. Thirteen individuals declined to participate by varieties of reasons, such as, no longer in close contact with the SMP, no time to participate in the whole Delphi rounds, not keen in this area, and not involving the SMP. Finally 32 experts remained in the study expert panels (Figure 5.2).

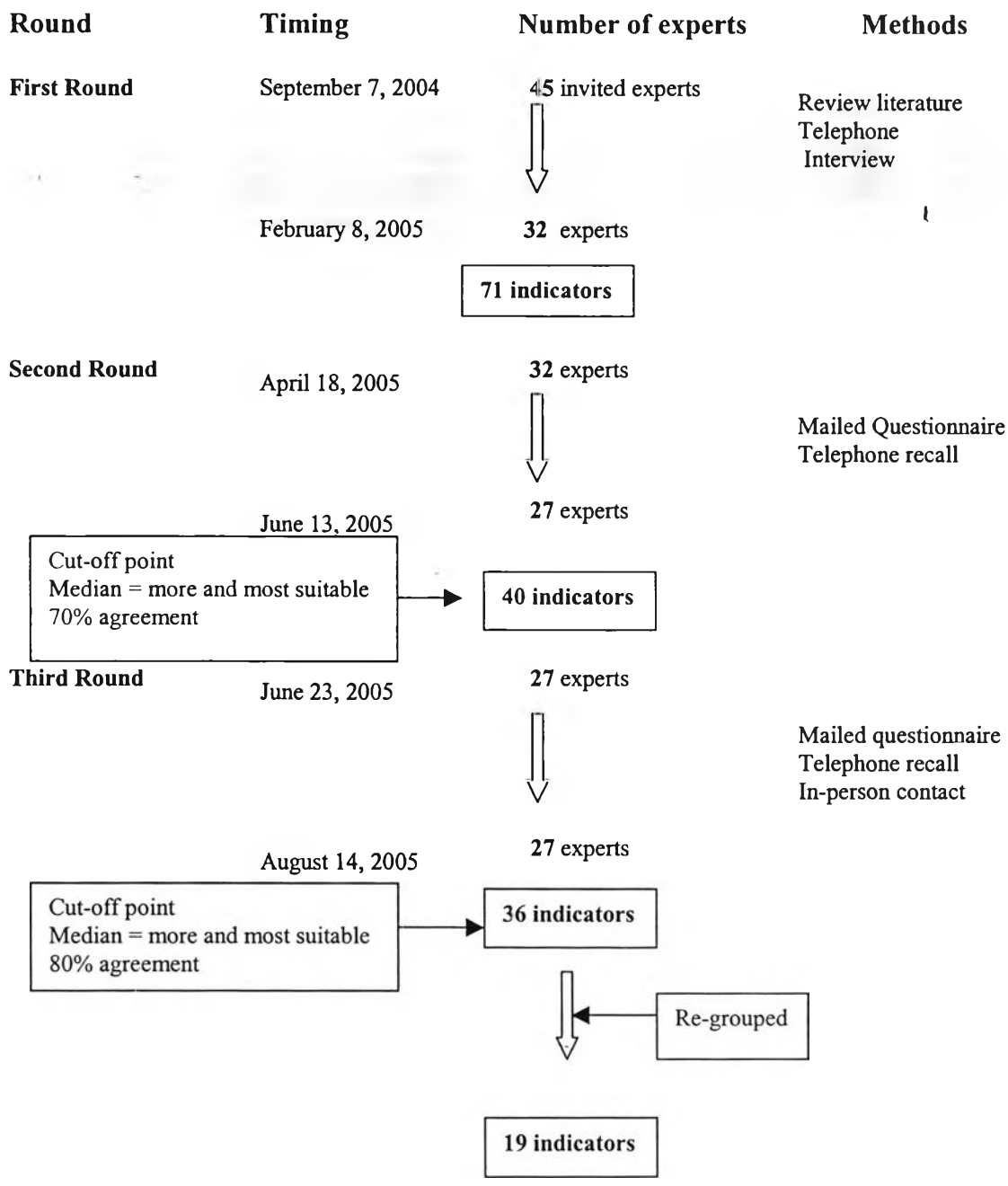

Figure 5.2 Procedure in the Modified Delphi Method

Three Rounds of Delphi

The First Round

The first round of Delphi method was performed from September 7, 2004 to February 8, 2005. This 5-month period was for contacts and interviews. The open-ended question asking what kinds of safety indicator of the SMP they know or have experiences with was mailed to all experts along with a brief explanation on the SMP system. One week after the experts received the question, the appointment for individual interview was set by telephone. During the interview, not only the items of safety indicators of the SMP system were obtained but also the clarifications or definitions of each item. These clarifications were used later to better define each of indicators in the second round. All safety indicators obtained from all 32 interviews and from literatures were synthesized and summarized into 71 safety indicators. These safety indicators were then mailed to the expert panel for the second round Delphi.

The Second Round

The second round of Delphi was conducted from April 18, 2005 to June 13, 2005, with one week for mailing the questionnaires and one month for follow-up). The questionnaire with 71 indicators was mailed all of 32 experts. In the questionnaire, 5-point rating scale was used for rating suitability of each indicator ranging from "most suitable" to "least suitable". Space next to each item and rating scale was provided for the experts to give reasons or arguments about their decision (Appendix). Telephone recalls were performed at 2 and 4 weeks after deadline. Five experts declined to participate at this stage, thus only 27 questionnaires were received. The reasons for declining were mainly having too much work to participate in the Delphi. A lost contact happened in one expert during the follow- up period.

Responses on questionnaire from the experts were pooled and median and percentage of agreement of each indicator were calculated. Only agreement rating of "most suitable" and "more suitable" were defined as "agreed." Each indicator had to gain at least 70% of agreed rating to be candidate in the final Delphi round. Based on the 70% criteria, 40 indicators with at least 70% agreement were selected. Comments,

concerns and arguments obtained from the experts on each indicator were also given along with the rating scale.

The Final Round

Questionnaire of 40 indicators with a remarkable "Final Decision" notification was mailed to 27 experts. The **final round** was performed during June 23, 2005 to August 14, 2005, with 1 week for mailing and one month for follow-up). As described previously, comments, concerns and arguments from the second round were also given to help the experts better understand other people reasoning, and finally to assist their decision making on each indicator.

After telephone and, in some case, in-person recalls, complete questionnaires from all 27 experts were returned. The safety indicators were selected using the same techniques as in the second round but a higher level of agreement (80% instead of 70%) was set to capture the most suitable indicators. As a result, only 19 safety indicators remained.

5.3 Characteristics of Delphi Experts

Of these 32 experts, 9 were the FDA officers, 7 were FDA external experts, 3 were physicians from hospitals, 4 were hospital pharmacists, 7 were pharmacist from drug companies, 1 was pharmacist in academic and 1 physician in clinic (Table 5.1). Five experts who left the study in the second and third rounds were 1 FDA officer, 2 FDA external experts and 2 physicians from hospitals. As a result the final number of 27 experts included 8 FDA officers, 5 FDA external experts, 1 physician from hospital, 4 hospital pharmacists, 7 pharmacists from drug company, 1 pharmacist in academic and 1 physician in clinic. Percentage of the remainders in the third to the first round was 84.37% (27 of 32 persons).

A large portion of expertise was from pharmacy. It was found that in the first round, there were 22 Pharmacists (68.75 %) and 10 physicians (31.25%). With a decline to participate among physicians, proportion of pharmacists to physicians was

further bigger with 21 Pharmacists (77.77 %) and 6 physicians (22.22%) in the second and final rounds.

When categorized into types of stakeholders involving in the SMP, in the first round, the majority of these experts was external experts (16 or 50.00%), followed by FDA officers (9 or 28.12%) and persons from drug company (7 or 21.88%). In the final round, external experts was still a majority (12 or 44.44%), followed by FDA officers and persons from drug company (Table 5.1).

Table 5.1 Type of Experts in each Round

Type of experts	First round (n=32)		Second round (n=27)		Third round (n=27)	
	Frequency	(%)	Frequency	(%)	Frequency	(%)
Type of experts						
FDA officer	9	(28.12)	8	(29.63)	8	(29.63)
FDA external expert	7	(21.88)	5	(18.52)	5	(18.52)
Physician at hospital	3	(9.38)	1	(3.70)	1	(3.70)
Pharmacist at hospital	4	(12.50)	4	(14.82)	4	(14.82)
Drug company	7	(21.88)	7	(25.93)	7	(25.93)
Pharmacist in academic	1	(3.13)	1	(3.70)	1	(3.70)
Physician in clinic	1	(3.13)	1	(3.70)	1	(3.70)
Stakeholders in the SMP						
FDA officer	9	(28.12)	8	(29.63)	8	(29.63)
FDA external expert	16	(50.00)	12	(44.44)	12	(44.44)
Drug company	7	(21.88)	7	(25.93)	7	(25.93)

5.4 Safety Indicators of the SMP in Each Round

5.4.1 Safety Indicators of the SMP from the First Round

Seventy-one safety indicators of the SMP were identified by the 32 experts in the first round. Of these 71 indicators, 29 were structure indicators, 17 process indicators and 25 outcome indicators (Table 5.2- Table 5.4).

Of 29 structure indicators, 10 indicators were related to policy, law, regulation and guideline, 2 indicators were related to organization element, 5 indicators were involving in personnel element, and 12 indicators were related to information system in the SMP (Table 5.2).

Table 5.2 Safety Indicators of the SMP from the First Round: **29 Structure indicators**

Type of indicator (Number)	No	Safety Indicators of the SMP
Policy , law, regulation and guideline (10)	1	SMP evaluation system
	2	National policy of safety monitoring of new drug
	3	Systematic safety monitoring of new drug at national level
	4	Systematic safety monitoring of new drug at hospital level
	5	New drug have to be available in countries which having good monitoring
	6	Hospitals report new drug use profile directly to FDA
	7	Certain law assigning drug company to be responsible for monitoring new drug safety
	8	Certain guideline for new drug safety monitoring procedure in FDA
	9	Certain criteria for the expert consideration
	10	Certain guideline for new drug safety monitoring procedure in drug company
Organization (2)	11	Quality in drug manufacturing
	12	Safety monitoring system in drug company
Personnel (5)	13	Certain personnel in safety monitoring activity in company
	14	Sufficient staffs in FDA for performing safety monitoring
	15	Experienced staffs in FDA for performing safety monitoring
	16	Experienced experts in new drug
	17	Experienced responsible person in drug company
Information system (12)	18	ADR database linkage to WHO
	19	Information of new drug in text book
	20	Information of new drug from drug company
	21	Information of new drug from literature
	22	Information of mechanism of action of new drug
	23	Information of therapeutic index of new drug
	24	Information of drug interaction of new drug
	25	Information of ADR in clinical trial period
	26	Background information of drug mechanism of drug group
	27	Information of Indication and contraindication of new drug
	28	Information of regulatory measures of new drugs in other countries
	29	Good information system, ready to use, in drug company

The first round Delphi resulted in 17 process indicators. These indicators were grouped into the indicator of an evaluation process for the application to the SMP (1 indicator), indicators of ADR management system (13 indicators) and indicators of the evaluation process for releasing from the SMP (3 indicators) (Table 5.3).

Table 5.3 Safety Indicators of the SMP from the First Round: **17 Process Indicators**

Type of indicator (Number)		**Safety Indicators of the SMP**
Evaluation process for application to the SMP (1)	1	Relevant criteria for each type of new drugs
ADRs management system (13)	2	Limitation of patient use or institution in a certain period
	3	Awareness of health professional in the SMP
	4	Co-operation of health professional in reporting ADR of new drug
	5	Validity in ADR reporting from health professional
	6	Strictly performing in collecting ADR of drug company
	7	Risk detection system
	8	Risk assessment system
	9	Risk management system
	10	Risk communication system
	11	Awareness of new drug in patient
	12	Concern of new drug use in physician
	13	Timely reporting of ADR
	14	Precise and timely ADR assessment procedure
Evaluation process for releasing from the SMP (3)	15	Certain criteria for the SMP releasing process
	16	Asking for more ADR profiles when there is insufficient data
	17	Transparency and accountability procedures in the SMP

Twenty-five outcome indicators were identified from the first round. These included 2 administrative, 19 safety and 4 regulatory outcome indicators.

Table 5.4 Safety Indicators of the SMP from the First Round: **25 Outcome indicators**

Type of indicator (Number)		**Safety Indicators of the SMP**
Administrative outcome (2)	1	Number of drug entered and released from the SMP
	2	Timing of new drug in the SMP period
Safety indicator (19)	3	Incidence of ADR
	4	Incidence of ADR (per volume of drug use)
	5	Incidence of ADR (per Defined Daily Dose:DDD)
	6	Incidence of ADR (per number of patient use)
	7	Sufficient number of new drug exposed patients
	8	Case report of ADR in Thailand
	9	Case report of ADR from world wide
	10	Efficiency in ADR reporting in Thailand
	11	Sufficient number of ADR report
	12	Detection of serious ADR
	13	Detection of serious ADR type A
	14	Detection of serious ADR type B
	15	Detection of unlabelled ADR
	16	Detection of death from ADR
	17	Detection of permanent ADR
	18	Detection of non-permanent ADR
	19	Detection of ADR causing uncomfortable in every day life
	20	Information shows benefit of new drug outweigh ADR
	21	Time for detecting ADR after drug marketed
Regulatory outcome (4)	22	Number of withdrawn drug during the SMP period
	23	Labeling changes due to ADR of new drug
	24	Adjustment of drug status/classification due to ADR of new drug
	25	Times for labeling changes from ADR after drug marketed

5.4.2 Safety Indicators of the SMP from the Second Round

Of the 71 indicators from the first round, only 40 indicators remained. They were 17 structure, 12 process and 11 outcome indicators (Table 5.5-Table 5.7).

Among 17 structure indicators, 5 of 10 indicators from the first round remained. These indicators were related to policy, law, regulation and guideline. In addition, 1 of 2 indicators of organization element and 4 of 5 indicators of personnel indicators were chosen. For the indicators related to the information system, 7 from 12 indicators were selected (Table 5.5).

The highest rated indicators were "experienced experts on new drug" (95.83% agreement), followed by "systematic safety monitoring of new drug at hospital level" (88.00% agreement), and the "information of therapeutic index of new drug and information of drug interaction of new drug" with an 86.96% agreement (Table 5.5).

In terms of the median of rating, there was no indicator consensus given a level of "most suitable." Only the indicator named "certain criteria for expert consideration" received the highest consensus level of between "more suitable" and "most suitable."

Table 5.5 Safety Indicators of the SMP from the Second Round: **17 Structure indicators**

Type of indicator (Number)	No. in Round 1	No. in Round 2	Safety Indicators of the SMP	Median	% Agreement (70% cut point)
Policy , law, regulation and guideline (5)	3	1	Systematic safety monitoring of new drug at national level	more suitable	76.92
	4	2	Systematic safety monitoring of new drug at hospital level	more suitable	88.00
	7	3	Certain law assigning drug company to be responsible for monitoring new drug safety	more suitable	70.83
	8	4	Certain guideline for new drug safety monitoring procedure in FDA	more suitable	84.00
	9	5	Certain criteria for the expert consideration	more - most suitable	75.00

Table 5.5 Safety Indicators of the SMP from the Second Round: **17 Structure indicators** (Continue)

Type of indicator (Number)	No. in Round 1	No. in Round 2	Safety Indicators of the SMP	Median	% Agreement (70% cut point)
Organization (1)	12	6	Safety monitoring system in drug company	more suitable	76.92
	13	7	Certain personnel in safety monitoring activity in company	more suitable	72.00
Personnel (4)	15	8	Experienced staffs in FDA for performing safety monitoring	more suitable	70.83
	16	9	Experienced experts in new drug	more suitable	95.83
	17	10	Experienced responsible person in drug company	more suitable	79.17
	18	11	ADR database linkage to WHO	more suitable	73.08
	21	12	Information of new drug from literature	more suitable	86.96
	23	13	Information of therapeutic index of new drug	more suitable	86.96
Information system (7)	24	14	Information of drug interaction of new drug	more suitable	82.60
	25	15	Information of ADR in clinical trial period	more suitable	75.00
	27	16	Information of Indication and contraindication of new drug	more suitable	70.83
	28	17	Information of regulatory measures of new drugs in other countries	more suitable	83.33

From 17 process indicators in the first round, only 12 passed the criteria in the second round. One indicator of the evaluation process for the application to the SMP was retained since the first round. Nine indicators relating to ADR management system passed the criteria applying to 13 indicators from the previous round. There remained 2 of 3 indicators of evaluation process for releasing new drug from the SMP (Table 5.6).

The process indicator called "certain criteria for the SMP releasing" received the highest agreement of 95.83%. The process indicators with the second highest agreement were "precise and timely ADR assessment procedure," and "transparency

and accountability procedures in the SMP," both with agreement of 87.50%. "Risk assessment" with an 80.77% agreement was the third-ranked process indicator.

Among these 12 process indicators, only 4 indicators were rated the most suitable indicator. These indicators included 1) co-operation of health professional in reporting ADR of new drug, 2) validity in ADR reporting from health professional, 3) strictly performing in collecting ADR of drug company, and 4) transparency and accountability procedures in the SMP (Table 5.6).

Table 5.6 Safety Indicators of the SMP from the Second Round: **12 Process indicators**

Type of indicator (number)	No. in Round 1	No. in Round 2	Safety Indicators of the SMP	Round 2 (n=27) Median	% Agreement (70% cut point)
Evaluation process for application to the SMP (1)	1	1	Relevant criteria for each type of new drugs	more suitable	76.00
ADR management system (9)	4	2	Co-operation of health professional in reporting ADR of new drug	most suitable	76.00
	5	3	Validity in ADR reporting from health professional	most suitable	76.00
	6	4	Strictly performing in collecting ADR of drug company	most suitable	80.00
	7	5	Risk detection system	more suitable	76.92
	8	6	Risk assessment system	more suitable	80.77
	9	7	Risk management system	more suitable	76.92
	10	8	Risk communication system	more suitable	73.08
	13	9	Timely reporting of ADR	more suitable	72.00
	14	10	Precise and timely ADR assessment procedure	more suitable	87.50
Evaluation process for releasing from the SMP (2)	15	11	Certain criteria for the SMP releasing process	more suitable	95.83
	17	12	Transparency and accountability procedures in the SMP	most suitable	87.50

None of indicators of administrative and regulatory outcomes from the first round met the criteria. Therefore all of these indicators were excluded from outcome

elements. Of 19 safety related indicators from the first round, 11 indicators passed the criteria of 70% agreement (Table 5.7).

The highest agreement of consensus was found in the indicator called "detection of death from ADR" (84%), followed by the indicator "efficiency in ADR reporting in Thailand" (83.33%), and "case report of ADR from world wide" (76.92%).

The indicator "detection of death from ADR indicator" was rated the most suitable indicator, while others received a "more suitable" level (Table 5.7).

Table 5.7 Safety Indicators of the SMP from the Second Round: **11 Outcome Indicators**

Type of indicators	No. in Round 1	No. in Round 2	Safety Indicators of the SMP	Round 2 (n=27) Median	% Agreement (70% cut point)
Safety indicator (11)	3	1	Incidence of ADR	more suitable	73.08
	6	2	Incidence of ADR (per number of patient use)	more suitable	74.07
	7	3	Sufficient number of new drug exposed patients	more suitable	70.37
	9	4	Case report of ADR from world wide	more suitable	76.92
	10	5	Efficiency in ADR reporting in Thailand	more suitable	83.33
	12	6	Detection of serious ADR	more suitable	72.00
	13	7	Detection of serious ADR type A	more suitable	76.00
	14	8	Detection of serious ADR type B	more suitable	72.00
	15	9	Detection of unlabelled ADR	more suitable	72.00
	16	10	Detection of death from ADR	**most suitable**	84.00
	17	11	Detection of permanent ADR	more suitable	76.00

5.4.3 Safety Indicators of the SMP from the Third Round:

With more specific criteria of 80% agreement or higher, a few more indicators were excluded in this round. Four of 40 indicators from the second round were eliminated due to a low level of agreement. The indicators retained in the third round were presented in Table 5.8-5.10.

Of 17 structure indicators, 3 indicators were eliminated, resulting in a final number of 14 indicators. Two of 5 indicators relating to policy, law, regulation and guideline were excluded, leaving 3 indicators in this round. In terms of organization element, an only indicator called "safety monitoring system in drug company" survived a more restrictive criteria in this round. Three indicators relating to personnel element and 7 indicators associating with information system were all kept in this final round (Table 5.8).

In this set of indicators, 2 indicators reached 100% agreement including the one called "ADR database linkage to WHO" and another called "information of ADR in clinical trial period." The other two indicators also received a high rated agreement level; the one called "systematic safety monitoring of new drug at hospital level" (96.30%) and another called "experienced expert in new drug" (92.31%) (Table 5.8).

In this final round, only one structure indicator, "information of ADR in clinical trial," was rated the most suitable indicator (Table 5.8).

Table 5.8 Safety Indicators of the SMP from the Third Round: **14 Structure indicators**

Type of indicators	No. in Round 1	No. in Round 2	Safety Indicators of the SMP	Round 3 (n=27) Median	% Agreement (80% cut point)
Policy , law, regulation and guideline (3)	3	1	Systematic safety monitoring of new drug at national level	more suitable	88.89
	4	2	Systematic safety monitoring of new drug at hospital level	more suitable	96.30
	8	3	Certain guideline for new drug safety monitoring procedure in FDA	more suitable	85.19
Organization (1)	12	4	Safety monitoring system in drug company	more suitable	88.89
Personnel (3)	13	5	Certain personnel in safety monitoring activity in company	more suitable	85.19
	16	6	Experienced experts in new drug	more suitable	92.31
	17	7	Experienced responsible person in drug company	more suitable	88.89
Information system (7)	18	8	ADR database linkage to WHO	more suitable	100.00
	21	9	Information of new drug from literature	more suitable	81.48
	23	10	Information of therapeutic index of new drug	more suitable	88.89
	24	11	Information of drug interaction of new drug	more suitable	85.19
	25	12	Information of ADR in clinical trial period	**most suitable**	100.00
	27	13	Information of Indication and contraindication of new drug	more suitable	85.19
	28	14	Information of regulatory measures of new drugs in other countries	more suitable	88.89

In terms of process indicators, all 12 indicators from the second round were retained (Table 5.9). Again, these included 1 in component of evaluation process for application to the SMP, 9 in component of ADR management system, and 2 in component of evaluation process for releasing from the SMP.

The highest agreement (96.30%) was found in the indicator called "risk management system indicator," followed by "risk communication," "timely reporting of ADR" and "precise and timely ADR assessment" indicators each with a 92.59%

agreement, and finally "certain criteria for the SMP releasing process" indicator (96.15%).

Several indicators were rated the most suitable ones which included 1) co-operation of health professional in reporting ADR of new drug 2) validity in ADR reporting from health professional 3) strictly performing in collecting ADR of drug company 4) certain criteria for the SMP releasing process and 5) transparency and accountability procedures in the SMP (Table 5.9).

Table 5.9 Safety Indicators of the SMP from the Third Round: **12 Process Indicators**

Type of indicators	No. in Round 1	No. in Round 2	Safety Indicators of the SMP	Round 3 (n=27) Median	% of Agreement (80 % cut point)
Evaluation process for application to the SMP (1)	1	1	Relevant criteria for each type of new drugs	more suitable	81.48
ADR management system (9)	4	2	Cooperation of health professional in reporting ADR of new drug	most suitable	88.89
	5	3	Validity in ADR reporting from health professional	most suitable	81.48
	6	4	Strictly performing in collecting ADR of drug company	most suitable	88.89
	7	5	Risk detection system	more suitable	81.48
	8	6	Risk assessment system	more suitable	85.19
	9	7	Risk management system	more suitable	96.30
	10	8	Risk communication system	more suitable	92.59
	13	9	Timely reporting of ADR	more suitable	92.59
	14	10	Precise and timely ADR assessment procedure	more suitable	92.59
Evaluation process for releasing from the SMP (2)	15	11	Certain criteria for the SMP releasing process	most suitable	96.15
	17	12	Transparency and accountability procedures in the SMP	most suitable	84.61

Only 1 of 11 outcome indicators was excluded in the third round resulting in 10 indicators. The excluded one was the "incidence of ADR" indicator (Table 5.10).

A few indicators received high agreement levels. The indicator with the highest agreement was "case report of ADR from world wide" (96.30%), followed by "incidence of ADR (per number of patient use)" and "efficiency in ADR reporting in Thailand" (both with 88.89%). Another two indicators, "detection of serious ADR"

and "detection of serious ADR type A," received the third rank of agreement (both with 88.46%).

In terms of suitability of the indicator, "detection of death from ADR" was the only one with a rate of "most suitable" level.

Table 5.10 Safety Indicators of the SMP from the Third Round: **10 Outcome Indicators**

Type of indicators	No. in Round 1	No. in Round 2	Safety Indicators of the SMP	Round 3 (n=27) Median	% of Agreement (80 % cut point)
Safety outcome (10)	6	1	Incidence of ADR (per number of patient use)	more suitable	88.89
	7	2	Sufficient number of new drug exposed patients	more suitable	81.48
	9	3	Case report of ADR from world wide	more suitable	96.30
	10	4	Efficiency in ADR reporting in Thailand	more suitable	88.89
	12	5	Detection of serious ADR	more suitable	88.46
	13	6	Detection of serious ADR type A	more suitable	88.46
	14	7	Detection of serious ADR type B	more suitable	80.77
	15	8	Detection of unlabelled ADR	more suitable	80.77
	16	9	Detection of death from ADR	most suitable	80.77
	17	10	Detection of permanent ADR	more suitable	80.77

From the third round, 36 indicators were obtained. These included 14 structure, 12 process and 10 outcome indicators (Table 5.11). This number of indicators was, however, not the final set of indicators. After considering contextual feedbacks from all experts, indicators from the third round were re-grouped so that those with similar concepts merged together into one indicator. A more parsimonious set of 19 indicators was achieved. Summary of all procedures and number of indicators and experts in this Delphi study are presented in Table 5.11. Details of core indicators are demonstrated in Table 5.12-Table 5.14.

Table 5.11 Summary of the Modified Delphi procedure

Round	Methods	Number of experts		Number of indicators	Number of indicators in each indicator type
First	Interview	Started	45	71	S= 29 P=17 0=25
		Enrolled	32		
Second	Mailed Questionnaire and telephone recall	Started	32	40	S= 17 P= 12 O= 11
		Enrolled	27		
Third	Mailed Questionnaire, telephone recall and In-person contact	Started	27	36	S=14 P=12 O=10
		Enrolled	27		
Core safety indicators of the SMP				**19**	**S=9** **P=6** **O=4**

S = Structure indicator P = Process indicator O = Outcome indicator

Of 14 structure indicators from the third round, the indicators were re-grouped to 9 indicators. Only information system indicators were re-grouped from 7 to 2 indicators. The "ADR of new drug database linkage to WHO" indicator was clarified with contextual feedbacks to be "ADR of new drug database linkage and enabling to generate a signal from the WHO database" indicator (Table 5.12). The rest of indicators relating to information system were grouped to "information system of new drug" indicators including 1) information from literature, 2) information of therapeutic index, 3) information of drug interaction, 4) information of ADR in clinical trial, 5) information of indication and contraindication and 6) information of regulatory measures in other countries.

Table 5.12 Safety Indicators of the SMP: **9 Core Structure Indicators**

Type of indicators	No. in Round 1	No. in Round 2	No. in Round 3	Core Safety Indicators of the SMP
Policy, law, regulation and guideline (3)	3	1	1	Systematic safety monitoring of new drug at national level
	4	2	2	Systematic safety monitoring of new drug at hospital level
	8	3	3	Certain guideline for new drug safety monitoring procedure in FDA
Organization (1)	12	4	4	Safety monitoring system in drug company
Personnel (4)	13	5	5	Certain personnel in safety monitoring activity in company
	16	6	6	Experienced experts in new drug
	17	7	7	Experienced responsible person in drug company
Information system (1)	18	8	8	ADR of new drug database linkage and enabling to generate a signal from the WHO database
	21	9	9	Information system of new drug from literature regarding; information in literature, Information of therapeutic index, drug interaction, ADR in clinical trial, Indication and contraindication, and regulatory measures of new drug in other countries.
	23	10		
	24	11		
	25	12		
	27	13		
	28	14		

Twelve process indicators were re-grouped into 6 core indicators (Table 5.13) Those not changed were 1 indicator of the evaluation process for application to the SMP and 2 indicators of evaluation process for releasing from the SMP. The indicators relating to health professional in reporting ADR procedure including "co-operation of health professional in reporting ADR of new drug" and "validity in ADR reporting from health professional" were grouped together as "validity in ADR reporting from health professional" indicator. "ADR management system" was another indicator stemmed from all related activities of ADR from the step of ADR detection, to assessment, minimization and lastly ADR communication. Therefore these 6 ADR related indicators were transformed into one indicator.

Table 5.13 Safety Indicators of the SMP: **6 Core Process Indicators**

Type of indicators	No. in round 1	No. in round 2	No. in round 3	Core Safety Indicators of the SMP
Evaluation process for application to the SMP (1)	1	1	1	Relevant criteria for each type of new drugs
ADRs management system (3)	4	2	2	Validity in ADR reporting from health professional
	5	3		
	6	4	3	Strictly performing in collecting ADR of drug company
	7	5	4	Risk management system: risk detection, risk assessment, risk minimization and risk communication
	8	6		
	9	7		
	10	8		
	13	9		
	14	10		
Evaluation process for releasing from the SMP (2)	15	11	5	Certain criteria for the SMP releasing process
	17	12	6	Transparency and accountability procedures in the SMP

The last set of safety indicators of the SMP were 4 outcome indicators that were derived from 10 indicators (Table 5.14). The "**incidence of ADR (per number of patient use) with sufficient number of new drug expose patients**" was a new indicator of the safety indicators. Two indicators called "case report of ADR from worldwide" and "efficiency in ADR reporting in Thailand" were retained in this set of indicators. The "detection of serious ADR" was a new one derived from all indicators relating to detection of serious ADR.

Table 5.14 Safety Indicators of the SMP: **4 Core Outcome Indicators**

Type of indicators	No in Round 1	No in Round 2	No in Round 3	Core Safety Indicators of the SMP
Safety indicator (4)	6	1	1	Incidence of ADR (per number of patient use) with sufficient number of new drug exposed patients
	7	2		
	9	3	2	Case report of ADR from world wide
	10	4	3	Efficiency in ADR reporting in Thailand
	12	5	4	Detection of serious ADR: ADR type A, ADR type B, unlabelled ADR, permanent ADR, death from ADR
	13	6		
	14	7		
	15	8		
	16	9		
	17	10		

Experts' contextual feedbacks on the indicators on each in each round also provided some insight on the whole SMP system. Findings from content analysis on this textual information could be concluded into themes of agreements on indicators in two points.

1. **Usefulness of the indicators.**

Some experts responded that the indicators would be useful for monitoring safety of new drugs for Thai people. Furthermore, these indicators would strengthen confidence in using new drugs as some experts mentioned about the "detection of serious ADR" indicator that "*This indicator is the true indicator to identify safety of new drugs.*"

2. **Some indicators defined as a responsibility of drug companies or health professionals.**

Another theme from the feedbacks was that some indicators were main tasks and responsibilities of drug companies or health professionals. The examples were the indicators called "safety monitoring system in the drug company" and "strictly performing in collecting ADR of the drug company". The feedbacks strongly advocated such opinion as seen in a statement "*Drug company must perform this activity*" and "*This activity is a responsibility to society.*" Some experts also stated that "*Physician should directly take part in reporting ADR*".

Safety Indicators Excluded

Overall, 35 indicators were excluded from the first list as shown in Table 5.15. The feedbacks for not including these indicators included the reasons that these indicators were not applicable or not practical in real practice as seen in the statements like "*In real practice, no one will be an evaluator for the SMP system*" or "*There is no way to encourage physician to report every case of ADR (so the denominator for ADR incidence cannot be known)*".

Table 5.15 Safety Indicators of the SMP Excluded (36 indicators)

Type of Indicators	No.	Safety Indicators
Structure	1	SMP evaluation system
	2	National policy of safety monitoring of new drug
	3	New drug have to be available in countries which having good monitoring
	4	Hospitals report new drug use profile directly to FDA
	5	Certain law assigning drug company to be responsible for monitoring new drug safety
	6	Certain criteria for the expert consideration
	7	Certain guideline for new drug safety monitoring procedure in drug company
	8	Quality in drug manufacturing
	9	Sufficient staffs in FDA for performing safety monitoring

Table 5.15 Safety Indicators of the SMP Excluded (36 indicators) (Continue.)

Type of Indicators	No.	Safety Indicators
	10	Experienced staffs in FDA for performing safety monitoring
	11	Information of new drug in text book
	12	Information of new drug from drug company
	13	Information of mechanism of action of new drug
	14	Background information of drug mechanism of drug group
	15	Good information system, ready to use, in drug company
Process	1	Limitation of patient use or institution in a certain period
	2	Awareness of health professional in the SMP
	3	Awareness of new drug in patient
	4	Concern of new drug use in physician
	5	Asking for more ADR profiles when there is insufficient data
Outcome	1	Number of drug entered and released from the SMP
	2	Timing of new drug in the SMP period
	3	Incidence of ADR
	4	Incidence of ADR (per volume of drug use)
	5	Incidence of ADR (per Defined Daily Dose:DDD)
	6	Case report of ADR in Thailand
	7	Sufficient number of ADR report
	8	Detection of non-permanent ADR
	9	Detection of ADR causing uncomfortable in every day life
	10	Information shows benefit of new drug outweigh ADR
	11	Time for detecting ADR after drug marketed
	12	Number of withdrawn drug during the SMP period
	13	Labeling changes due to ADR of new drug
	14	Adjustment of drug status/classification due to ADR of new drug
	15	Times for labeling changes from ADR after drug marketed