

## **Research Protocol: REAP-AP-4**

### **Research on Asian Psychotropic Prescription Pattern (REAP) on Schizophrenic inpatients in 2016**

#### **Abbreviation (REAP-AP-4)**

- 1. Research protocol of REAP AP-3 (Survey in 2008) was drafted by Professor CHONG, Mian-Yoon. Kaohsiung Taiwan in 2007.**
- 2. REAP AP 4 research protocol is based on the REAP AP 3 protocol with several modifications.**
- 3. REAP Home page have been prepared in September 2015 and available to all participating members including new members.**
- 4. Preliminary research protocol have been prepared in September 2015 by Professor SHINFUKU, Naotaka. Fukuoka Japan**
- 5. The first draft REAP AP 4 Research protocol to be edited by senior members and the first draft will be completed by the end October 2015.**
- 6. The final draft will completed by the of November 2015 and approved by all participating members**
- 7. The list of participating centers and researchers will completed by the end November 2015.**
- 8. The web based questionnaire to be completed by the end of December 2015 by REAP team at Taipei Municipal hospital.**
- 9. The web based questionnaire will be sent to all national coordinators and leading members by e-mail be the end of January 2016.**
- 10. The survey will be carried out in 15 countries and areas in Asia from 1<sup>st</sup> to 31<sup>st</sup> March 2016.**

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## **1: Introduction**

### **1-1: Outline of REAP**

“International Collaborative Studies on psychotropic prescription” is the largest and the longest international collaborative research project in Asia in the field of psychiatry.

The study is known by its abbreviation REAP (Research on Asia Psychotropic Prescription Pattern). REAP undertook a large scale survey on prescription pattern of schizophrenic inpatients in Asia for three times on 2001, 2004 and 2008 and on the use of anti-depressants twice on 2004 and 2013. Ten countries and areas participated in the survey on ant-depressants use in 2013. In the past fifteen years, the outcomes of REAP surveys were reported many times at major international congress (WPA, WAPR, PRCP, AFPA, CINP et al.). Also, doctors from different countries and areas who participated REAP surveys published a number of papers based on data from REAP surveys. The papers were mostly in English and more than 50 papers were accepted by well recognized international scientific journals from 2001 to 2015.

### **1-2: The objectives of REAP are as follows**

1. To study psychotropic prescription pattern in countries and areas in Asia
2. To analyze factors affecting prescription pattern of psychotropic drugs in countries and areas in Asia.
3. To evaluate the impacts of prescription pattern to clinical practices in Asia.
4. To suggest ways to improve prescription pattern in Asian countries
5. foster research collaboration in psychiatry among Asian countries

### **1-3: Brief history of REAP 1999-2015**

In the previous REAP-AP1, REAP-AP2, and REAP-AP3, a total of 528 psychiatrists, 90 psychiatric inpatient units, and 6761 patient prescriptions information were collected and analyzed. (See Brief history of REAP and other references)

### **1-3-1: Beginning of REAP**

The beginning of REAP dated back to the Symposium on Neuropsycho Pharmacology held on 2 to 4 December 1999 at Singapore National University, Singapore. The symposium was jointly supported by National University Singapore (NUS) and the Japan Society for the Promotion of Sciences (JSPS). A number of presentations by psychiatrists and pharmacologists from Asian countries made it clear that prescription of psychotropic drugs differed greatly country by country. At the symposium, the proposal was made to undertake a collaborative research to elucidate the prescription pattern of psychotropic drugs in countries participated in the Symposium. A collaborative research project was proposed to survey the prescriptions of schizophrenic in patients in participating countries. The purpose of the collaborative research was to improve the prescription of psychotropic medication in Asia based on the concrete data of their prescription pattern in each country. The unified research protocol and the questionnaire were prepared after a number of communications by e-mails among interested researchers from different countries.

### **1-3-2: First survey in 2001 (REAP AP 1)**

The first survey on the prescription survey on inpatients schizophrenic was carried out in July 2001. In February 2002, researchers from China, Hong Kong, Indonesia, Japan, Korea, Malaysia, Singapore and Taiwan reported the outcomes of the collaborative survey at Kobe University. More than 2,000 prescriptions of schizophrenic inpatients were collected from six countries and areas: China, Hong Kong, Japan, Korea, Singapore and Taiwan. The findings resulted from the first survey in 2001 was presented at the 12th World Congress of World Psychiatric Association (WPA) held in Yokohama in August 2002. The survey in 2001 reported the dominant use of the first generation of anti-psychotics (FGA) such as Chlorpromazine and Haloperidol over the second generation anti-psychotics (SGA). Among countries and areas participated in the survey, Japan was marked with poly-pharmacy and high dose prescription of anti-psychotics. In China, Clozapine was the most commonly prescribed anti-psychotics. Singapore was marked with the frequent use of depot form anti-psychotics.

### **1-3-3: Second Survey in 2004 (REAP-AP 2)**

The second survey was carried out in July 2004 three years after the first survey. The survey used the same research protocol and questionnaire. In total 2,136 cases of

prescription of schizophrenic inpatients were collected from China, Korea, Japan, Singapore, Taiwan and Hong Kong.

The findings of the follow up survey were reported as symposium at the 18th World Congress of Social Psychiatry held in October 2014 in Kobe. From 2001 to 2004, the SGA increased sharply in Asian countries participated in the survey.

Changing pattern of prescription for schizophrenic inpatients in different Asian country from 2001 to 2004 was reported at reputed journals in psychopharmacology in Japanese and in English.

**REAP undertook the survey on the use of anti-depressants in China, Korea, Japan, Singapore and Taiwan (REAP AD-1) in 2004.**

#### **1-3-4: Third Survey in 2008 (REAP AP 3)**

REAP drew attention to psychiatrists from ASEAN and South Asia who attended REAP symposium at several international congresses. At the third survey in 2008, psychiatrists from India, Malaysia and Thailand joined REAP survey. The survey on prescription of schizophrenic inpatients in 2008 was carried out in 9 countries and areas in Asia.

Formerly REAP meant Research on East Asian Psychotropic Prescription Pattern. With the admission of India, Malaysia and Thailand to the group, REAP became Research on Asian Psychotropic Prescription Pattern.

## **2: REAP-AP 4**

### **2-1: Proposal of REAP AP 4 in 2015**

At the Board Meeting of REAP at the 5th World Congress of Asian Psychiatry (WCAP), 3rd March 2015, Fukuoka, the 4th follow up survey of REAP AP was proposed to take place in 2016 including several Asian countries who showed keen interest to participate in REAP AP survey.

The proposal was submitted by members of Taipei City Hospital and Psychiatric Center.

REAP Board Meeting agreed to undertake the REAP survey on the prescription pattern of schizophrenic in patients (REAP AP4) in 2016 involving 15 countries and areas in Asia.

### **2-2: Research design and methods of REAP AP 4**

REAP AP 4 will follow the previous three REAP surveys on the prescription pattern of schizophrenic inpatients. Participating country and area will collect the data based on a unified questionnaire-based research protocol, to assess the trend and change of psychotropic drug prescriptions for inpatients with schizophrenia.

The design of this project is a quantitative study of descriptive epidemiology. Data will be collected on a unified protocol (Appendix 3) by the psychiatrists of the participating centers. Cases with schizophrenia admitted for treatment at a single month of a year will be recruited. The prescribing habits of psychiatrist will be analyzed, taking consideration of the available psychotropic drugs on the market and different geographical and practicing system. It attempts to answer questions regarding the disparity between therapeutic guidelines and actual clinical practices in Asia.

### **2-3: National coordinator (Principle Investigator at country/area)**

**Each country and area will have one or a small number of members responsible to collect data from several participating centers in his (her) country (or center) and send all web-based data to Taipei City Hospital with a copy to the overall coordinator.**

#### **2-4: Participating centers**

REAP survey on the use of anti-depressants in 2014 were supported by 50 major research institutes and hospitals from 10 countries and areas in Asia (East Asia, ASEAN and South Asia).

**REAP AP 4 in 2016 will be joined by 70-80 research institutes and psychiatric hospitals from 15 countries and areas of Asia.**

##### **2-4-1: Countries and areas showed to join in the REAP AP 4 survey in 2016.**

1. China (2001)
2. Hong Kong (2001)
3. Japan (2001)
4. Korea (2001)
5. Singapore (2001)
6. Taiwan (2001)
7. India (2008)
8. Malaysia (2008)
9. Thailand (2008)
10. Indonesia (2013)
11. Bangladesh (New)
12. Myanmar (New)
13. Pakistan (New )
14. Sri Lanka (New)
15. Viet Nam (New)

**(----) is the year first joined the REAP survey.**

##### **2-4-2: Duty of each participating centers**

1. Each countries and areas will decide the centers (Research institutes and hospitals) to participate in the survey.
2. From each country and area, the maximum number of centers will be **ten**.
3. In total, samples could be collected from 60-80 centers in Asia (15 countries and areas).
4. **From each country and area, the minimum number of cases to be collected will be 100 and the maximum 500.**

5. From each center, the minimum of 30 cases could be collected. Big countries may wish to involve 5 to 10 centers ,collect 30 cases from each center totaling from 150-300 cases
6. The total number of cases could be around 3,000. (Average 200 cases from 15 countries and areas)
7. We have to take into consideration of capacity at **Taipei City Hospital** to compile and analyze the data.
8. Participating center is asked to provide the information of the participating center.

**The form to provide the information is attached as Annex 1**

## **2-5: Target dates of the REAP AP 4 Survey**

**Survey date: 1st to 31st March 2016.**

## **2-6: Samples and data inputs**

Patients admitted for treatment of schizophrenia (**Both inpatients and outpatients**) will be recruited for the study.

### **2-6-1: The inclusion criteria are**

1. Diagnosis of schizophrenic disorders according to the DSM-5 criteria (APA) or the ICD-10 Classification of Mental and Behavioral Disorders (WHO)
2. **Being an inpatient or outpatient on the day of the survey**
3. Comply to study

### **2-6-2: Exclusion criteria are**

1. Refuse of not comply to the study
2. Presence of serious physical diseases.

## **2-7: Data collection**

Cases will be collected from **inpatients and/or outpatients population which research collaborators in each countries and areas have easy access as doctors in charge**. This method, called as “Window” or “Handy Sampling”, is often used to

collect data in countries with scarce resources. Therefore, REAP is not an epidemiological survey in strict sense but an amalgamation of surveys in different countries using the same questionnaire based on a unified research protocol. However, it was possible to understand the outline of prescription pattern for schizophrenic inpatients in Asia by analyzing the large sample collected from different countries and areas. Very simple research protocol and the survey method made REAP accepted by researchers in countries with limited psychiatric resources in Asia and enabled to continue more than 15 years.

## **2-8: Questionnaire**

The content of the questionnaire includes demographic data, psychiatric symptoms, psychotropic medications, and adverse drug reactions as previous REAPs.

In addition, comorbidities and physical condition will be also recorded. For quality assurance, the web-based recording system will be used for data collection.

All participating centers will receive the web based questionnaire before the survey.

## **Web based questionnaire for REAP AP4 is attached as Annex 2**

## **2-9: Classification of psychotropic drugs**

The WHO Anatomic Therapeutic Chemical (ATC) system will be used to classify the drug classification system in this study. The drugs to be investigated in this project are psychotropic drugs, and fall into the category of psychoactive drugs by the ATC classification system [WHO, 2016]. It consists of five hierarchical levels: a main anatomical group, two therapeutic subgroups, a chemical-therapeutic subgroup and a chemical substance subgroup. Psychotropic drugs for example, were categorized in such system included antipsychotics (N05A: FGAs, SGAs, and depot antipsychotics), antidepressants (N06A), anti-epileptics and lithium (or mood stabilizers, N03A and N05AN), anxiolytics (N05B), hypnotics and sedatives (N05C), and anti-Parkinson drugs (N04).

The ATC classification system is useful for reporting drug consumption statistics and conducting comparative drug utilization research. The WHO international Drug Monitoring Program uses the system for drug coding in adverse drug reaction

monitoring. Many countries also employ the ATC system to classify their essential drugs.

## **2-10: Ethical consideration and Informed consent**

The overall research protocol was approved by the review committee of the Taipei City Hospital and Psychiatric center. Taipei city Hospital and Psychiatric Center will provide the staff and fund necessary for the management of data to be submitted from more than 50 centers of 15 countries and areas in Asia.

This proposed project does not involve in the experimental trials or laboratory investigations of the subjects, and thus will not pose any physical hazard to the study subjects concerned.

The survey will be carried out in countries and areas who have never participated in REAP projects and who have no research review committee.

All participating centers are asked to keep strict confidentiality of the personal data of patients.

**It is necessary for each center to get the informed consent from the patients to participate in REAP survey.**

**The form to get the informed consent is attached as Annex 5**

### **3. Compilation and analysis of the data**

**Compilation and analysis of the data will be carried out by Taipei City Hospital and Psychiatric Center.**

Participating country and area will send the web-based data to Taipei City Hospital **by the end of April 2015 at the latest.**

Data with missing entries (incomplete data) will not be accepted.

Data compiling and analysis will be performed by Taipei City Hospital and Psychiatric Center.

**Dr Lian-Yu Chen, Asst Prof. Shu-Yu Yang, Dr Shih-ku Lin and Prof .Chong Mian-Yoon will be in charge of the management of all the data received from you.**

#### **3-1: Report**

The results, once completed and analyzed, will be reported to all national coordinators and key members. These reports will be further compared with each center in Asia, also with previous survey results conducted in 2001, 2004, and 2008. These results will provide the information on the prescription of antipsychotics and for the future proper prescription patterns.

#### **3-2: Fund**

Taipei City Government will prepare a necessary fund for web system construction, data compilation and analysis. Centers who wish to participate will prepare necessary fund or manpower to conduct the survey.

## **4. Publication and authorship**

Members who participate in the survey are entitled to write papers or make presentation at meetings (both international and domestic) based on the results from the survey. Senior members will assist in writing papers and in presenting at meetings (Oral and poster)

### **4-1: Publication**

**All researchers who participated in the survey is encouraged to write papers at domestic and international journals using the data obtained from the REAP AP 4 survey and previous surveys.**

### **4-2. Authorship**

**It is advisable to list the names of all national coordinators and key members in the list of authors. However, it is sometimes difficult as publishers limit the number of authors for some articles, review papers and letters.**

**The first author and the corresponding authors have the right to decide the list and order of the authors.**

### **4-3. Presentations**

**All members are encouraged to make presentations at domestic and international meeting using the data from REAP survey. Proposal for symposium by REAP members at major international congress are encouraged.**

## **5. Acknowledgement**

**The organizer would like to express thanks for the support provided by REAP members. It has been a miracle for a small seed planted in Singapore in 1999 to develop such a large scale international collaborative research in Asia.**

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