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List of abbreviations

CRC	Clinical Research Center
CRF	Case Report Form
DG	Director General of Health, Ministry of Health, Malaysia
EC	Ethnics Committee
eCRF	Electronic CRF
ICT	Information and Communication Technology
ID	Identification
IEC	Independent Ethnics Committee
MOH	Ministry of Health
MREC	Medical Research Ethnics Committee
NIH	National Institute of Health
PDF	Portable Document Format
PI	Principal Investigator
PM	Project Manager
RA	Research Associate
RCC	Research Coordinating Center
RT-PCR	Real Time – Polymerase Chain Reaction
SDP	Source Data Provider
SSL	Secure Sockets Layer
US	United States
WHO	World Health Organization

Section 1 Background and rationale

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Section 2 Study objective

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Section 2.1 Specific aims

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Section 3 Study design

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Section 3.1 Study population

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Section 3.2 Patient withdrawal

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Section 3.3 Study duration

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Section 4 Data collection

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The data domains and related specific data elements to be collected by this study is tabulated below:

A	Demographic	Name, IC, Other identifying document #, address, family contact numbers, gender, ethnic group, schooling/working
B	Clinical sign and symptoms	Date of illness onset, symptoms at anytime during the course of illness
C	Past history of illness	History of visit to health care facility, history of admission, history of contact , vaccination history, treatment before admission
D	Pre-existing conditions / co-morbidity	Pre-existing conditions / co-morbidity
E	Clinical features / vital signs	Vital signs at time of admission and at time of deterioration
F	Disease deterioration / severity of illness	Date of admission, diagnosis
G	Investigations	Date of blood specimen taken and results at time of admission and/or time of deterioration
H	Diagnostic testing	Specimen type, collection date, results
I	Microbiology	Collection date, results, note organism if positive
J	Radiology	Date, abnormal findings
K	Management	List of medications patient taking at time of hospital admission
L	Outcome	Patient status

Section 4.1 Data collection schedule and flow chart

The study data collection schedule is summarized in the table below:-

	Baseline at notification to study	**Monthly reporting to study**
Timeline	At any time	Month 12 of each calendar year
Procedures		
Check eligibility	X	
Collect information on demography, clinical sign and symptoms, past history of influenza like-illness	X	
Pre-existing conditions / co-morbidity	X	
Clinical features / vital signs	X	
Disease deterioration / severity of illness		X
Investigations	X	X
diagnostic testing		X
Microbiology result		X
Radiology		X
Management	X	
Outcome		X

Section 4.2 Electronic CRF (if applicable)

CRFs are implemented electronically (eCRF), using third party software application that is fully validated and conforms to regulatory requirements for electronic data capture, where applicable.

The eCRF enables data capture via an on-line system on a personal computer (PC).

- Designated staff at participating site shall enter data required by the protocol into the eCRF.
- The data will be recorded via the application into a central database over encrypted lines using the SSL (Secure Sockets Layer) protocol.
- Personal health identifiers are stored in the central database in encrypted form.
- All entries and modifications of data are logged in an audit trail.
- All access to the system is administered by the eCRF Administrator, and will only be granted after appropriate and documented training.
- Electronic signatures will be used where required.
- Automated validation program check for data discrepancies in the eCRFs will be implemented where appropriate.
- In the unlikely event of system failures, data shall be captured on a back-up paper CRF and is to be later transferred to the eCRF. The back-up paper CRFs are considered source data and the RA should monitor the transcription of data into the eCRF.

Where eCRF could not be implemented for technical or resource reason or as a backup measure, the site coordinator can download pdf. version via the web. These forms may also be used to record and transmit all information collected in the study. Refer Appendix for a sample copy of the paper CRF.

Section 4.3 Selection of data elements

The data elements (also known as data items or variables) to be collected by the study are selected based on the following rules:

- Data to be collected must be relevant, may be collected reliably, with modest burden to patients, physicians and sites, and yet is affordable.
- Comply with existing data standard, where this exists
- Compatible with established data set used by other existing registries
- Employ standard terminology (dictionary), where this exits

Section 5 Data management

Section 5.1 Integration within Clinical Research Center (CRC) and nationwide clinician network (if applicable)

…… (explain the various steps involved in the network data management)

…….

Section 5.2 CRF review and data clarification (example)

- A responsible CRA will visually review the CRFs for completeness and accuracy
- Automated validation program check for data discrepancies (non-allowed or out of range values and consistency checks) in the CRFs will also be implemented where appropriate.
- Errors or discrepancies detected or suspected from the above will be queried. This will be communicated to site for resolution.
- When the database has been declared to be complete and accurate, the database will be locked. Any data changes after the database lock have to be documented in writing and approved by the PM, Biostatistics and Clinical Data Management.

Section 5.3 Clinical database management system (if applicable)

All data captured whether electronically via eCRF or manually via paper CRF is stored in a third party database.

Remote data capture via eCRF and central database management functions is underpinned by an ICT infrastructure, at the heart of which is the highly secured data centre which host the registry database. Refer Appendix for a description of the IT infrastructure supporting the registry data operations, the network architecture of the data centre and security features installed to assure information security.

Section 5.3 Methods for handling missing data and outliers
Missing demographics data, such as age, gender etc., will be resolved by using other forms of documentation such as the identification card. If a missing on other variables such as the social demographic factors cannot be rectified using the original data source, then they will be imputed by using a hot-deck imputation technique based on age-gender distribution. No imputation will be performed on missing treatment and outcome data.

A range check will be used to check for the potential outliers and extreme values for the continuous data. These values will then be verified against the original source data. If the values cannot be resolved, then they will be treated as missing data and the value will be imputed using a hot-deck method.

Section 6 Pilot study site

……..
…….(Please also attached the complete list of study sites)…….

Section 7 Statistical analysis (example)
The data will be analyzed using STATA statistical software to perform descriptive data and perform logistic regression and survival analysis. There are five regression models to be explored based on these outcome/end points:-

1. Complications
2. Respiratory distress requiring ventilation
3. CNS involvement (seizures)
4. Death
5. Severe progression

Section 7.1 Demographics and baseline characteristics
Demographic, baseline characteristic and laboratory evaluations will be summarized and tabulated. Continuous variables will be summarized by descriptive statistics, which constitutes sample size, mean, median, standard deviation, minimum and maximum.
Discrete variables will be summarized by frequencies and percentages (contingency tables).

Section 7.2 Methods for dealing with confounding and other biases in observational data
The confounding and other biases will be minimized by adjusting for the known covariates. This is done by using statistical methods such as stratification (9,10)

Section 8 Ethics and regulatory considerations

Section 8.1 Independent Ethics Committee

This(title of study)) is an observational research that involves the participation of human subjects. In compliance with current MOH NIH research guideline and applicable research guidelines (1) , the registry protocol and any other documents that the IEC may need to fulfill its responsibilities will be submitted to a properly constituted Independent Ethics Committee (IEC). Approval from the committee must be documented in a letter to the investigator specifying the registry title, protocol number, the documents reviewed, the date on which the committee met and granted the approval, the name and institutional affiliation of the chairman and members of the IEC, and provisions for periodic review if any.

Any amendments to the protocol, other than administrative ones, must also be approved by this committee.

The principal investigator will inform the IEC of:

a. Any amendment to the protocol and revisions of other documents originally submitted for review.
b. Any serious and/or unexpected events occurring during the registry, where required.
c. Any new information that may adversely affect the safety of subjects or the conduct of the registry.
d. An annual update on the progress of the registry and/or request for re-approval, where required.
e. Regular registry report and other scientific publications arising of the registry, where required.

All correspondence with the IEC should be filed by the principal investigator in the Investigator's Study File and a copy forwarded to CRC

Section 8.2 Ethical conduct of the study

The study will also be conducted in compliance with the protocol and CRC's standard operating procedures. These are designed to ensure adherence with the ethical principles that have their origin in the Declaration of Helsinki, CIOMS's International Guidelines for Ethical Review of Epidemiological Studies (2), Good Pharmacoepidemiological Practice (3) and applicable regulatory requirements.

The registry study will also be registered with the National Medical Research Register, in compliance with current NIH guideline (1).

Section 8.2 Patient information and consent

We will obtain signed informed consent form from patient or next of kin who admitted to Malaysia hospital

Section 8.2 Patient data protection

To ensure that requirements regarding personal data protection are met, data will be collected and stored in accordance with applicable local regulation where the patients are recruited (4,5), and with applicable US and European specifications (6,7,8) or until such time Malaysian Data Protection regulation are enforced.

If a third party is processing data on behalf of the registry and sponsor, a contractual procedure will be signed between the registry/sponsor and the third party to ensure compliance with above mentioned requirements.

The registry, its staff and its third party vendor will protect the confidentiality of registry data as follows:

- Patient's medical information obtained by the registry is confidential and disclosure to third parties other than the clinical site providing the data is prohibited
- All electronic data processed by the RCC will be identified by patient number only, unless there is a specific need to know the identity of an individual when processing data.
- All confidential electronic data will be protected by using passwords for electronic data, and the electronic data stored in a database located in a highly secured data centre
- All paper copies of data and reports must be stored in a secure archive.
- All electronic data transmission should be encrypted before sending. If possible, transmit data though a secure data network
- Only aggregate results will be reported by the registry such that it will not be possible to identify individual subjects.

The study will institute stringent information security policies and procedures, supported by state of the art data protection technology, which will be in accord with standard disease registration practice, and in compliance with applicable regulatory guidelines.

Section 9 Study organization

Section 9.1 Sponsor

This study is funded by Ministry of Health, Malaysia

Section 9.2 Research committee

The committee shall

- Provide leadership and direction for the **Project EER**
- Appoint one site coordinator amongst the site investigators in each hospital (Each hospital can have more than one site investigators)
- Communicate the study's, strategic direction, policies and decisions to all interested parties.
- Determine the objectives of the study.
- Provide subject matter expertise input for the study
- Provide avenues for users input to the study, and to convey their needs and concerns.
- Secure ongoing funder support for the study.
- Galvanize commitment of all interested parties to the study.
- Provide oversight for the operations of the study
- Coordinate with PI of the study
- Approve, and if necessary validate, the statistical analysis plan,
- Determines policy and procedures for the operations of the database.
- Disseminate information about the study
- Communicate results locally and internationally
- Provide other resources when required

Refer Appendix for current research committee membership

Section 10 Administration matters

Section 10.1 Notification of regulatory authority(ies)

All necessary arrangements for the registration and approval of this study with the responsible authorities and the deposition of the required data and document will be undertaken by the Principal Investigator.

Section 10.2 Study documentation and record keeping

The SDP must maintain adequate and accurate records to document the conduct of the study and substantiate the study data. These documents are the Essential Documents; these documents individually and collectively permit evaluation of the study and the quality of the data produced. The site investigators shall be responsible for maintaining and updating a study master file to file all essential documents. Site investigator will be responsible for keeping site study file updated and ensuring that all required documents are filed.

Section 10.3 Confidentiality

SDP agrees that all information communicated to him/her is the exclusive property of sponsor, and ensure that the same will be kept strictly confidential by the SDP or any person connected with the work and shall not be disclosed to any third party without the prior written consent of sponsor.

Section 11 Investigator and sponsor signature

I understand that this protocol contains information that is confidential and proprietary to the Clinical Research Centre MOH.
I have reviewed the protocol and I will participate in the study as described and will adhere to the Ethical and Regulatory Considerations stated in the protocol.
I will provide copies of the protocol to personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the study, its purpose and the study procedure.
I understand that I may terminate or suspend my centre's participation in the study at any time if it becomes necessary to protect the best interests of my patients.
This study may also be terminated at any time by the CRC.

Name of Investigator at SDP site	
Signature	
Date	
Protocol number	
Site Number	

Section 12 References (example)

1. National Institute of Health Ministry of health Malaysia. NIH Guidelines for conducting research at MOH Institutes and facilities. Available at: http://www.nmrr.gov.my
2. Council for International Organizations of Medical Sciences: 1991 International Guidelines for Ethical Review of Epidemiological Studies. Available at: http://www.cioms.ch/
3. Code of Federal Regulations. Title 45-Department of Health and Human Services; Part 46-Protection of Human subjects. Updated 1 Oct 1997. Available at: www4.law.cornell.edu/cfr
4. ISO/IEC17799:2002
5. Malaysian Public sector management of ICT Security handbook. MAMPU 2001
6. Directive 94/ /EC and 95/EC Council On the protection of individuals with regard to the processing of personal data and on the free movement of such data. 1995. *Implementation 2000*
7. European Network of DiseaseX Registries. Guidelines on Confidentiality in population-based DiseaseX Registration in the EU. Feb 2002
8. US Health Insurance Portability and Accountability Act 1996 (HIPAA).

Section 13 Appendix

Section 13.1 Helsinki declaration

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects
Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964; and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. *The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.*
2. *It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.*
3. *The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."*
4. *Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.*
5. *In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.*
6. *The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.*
7. *In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.*
8. *Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit*

17. *Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.*
18. *Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.*
19. *Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.*
20. *The subjects must be volunteers and informed participants in the research project.*
21. *The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.*
22. *In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.*
23. *When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.*
24. *For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.*
25. *When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.*
26. *Research on individuals from whom it is not possible to obain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them*

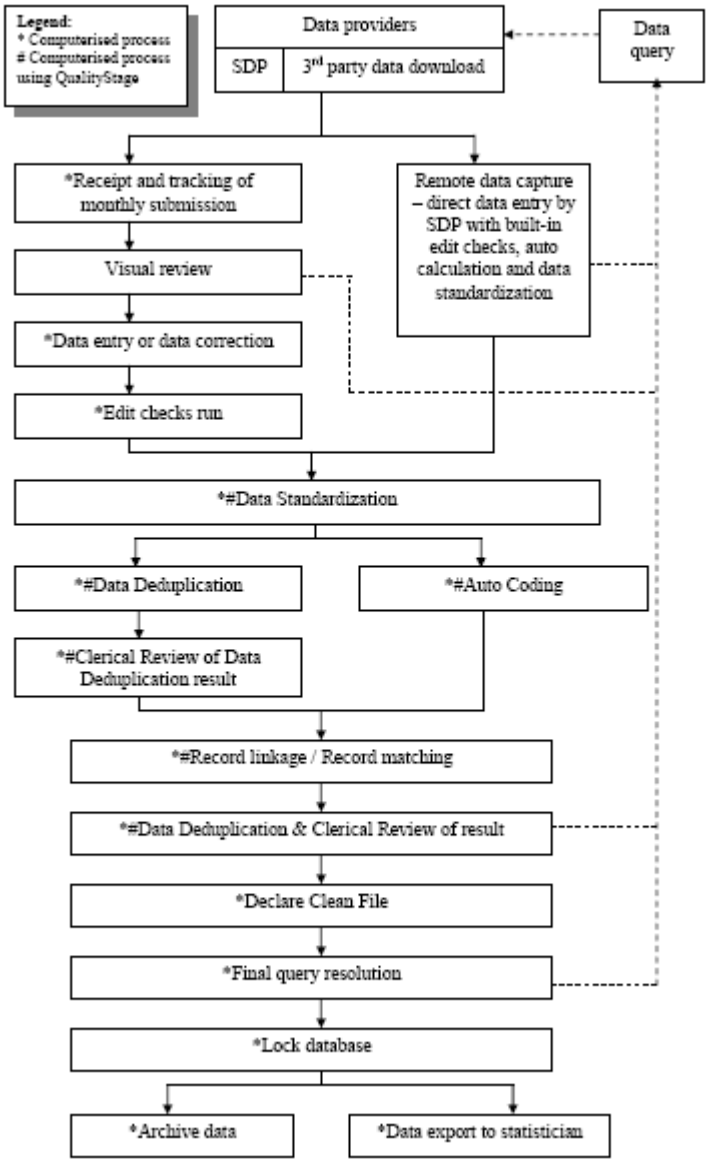
Section 13.3 CLINICAL DATABASE MANAGEMENT

The Clinical Database Management group, comprising both Clinical Data Management and IT professionals, works hand in hand with the Registry manager, to manage the registry data flow after its has been captured into the registry database via eCRF or manual data entry, as depicted in the flow diagram below. The objectives of the group are to ensure that:

- The collected data is complete and accurate.
- The registry database is complete and accurate, and a true representation of what took place in the participating clinical unit
- The registry database is sufficiently clean to support the statistical analysis, and its subsequent presentation and interpretation the registry reports and publications

Example of Case Report Forms

Data management work flow



Section 13.4 Research committee members

1. Dr. ABC
   Head of Department of Medicine
   Hospital Kuala Lumpur

2. Dr. KLM
   Head of Department of Surgery
   Hospital Serdang

Section 13.5 List of complete study sites (example)

No.	State	Site
1	Perlis	Hospital Tuanku Fauziah
2	Kedah	Hospital Sultanah Bahiyah
3		Hospital Sultan Abdul Halim (HSAH)
4		Hospital Kulim
5	Pulau Pinang	Hospital Pulau Pinang
6		Hospital Bukit Mertajam
7		Hospital Seberang Jaya
8	Perak	Hospital Raja Permaisuri Bainun
9		Hospital Taiping
10		Hospital Teluk Intan
11		Hospital Slim River
12		Hospital Seri Manjung
13	Selangor	Hospital Tengku Ampuan Rahimah
14		Hospital Selayang
15		Hospital Serdang
16		Hospital Ampang
17		Hospital Sungai Buloh
18		Hospital Kajang
19		Hospital Banting

Section 13.6 Investigator's CVs