



**The ethics of research in rapidly evolving
epidemics: an international perspective**

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Abstract

Background: The world is at risk of epidemics of novel and reemerging infectious diseases. These may be national, regional or international as in the case of Nipah, African Viral Haemorrhagic Fevers, SARS and H1N1 respectively. It is crucial that public health and clinical research is conducted in such epidemics. Yet the conduct of health research during rapidly evolving epidemics or disasters represents an enormous challenge. In addition to the large number of practical challenges to undertaking such research there are also major ethical issues to consider. However, there is very little understanding of these ethical issues and very little empirical evidence of the views of patients, their families, society and key stakeholders.

Objective: To collect and analyse data on ethical considerations arising in the setting of research on rapidly evolving epidemics posed by the urgent and unpredictable nature of epidemics.

Design: The study was conducted in Oxford University Clinical Research Unit (OUCRU), Viet Nam and 3 other hospitals in Viet Nam with experience of epidemics. Data were collected by semi-structured interviews with key stakeholders representing research staff, IRB members, patients/family members and study sponsors/funders who have participated in or reviewed research projects on infectious diseases including SARS, H5N1, H1N1, dengue and Hand, Foot, Mouth disease.

Result: A total of 64 interviews with all key stakeholders were conducted. Analysis of the ethical problems/challenges discussed in the interviews led to the identification of three themes 1) International research collaboration, 2) IRB review and 3) Consent. These tended to arise at three levels of relationship: macro (between institutions internationally), meso (within and between institutions nationally) and micro (within institutions and between health professionals and patients).

Conclusion: The issues and types of considerations and their relative importance were raised and/or valued differently by the members of different key stakeholder groups due to their role and experience in research participation. Some of the issues raised also related to health research in other settings. However, many were unique to the setting of rapidly evolving epidemics. Addressing these issues is crucial for successful and appropriate research in the context of epidemics. It is inevitable that epidemics of emerging and reemerging infectious diseases will occur in the future and there is a clear need to undertake crucial scientific research in such settings. It is therefore imperative that we understand the challenges and ethical issues surrounding such research. It is desirable that further research into the ethical challenges identified in this thesis takes place in the inter-epidemic period in order to better prepare for the next epidemic.

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Abbreviations

AIDS	: Acquired immune deficiency syndrome
APEIR	: The Asia Partnership on Emerging Infectious Diseases Research
CIOMS	: Council for International Organization of Medical Sciences
CDC	: Centers for Disease Control and Prevention
COHRED	: International Conference on Health Research for Development
CH2	: Children Hospital Number 2
DHO	: District health offices
DoH	: Declaration of Helsinki
EV71	: Enterovirus 71
FERCAP	: Forum for Ethical Review Committees in the Asian and Western Pacific Region
FHF	: Filovirus hemorrhagic fever
GCP	: Good Clinical Practice
GOARN	: The Global Outbreak Alert and Response Network
HIV	: Human Immunodeficiency Virus
HFMD	: Hand, foot, mouth disease
HTD	: Hospital for Tropical Diseases
ICH	: International conference on Harmonisation
IRO	: International research organization
IRB	: Institutional Review Board
ISARIC	: International Severe Acute Respiratory and Emerging Infection Consortium
MDR	: Multidrug-resistant

MOST : Ministry of Science and Technology

NBAC : National Bioethics Advisory Commission

NHTD : National Hospital of Tropical Diseases

NIHE : National Institute of Hygiene & Epidemiology

OUCRU : Oxford University Clinical Research Unit

OXTREC : Oxford Tropical Research Ethics Committee

PHD : Provincial health departments

PI : Principal investigator

REE : Rapidly evolving epidemics

SARS : Severe Acute Respiratory Syndrome

SEAICRN : South East Asia Infectious Disease Clinical Research Network

TB : Tuberculosis

US FDA : United States Food and Drug Administration

UK : United Kingdom

WHO : World Health Organization

WMA : World Medical Association

XDR : Extensively drug resistant

Chapter 1 Review of the literature on ethical issues of research in rapidly evolving epidemics

In the recent years, the emergence of rapidly evolving epidemics such as SARS, bird flu H5N1, swine flu H1N1 and multidrug-resistant (MDR)/extensively drug resistant (XDR) tuberculosis has had dramatic global consequences. These epidemics share a number of special characteristics. They spread rapidly, often transnationally and/or globally; they have sudden or repeated onset; and they tend to be of short duration. In response to these epidemics and to the threat of those in the future, increasing efforts have been made to plan and implement research including clinical trials on human subjects often involving collaboration between many countries and international organizations. Some of this research has had promising results in relation to disease control and prevention.

In addition to the scientific and logistical complexity of conducting research - and the development of potential interventions, this research presents a number of important ethical challenges. In this, my first chapter, as an initial step towards identifying and engaging with these challenges, I will review the literature on research practice in the context of rapidly evolving epidemics and present an overview of the ethical issues and challenges identified in the relevant literature. This chapter forms an important element of the background justification for my empirical research, the results of which are presented in later chapters.

This chapter is divided into two main sections. The first provides a short summary of the scientific characteristics of rapidly evolving epidemics. The second reviews existing international research ethics guidelines and their relevance to the setting of rapidly evolving epidemics, and also explores the existing literature on the ethics of research in rapidly evolving epidemics and its limitations, highlighting the need for

further research on this increasingly important topic. Particularly in my research, it is to answer the question of what ethical issues arise and how the relevant key stakeholders participating in the research practice of rapidly evolving epidemics understand and resolve the issues they identify and experience.

It is important to point out at this stage before beginning the review, that in this chapter and in the thesis more generally, I use the terms “rapidly evolving epidemics” or “emergency epidemics” interchangeably and use the term “emergency” to refer to the rapid progress of such epidemics, rather than to their severity or acuteness.

1.1 Rapidly evolving epidemics: their characteristics and research practice

An epidemic is formally defined as an occurrence of more cases of disease than expected in a given area or among a specific group of people over a particular period of time (CDC 2011). They often involve communicable diseases and tend to be repeated in cycles and waves. They frequently occur in resource-poor countries and communities that are least able to deal with their consequences or to learn from the experiences to help inform future policy. Their transmissibility means that epidemics sometimes affect several different communities, regions, and countries as ‘pandemics’ (Calain et al. 2011). The progress of an epidemic can be unpredictable (Ezeome and Simon 2010). Epidemics are regarded as public health problems because of their potential to have a significant impact on the health of large sections of the public and indeed whole societies in many ways which lead to a sharp decline in public health, economic loss and even social disruption. They also have the potential to threaten global security (Laegreid 2008).

To illustrate all the characteristics listed above, I will look more closely at some selected specific emerging infectious diseases that have made a significant appearance

in the 21st century to explore in more depth about their great impact which either already happened or potentially in the near future to human. Following this overview I will go on to look at some of the ethical challenges presented by research into these conditions.

(i) Hemorrhagic Fevers: The Ebola and Marburg Viruses

The Ebola and Marburg viruses are the only known members of the filovirus family. They can cause severe hemorrhagic fever with high fatality rates called Ebola virus disease (EVD). There is currently no specific treatment.

Ebolavirus first emerged in 1976 in outbreaks of Ebola hemorrhagic fever in Zaire and Sudan (Bennett and Brown May 1995). The average EVD case fatality rate is around 50% (WHO September 2014). Case fatality rates have varied from 25% to 90% in past outbreaks. There are five species of the genus *Ebolavirus* (Filoviridae family) now known: *Zaire ebolavirus*, *Sudan ebolavirus*, *Reston ebolavirus*, *Tai Forest ebolavirus* and *Bundibugyo ebolavirus* (European Centre for Disease Prevention and Control 2014; Li and Chen 2014). The main mode of transmission in human outbreaks is human-to-human transmission through direct contact with a symptomatic or dead EVD case (ECDC 2014). Since its re-emergence in March 2014 in Guinea, EVD has spread to other countries with the majority of case distribution in West Africa. As of 12 October 2014, 8 994 cases of EVD including 4 492 deaths have been reported by WHO in seven reporting countries (Guinea, Liberia, Nigeria, Senegal, Sierra Leone, Spain and the USA) (WHO October 2014). Out of these countries, the most severely affected countries, Guinea, Sierra Leone and Liberia, also the ones that endured long periods of conflict and instability and have very weak health systems with the lack of human and infrastructural resources (WHO September 2014). Due to its capability of widespread and intense transmission, on 8th August

2014, WHO declared this outbreak a Public Health Event of International Concern. Subsequently in September 2014, the United Nations Security Council recognized the 2014 EVD outbreak as a ‘threat to international peace and security’ (ECDC 2014). The following figures illustrate the rapid progression of EVD through the distributions of EVD cases by weeks in most of West African countries and situation outside West Africa.

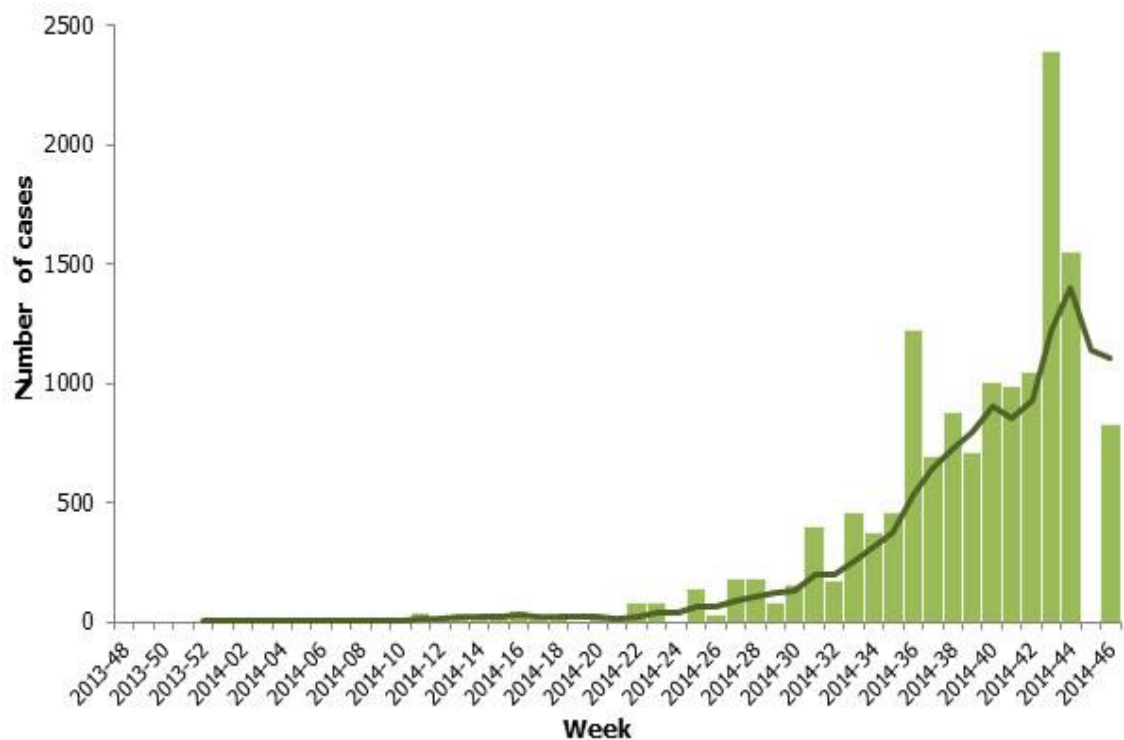


Figure 1.1 Distribution of cases of EVD by week of reporting in Guinea, Sierra Leone, Liberia, Nigeria, Senegal and Mali, weeks 48/2013 to 46/2014, as of 12 November 2014

* In week 45/2014, WHO carried-out retrospective correction in the data resulting in reporting 299 fewer cases resulting in a negative value for new cases in week 45 which is not plotted (See [World Health Organization. Ebola response roadmap situation report. 5 November 2014 \[Internet\]. Geneva: WHO; 2014](#)).

** According to WHO the marked increase in the cumulative total number of cases in week 43 is due to a more comprehensive assessment of patient databases leading to 3 792 additional reported cases. However, these cases have occurred throughout the

epidemic period (See: World Health Organization. Ebola response roadmap situation report. 29 October 2014 [Internet]. Geneva: WHO; 2014).

The solid green line represents the trend based on a five week moving average plotted on the fifth week of the moving average window. The figure includes cases in Nigeria (20), Senegal (1) and Mali (4) (See: World Health Organization. Ebola response roadmap situation report. 12 November 2014 [Internet]. Geneva: WHO; 2014).

(Reported by European Centre for Disease Prevention and Control, Rapid Risk Assessment. Outbreak of Ebola virus disease in West Africa, Seventh update, 17 October 2014)



Figure 1.2. Medical evacuations and repatriations from EVD-affected countries, as of 06 November 2014

(Reported by European Centre for Disease Prevention and Control, Rapid Risk Assessment. Outbreak of Ebola virus disease in West Africa, Seventh update, 17 October 2014)

Marburg virus or simply Marburg is the common name for the genus of viruses *Marburgvirus*, which contains one species, *Lake Victoria marburgvirus*. The virus causes the disease Marburg Hemorrhagic Fever (MHF). Marburg originated in Central and East Africa, and infects both human and nonhuman primates. The disease is spread through bodily fluids, including blood, excrement, saliva, and vomit. Outbreaks of Marburg are centered in Africa, where the natural reservoir is believed to be located. The fatality rate is from 23% to over 90% (CDC 2005; Towner et al. 2006).

(ii) SARS (Severe Acute Respiratory Syndrome)

Another example of the rapid emergence of a newly recognized human disease agent is the human coronavirus that causes SARS. SARS has been called the first pandemic in the 21st century (Skowronski et al. 2005) and considered as an indicator that the impact of EIDs will continue to be severe (Selgelid 2005). SARS first appeared in Guangdong Province, China in November 2002 and rapidly infected individuals in some 37 countries around the world (Smith 2006). Between the months of November 2002 and July 2003, there were 8,096 known infected cases and 774 deaths (a case-fatality rate of 9.6%) worldwide being listed in the World Health Organization's 21 April 2004 summary report (WHO Report 2004).

By May 2004, the spread of SARS had been fully contained, with the last infected human case in June 2003 (Bisen and Raghuvanshi 2013). However, SARS may be able to return since it may still be present in its natural host reservoirs (animal populations) (NIH 2013).

(iii) Influenza

To some extent, the influenza virus has excited the imagination to a lesser degree than many other emerging viral infections. However, it indeed fits into this category due to

its ability to genetically change often and rapidly. Influenza spreads around the world in seasonal epidemics, resulting in the deaths of hundreds of thousands worldwide annually, and millions in pandemic years. On average 41,400 people died each year in the United States between 1979 and 2001 from influenza (Dushoff et al. 2006). Three influenza pandemics occurred in the 20th century and killed tens of millions of people, with each of these pandemics being caused by the appearance of a new strain of the virus in humans. Often, these new strains appear when an existing flu virus spreads to humans from other animal species, or when an existing human strain picks up new genes from a virus that usually infects birds or pigs. An avian strain named H5N1 raised the concern of a new influenza pandemic, after it emerged in Asia in the 1990s, but it has not evolved to a form that spreads easily between people. In April 2009 a novel flu strain evolved that combined genes from human, pig, and bird flu, initially dubbed "swine flu" and also known as influenza A/H1N1, emerged in Mexico, the United States, and several other nations. The World Health Organization officially declared the outbreak to be a pandemic on June 11, 2009. The WHO's declaration of a pandemic level 6 was an indication of spread (WHO 2009).

Illustrated in Figure 1-3 below is the outbreak of H5N1 in 15 affected countries. Since 2003 and as of December 20, 2011, 573 human cases of H5N1 infection have been reported to the World Health Organization (WHO).

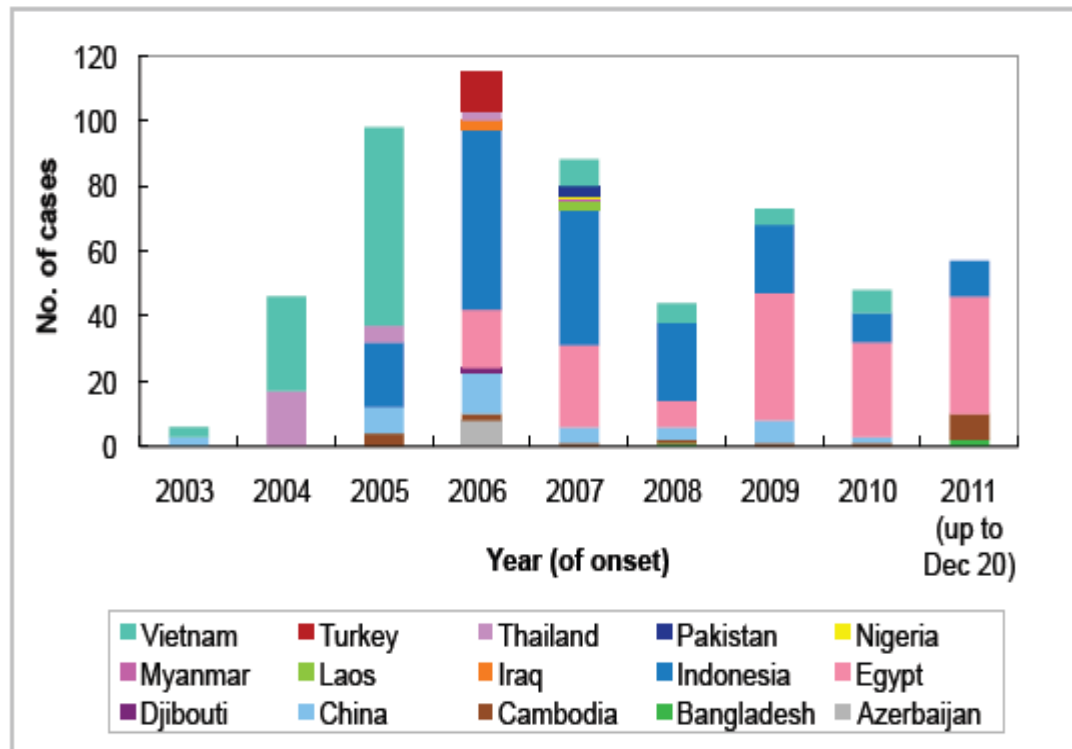


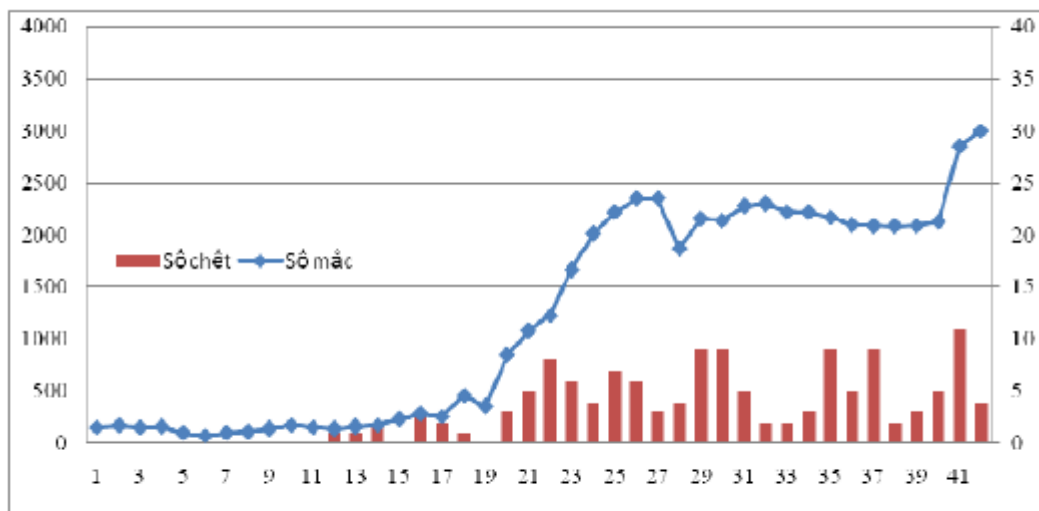
Figure 1.3 Human cases of H5N1 infection confirmed by WHO

(Source: Central for Health Protection, Department of Health, Hong Kong, Update on H5N1 avian influenza, December 11 – December 24, 2011)

(iv) Hand, Foot, Mouth Disease

Hand, foot and mouth disease (HFMD), first reported in New Zealand in 1957, is a common infectious disease of childhood caused by a group of enteroviruses, including Coxsackievirus A16 (CA16), Enterovirus 71 (EV71) and occasionally by Coxsackievirus A4-A7, A9, A10, B1-B3, and B5 (Yang et al. 2011; Sarma 2013). Only small scale outbreaks have been reported from United States, Europe, Australia, Japan and Brazil for the first few decades (Sarma 2013). However, since 1997, large outbreaks of HFMD associated with EV71 have been reported in Malaysia (Chan et al. 2000), Taiwan (Ho et al. 1999), Singapore (Chan et al. 2003), Japan (Shimizu et al. 1999), and other Asian countries (Tu et al. 2007; Yang et al. 2011) with severe neurological complications and a high case-fatality rate in children. In Southeast Asia, EV71 is a frequent cause of HFMD and resulting neurologic and cardiopulmonary

complications (Khanh et al. 2012). Regarding the number of case specific, it was reported to cause large HFMD outbreaks in Taiwan with 1.5 million cases and in Malaysia (Sarawak) with 2628 case in the late 1990s (WHO. WPRO 2011). In 2008 and 2011 large outbreaks were also recorded in China (490 000 cases) and Vietnam (110 000 cases) (WHO. WPRO 2011; Chu et al. 2013). Currently, there is no specific treatment and no vaccine to protect against the viruses.



**Viet Nam, up to 19 October 2011 (source MOH)
(Blue: no. cases; Red: no. deaths)**

Figure 1.4 Number of overall infected and dead cases per week up to October 2011
(Source: Report from Vietnamese MOH in October 2011)

Summary

As we can see from examples of rapidly evolving epidemics above, some cases of epidemics are acute, such as Severe Acute Respiratory Syndrome (SARS) and H5N1 Influenza, and are classified as public health emergencies i.e. as occurrences or imminent threats of an illness or health condition believed to be caused by the appearance of a novel or previously controlled or eradicated infectious agent and to pose a high probability of a large number of deaths, of long-term disabilities or a significant risk of substantial future harm in the affected population (Tri-Council

Policy Statement TCPS 2 2010; Calain et al. 2011). In such cases, it is likely that the reduction or prevention of such harm requires appropriate decisions and actions to be taken urgently (Gert 2005). For this reason, although many of the moral considerations relevant to all research involving human beings are likely to continue to be relevant, it is likely that the conduct of research in the context of rapidly emerging epidemics will present new ethical challenges and that what constitutes ethical practice might differ in important respects from other kinds of research (Gert 2005). Part of this is because, as already mentioned, epidemics can occur suddenly and unpredictably with massive horrendous consequences and the potential for affected communities' resources to be overwhelmed (Ezeome and Simon 2010). In the remainder of this chapter, I will review the international guidelines on research ethics and the literature relevant to the ethical considerations arising in the context of research on epidemics and emergencies.

With all the characteristics characterized above, conducting research on rapidly evolving epidemics has had to confront unique challenges and issues in the overlapping contexts of infectious disease, emergency conditions, disaster conditions and public health conditions, and on transnational or global scale. This means, on one hand, we could see most of the ethical issues related to research in emergency epidemics will be the same as those already discussed and addressed in literature on ethics of each of the contexts aforementioned and general normative guidelines governing biomedical research (WHO Meeting Report 2009). On the other hand, there will be some issues subject to the complex nature of the epidemic, can make research in rapidly evolving epidemics less or more challenging.

1.2 Ethical issues in research in emergency epidemics

In this section of the chapter I will review existing international research ethics guidelines with their relevance to emergency epidemics and academic papers on the ethics of research in rapidly evolving epidemics (REEs) and their limitations in the application into the disease context. The aim of the following review is to map out main areas of debate in light of what is considered as ethical research conduct in the setting of REEs. Against this background, I will then outline my research question and how my review of the guidelines and literature inform the overall research approach I have adopted.

1.2.1 Existing research ethics guidelines and their relevance

While there are not currently any specific guidelines for addressing ethical issues raised by research practice in rapidly evolving epidemics, there are a number of existing international research ethics guidelines and national law of relevance, to such research. Bearing this in mind, in what follows I outline some of the main important international research ethics guidelines and national regulations governing research activities involving human subjects.

1.2.1.1 Declaration of Helsinki

The Declaration of Helsinki was developed by the World Medical Association (WMA) and first adopted in 1964. In its earliest form, the Declaration was informed by two core principles: the need to protect research participants from harm and the requirement to obtain informed consent. The Declaration of Helsinki has been revised and updated a number of times and incorporated more principles for medical research involving human subjects. Of particular relevance to this project, in the eighth

revision in 2008, the Declaration included some important additions which lay the ground for research in emergency situations. For example, Section 29 points out: “Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be carried out only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population” and this type of research can only be implemented if informed consent is sought from the legally authorized representative or in cases where “no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee” (Section 29, WMA 2008). The Declaration goes on to state that consent to remain in the research must be sought as soon as possible from the subject or a legally authorized representative afterwards (Section 29, WMA 2008). On one interpretation, this might be seen to have opened up the possibility of research in acute epidemics – involving patients who are unable to consent because of their illness - where the chance of disease outbreak is rare, patients are critically ill and the question to be answered by the study cannot be answered outside of the epidemics. This might be especially the case where, any delay of research may result in a greater number of deaths or increased serious harm on a large scale.

Part C provides additional principles for medical research combined with medical care, which establish the basis for the conduct of public health research in outbreaks (WMA 2008). Among those principles, two sections (33 and 34) which elaborate on information to patients including the outcome of the study, and emphasise the importance of sharing any benefits that result from it, have implicit relevance to

epidemiological research (Calain et al. 2009). In particular, this version of the Declaration outlines a duty of investigators and other stakeholders participating in international collaborative research – in which the host community will collaborate with other foreign research organizations for research capacity – to share the benefits of such research with the host community where the research takes place (Section 34, WMA 2008).

In the latest version of the Declaration, released in 2013, in addition to reinforcing the importance of protecting research subjects and emphasizing the importance of continual monitoring and evaluation research projects, DoH also advocates the importance and value of research on unproven interventions in clinical practice (Section 37, WMA 2013). This is of importance in the context of epidemics where there is a long tradition of the use of unproven interventions as a public health standard of practice. A good example of this is the FDA's authorization of the use of Peramivir for the H1N1 influenza. In this context, research into safety and efficacy of these novel interventions is obviously crucial.

While the Declaration makes it clear that the duties it outlines are applicable to all research (Section 2- Introduction WMA 2008, Preamble - WMA 2013), interpretation is inevitably required in particular contexts and much in practice depends upon the experience, practice and knowledge of investigators. Some ambiguity is created by the fact that none of the sections mentioned above specifically addresses the question of the principles to be applied in the setting of emergency epidemics and this may mean that some investigators and possibly research ethics committees (RECs) may see the Declaration of Helsinki as being of relevance only to 'normal' research settings and, possibly to emergency medicine research. It is possible because of this when considering research epidemics, emergency epidemics, international

collaborative research, researchers may not turn to the Declaration but, rather, seek for other principles and guidelines. Alternatively, given the ambiguity of the Declaration in relation to epidemic settings, there is the possibility that different researchers and or RECs may interpret the requirements of the Declaration differently and come to different conclusions about its requirements. This may lead to different practices in different settings, disagreements about what constitutes good practice and, in some cases an overly cautious approach to the review and regulation of ethics of such research. This may lead, that is, to inconsistency, unfairness, and waste a great deal of precious time.

1.2.1.2 Council for International Organization of Medical Sciences (CIOMS)

The “International guidelines for epidemiological studies” (2008) published by the Council of International Organizations of Medical Sciences, a guideline specifically addressed to the ethics of research in low-income settings, makes a distinction between research on the one hand and public health practice required to protect individuals and society from contagion such as mandatory testing, surveillance on the other. Reflecting on the relevance of this guideline to epidemic emergencies, Calain et al, (Calain et al. 2009) argue that the criterion for the distinction between research and public health investigations in the guidelines implies that the mark of research is the involvement of “activities that are designed to develop or contribute to generalizable knowledge”. To generalize means to infer the findings from the analysis of one data set to other settings or populations where the data were not collected. This distinction is important for the question of whether an activity requires formal review by an Institutional Review Board (IRB) or Research Ethics Committee (REC) prior to the implementation of research activities.

The CIOMS guidelines recognize the difficulty of applying “generalizable knowledge” definition to the field of epidemiology, and state that a careful judgment is required for the classification from researchers and those examining research activities. This implies a need for the activity to be reviewed by IRB or REC prior to its implementation. This is made more explicit by the commentaries to Guideline 2 (“Ethical review committees”), which specifically address the case of research during an emergency including disease outbreaks. Here it is suggested that best practice is “to establish the basic research design for various categories of research prior to the emergency” and allows “prior ethical review of at least the major features of the research design”, and “when prior review has not occurred, a review should be provided as quickly as possible”. However, it is still unclear for identifying which major features should be prioritized since each IRB/REC of each region and country has different requirements and concerns over type of diseases and their urgent level.

In addition to consideration of the distinction between public health and research, the guidelines also set out a number of situations in which the waiving of consent may be acceptable in epidemiological studies. In the commentaries to Guideline 4 (‘Individual informed consent’), a number of such conditions are listed: minimization of risk; anonymization of samples; impracticability to locate persons whose samples or records are to be examined; or studies “which are carried out under legislative or regulatory authority for public health, such as disease surveillance”. Whilst important, these distinctions can be difficult to interpret in practice. Taking the case of the outbreaks of Marburg and Ebola hemorrhagic fevers (filovirus hemorrhagic fever, FHF) as an example, which “can be seen as a paradigm for ethical issues posed by epidemic emergencies”(Calain et al. 2009), Calain et al. have argued that “it is not clear from Guideline 4 if systematic blood sampling of suspect FHF cases or

otherwise exposed persons would fall within the definition of ‘disease surveillance’”. They argue that this ambiguity is having important consequences and argue that “...in order to define an adequate process for informed consent for research during FHF outbreaks, it is crucial that these points be clarified, in particular the exact meaning of ‘disease surveillance’ in this context”. This is an increasingly complex challenge, as the scope of ‘disease surveillance’ expands to global dimensions (illustrated in the revised (2005) International Health Regulations) due to concerns about the rapid spread of diseases, and as the boundaries between locally affected communities and globally threatened populations become less clear.

A related area in which there is a need for further clarification is Guideline 24 (‘Use of stored biological samples and related data’) and the related commentaries which make it clear that the constitution of sample repositories and their secondary use are subject to individual consent and submission to an ethical review committee.

Calain et al. also consider the ‘minimal risk’ criterion to be problematic: FHF patients’ baseline risk is high, i.e., ineffective coagulation, making even small incremental risks potentially highly significant (Calain et al. 2009).

Taken together, these issues show that further work is required to clarify the standards of good ethical practice in emergency epidemic settings and how and to what extent these differ from those in other forms of research. This does not necessarily mean a radical departure from the moral values that have been established and upheld during a long history of research involving human subjects but it does mean a careful consideration of the requirements of ethical practice in these complex and rapidly changing contexts. This suggests that although the CIOMS “International Ethical Guidelines for Epidemiological Studies” (2008) have made an important contribution

and have addressed some specific matters of research activities in emergency epidemic situation further work is required.

1.2.1.3 Revised (2005) International Health Regulations

The International Health Regulations (IHR) (WHO 2005) are an international instrument that is legally binding on all World Health Organization (WHO) Member States. Though these regulations are issued with the aims “to prevent, protect against, control and provide a public health response to the international spread of disease”, they do not refer explicitly to ethical concepts, but to a number of human rights considerations concerning restrictions and other measures imposed upon travellers (Fidler 2005). The IHR generally fail to elaborate on which ethical standards apply during public health surveillance, outbreak investigations and outbreak responses (Calain 2007). A possible exception might be found in Article 45 covering questions of confidentiality in the “Treatment of personal data”, but these do not specify the exact circumstances (control of travelers or local outbreak investigations) under which these should be applied (Calain et al. 2009).

1.2.1.4 Guidelines for Good Clinical Practice (GCP) – International Conference on Harmonisation (ICH)

Discussion of the GCP guidelines in the context of an account of international ethics guidelines is relevant for two reasons. Firstly, the fact that the GCP guidelines have broad scope of applicability; and secondly, because in 2008, the US Food and Drug Administration (FDA) decided that research studies submitted to it for review no longer needed to be bound by the Declaration of Helsinki — they were required only to follow the industry-sponsored Guidelines for Good Clinical Practice outlined by

the International Conference on Harmonisation (Annas 2009). This is to some extent a reflection of and to some extent a cause of the fact that although the ICH initiative was originally intended to be limited to the evaluation and registration of products containing new chemical entities and new products obtained by biotechnology introduced on the market of the ICH countries including 17 high-income countries: European countries, Japan and USA, with time, and with the expanding use of ICH recommendations to non-ICH countries, ICH-GCP guidelines have become a de facto international standard (WHO Meeting Report 2002), and have a legal status which varies from country to country.

Despite their increasing influence, these standards and the associated of process and paperwork are often perceived to be burdensome and inadequate to the research conduct in poor resource settings - even in non-emergency settings (White 2006; Lang et al. 2010).

Summary

In summary, despite their important and enduring relevance to all research, the international guidelines summarized above were not developed with rapidly evolving epidemics in mind and their relevance to these contexts is ambiguous and subject to different and potentially conflicting interpretations. They only set out general principles and procedures. Although this does not mean these principles are out of date, it does suggest the need for further work to propose appropriate notions of standards and procedures for research activities in each of the contexts and to obtain mutual agreement and consistency across countries.

1.2.1.5 National Regulations:

In this section, I consider regulations at the national level with a particular emphasis

on regulations in the United States (US), Canada and in Vietnam for their wide scope of applicability, relevance to the REE context and my focus of research setting respectively.

The United States:

a) The US 45 CFR 46 and Its Interpretation:

Sub-part A of 45 CFR 46 is known as the ‘Common Rule’ defining the federal policy for the protection of human research subjects. Its scope covers activities on foreign territories by the mention of “research conducted, supported, or otherwise subject to regulation by the Federal government outside the United States”. It means that any US funded research outside the United States is bound by this regulation. This explains its relevance to collaborative research in which organizations from the United States play the role of research sponsors or investigators. In very much the same way as with CIOMS, the Common Rule also defines research activities as those “...designed to develop or contribute to generalizable knowledge”. The US Centers for Disease Control and Prevention (CDC) provides further interpretation and clarification of this definition, identifying the distinction between ‘public health research’ and ‘public health non-research’ (Centers for Disease Control and Prevention, United States of America, 1999) with the primary intent of the activity. Here too, the primary intent of research is to generate or contribute to generalizable knowledge. And by contrast, the primary intent of non-research activities in public health practice is to prevent disease or injury, improve health, and ensure the efficient and effective use of resources.

There are a number of ways in which this distinction is unclear in the context of research in epidemics. One example relates to the exception to the requirement for research approval in cases where any identifiable private information of research

subjects has been or will be removed. In practice, regarding the example of Filovirus Haemorrhagic Fever discussed by Calain, “this is generally impractical with FHF outbreaks, considering the need to match separate databases accurately and the obligation to communicate results to concerned individuals” (Calain et al. 2009). It is because activities classified as ‘research’ according to the US CDC, will in most emergency responses include non-research components such as to identify, characterize and solve an immediate health problem and the knowledge gained will directly benefit research subjects, as well as research components such as the fact that collected samples will be stored for future use intended to generate generalizable knowledge (US CDC 1999).

In addition to the mixed nature of the activities, the primary intent distinction also has limitations. For example, to be credible, intents need to be specified in advance of potentially harmful activities, especially when very similar or identical activities are implemented with different intents. This can be taken advantage of by some researchers as a mean of avoiding the strict research ethics principles and the need for oversight. Another problem with intent as the basis of a regulatory distinction is that it would seem to imply the need for an independent body or agency capable of objectively assessing intents ahead of the deployment of activities and monitor research for the assurance of a true intention.

In addition to these difficulties arising out of problematic distinctions, the Common Rule and its interpretative documents do not provide an ethical review mechanism relevant to research in emergency settings.

An additional difficulty arises out of the fact that it is a national regulation and this leaves unanswered questions about its relevance to international contexts and about

how it ought to be applied particularly where there is the potential for conflict with other guidance (Calain et al. 2009).

Canada

b) Tri-Council Policy Statement: Ethical conduct for research involving humans, second edition (TCPS 2):

Although the application is limited at national level, the Tri-Council Policy Statement: Ethical conduct for research involving humans, second edition (TCPS 2) developed by the top three governmental research councils in Canada is the only research policy, to my knowledge, to be issued with explicit attention to emergency situations including large communicable diseases at the early time of emergency epidemics breaking out in 2009. Following experience in pandemic outbreaks, e.g. H1N1 in 2009 in Canada, and challenges encountered in public health research during other emergencies, the TCPS 2 has been developed to address fundamental questions raised in these particular situations. Accordingly, the TCPS 2 has characterized special features of public emergencies and the challenges posed by those features to research activities and research ethics review in the context. It has defined what may constitute ‘publicly declared emergencies’, and identified important ethical principles and values to be considered and upheld within this remit. Key recommendations that have been made in the TCPS 2 for research in the context of public emergencies are:

- 1) Necessary modifications to normal standards can be temporarily applied. This may involve “exceptions to, and infringements of, principles like informed consent may prove necessary to preserve or protect human life or public health, safety, order and welfare”.

- 2) Institutions and their research ethics committees should build up preparedness plans for policies and research ethics review plans in collaboration with researchers and affected communities during declared public emergencies. In this plan, TCPS has pointed out the need for a) reasonable adjustments for timing, locale, expertise, form and scope of research ethics review, b) proportionate ethics review which involves enhanced scrutiny when appropriate on the basis of risks involved in the research.
- 3) Vulnerability of individuals, potential participants, researchers, institutions, which might be caused by the nature of public emergencies should be recognized and addressed.

These recommendations can be seen as significant progress in terms of outlining an overarching ethical framework for research review and research in public health emergencies, which can be used in the development of specific plans for research in the context of REEs. Subsequent guidelines developed for research ethics review in public emergencies and multi-centred research have been partly built following TCPS 2 guidelines for public emergencies. One limitation of the TCPS 2 is that it almost solely focuses on research ethics review and, perhaps because it is developed for all cases of public emergencies, it does not specify detailed recommendations for ethical considerations that might happen in the case of REEs. On the whole the TCPS 2 leaves this process to the decision of research ethics committees and institutions.

Vietnam

c) Vietnamese regulations on clinical research:

Bolstered by the growing interest of the global pharmaceutical industry in Viet Nam and increasing numbers of international academic collaborations, more Vietnamese

hospitals and administrations are pushing towards compliance with international standards in clinical research. Although expedited research ethics review has been regulated in general guidelines for institutional review boards based at the Ministry of Health and local institutions who conduct clinical research involving human subjects to speed up the review process, public health emergencies like rapidly evolving epidemics or disease outbreaks so far have not been articulated under this type of review or anywhere in regulations or research ethics guidelines of the Ministry and local research institutions.

1.2.2 Literature on the ethics of research in relevant contexts:

As mentioned above, conducting research in rapidly evolving epidemics involves doing research in the convergence of each of these contexts: infectious disease, emergency conditions, disaster conditions and public health conditions, and on transnational or global scale. Current guidelines, even those on research in emergency medicine do not adequately address the unique complexity of research in emergency epidemics. Such settings differ from emergency research in a number of important ways. Firstly, in the context of an epidemic time pressure is an issue, even when it is not acute, due to its fast spread. Another point which, I think, makes research in rapidly evolving epidemic even harder to deal with arises out of the fact that healthcare workers and researchers are often the same people and unlike other forms of emergency medicine research and medical care where they are prepared and familiar with most of the emergency cases they encounter, emergency epidemics are novel, unexpected and unpredictable even if it is caused by the same pathogenic strains.

If we agree to the three interrelated criteria proposed by Gert that a situation should

meet in order to qualify as an emergency (Gert 2005), the two elements making up the emergency condition, i.e., expectation of serious harm and time pressure, rapidly evolving epidemic conditions thus bring a wider scale. Emergency epidemic is not merely a type of infectious disease though it carries the fundamental characteristics. While much of knowledge and discussion of ethics of research in epidemics is built around the HIV pandemic, doing research in rapidly evolving epidemics has its own set of issues and priorities distinct from chronic and persistent infections like tuberculosis and HIV, and this is characterized by the nature of unpredictability, rapid spread and short duration (Ezeome and Simon 2010). And compared with disaster and public health emergencies, rapidly evolving epidemics are sometimes not severe enough to cause great damage or suffering though they still happen unexpectedly and overwhelm the resources of the community.

In the remainder of this chapter I will review the literature on the research context associated with all aforementioned special characteristics of REEs, as I do so, I shall highlight some main categories of ethical concerns and challenges presented by the conduct of clinical research on REEs.

a) Scientific challenges in designing and planning research

Clinical research is crucial in advancing medical care in REEs. Clinical studies are needed to produce systematic information on pathogenesis, clinical course, potential interventions and response to treatment (Muller et al. 2004; Tran et al. 2009). Due to their unpredictable emergence, rapid evolution and short duration, REEs present unusual research challenges including those relating to scientific design and planning of clinical studies. Drawing upon experience from the cases of SARS and H5N1 influenza research, scientists have identified scientific challenges ranging from

formulating research questions, identifying research populations, defining research interventions and outcomes, having adequate knowledge and information to protect the safety of research participants and facilitate follow-up visits (Muller et al. 2004; Beigel 2009). This is specifically attributed to, first of all, the fact that scientific information of the epidemics is scarce but can quickly improve due to having more systematic surveillance and data accumulated over time, which for example might weaken the original hypothesis of a study before it could be completed. Secondly, there might be an absence of effective diagnostic tests or assays developed specific to the target viral strains at the beginning of an outbreak. Taken together these features make the design of studies in REEs very challenging in terms of methodology. Due to these challenges, rushing into an epidemic without an adequate scientific planning might cause ethical concerns for the safety of trial participants.

Based upon experiences of specific challenges drawn from particular acute epidemics, several solutions have been put forward for designing and planning clinical studies on REEs. Generally, these solutions call for local and international research collaboration across various experts in infectious diseases to generate a comprehensive approach in acquiring better clinical data and improving outcomes of treatment (Muller et al. 2004; Beigel 2009; Calain et al. 2009; Tran et al. 2009). Regarding the study design, suggestions have been made about the need for design and analysis methods flexible enough to allow later adaptation. Examples have included the proposed use of composite endpoints to reduce the sample size yet maximize observed outcomes, protocols with adapted changes in dose or duration of experimental therapies, simple, rapidly conducted trials for unproven and potentially harmful therapeutic agents (Muller et al. 2004). Based on arguments about the use of the precautionary principle, compassionate use and rule of rescue at population level, in her paper, Edwards has

introduced the usage of nonpharmaceutical methods (geographical quarantine and containment, and increased surveillance) and stepped wedge cluster designs (Edwards 2013) to manage the spread of disease and ensure a wider distribution to population desperately in need of a treatment in public health emergencies. This proposal has attracted many criticisms with regard to its application in situations of acute epidemics, which include both assertion on the value of these innovative ideas and criticism on possible flaws of the method and her interpretation on applied principles (Shoben 2013; Solomon 2013; van der Tweel and van der Graaf 2013). Above all, there emerge arguments about developing effective therapy for REEs centering on the tension between normal cautious approach required for developing an investigational agent and the duty to provide access to the agent to afflicted population given that there may be no proven therapy available for the disease during the course of an REE.

b) Research ethics governance

Ensuring that research project is properly conducted in terms of ethics is a fundamental function of research governance process. This basically requires “recognizing and responding to the ethical dimension of research” (Slowther et al. 2006). So once an activity is classified as research, it will be subject to relevant ethical principles and corresponding specifications according to the type of research and research in general. Research ethics governance in the situation of REEs or public health emergencies generally speaking has drawn a great deal of attention and debate in recent years. These discussions are largely around two major areas: distinction between public health practice and research, and research ethics review in response to the REEs.

Distinction between public health practice and research

Public health responses conducted in an epidemic context in some cases involve both research and non-research components. In my discussion above indicating sections of REE relevant international guidelines such as the CIOMS “*International Ethical Guidelines for Epidemiological Studies*” (2008) and *The US 45 CFR 46* and their application in the research practice in an outbreak context, there are difficulties in delineating a clear distinction between public health practice and research. In a report for public health practitioners on Public health practice versus research, Hodge et al. have shown ethical concerns arising in the blurred boundary of these two types of activities. Problems can occur when a public health investigation is classified as research and it has to go through research ethics review resulting in delays. On the other hand, if research is treated as public health practice, it may lead to infringements of the rights and safety of research participants by applying non-standard or experimental procedures. Disagreements between public health practitioners and their reviewing bodies on whether the proposed activity should be classified as research or not may impede the implementation of important public health procedures (Hodge et al. 2004), for example, collecting clinical samples to refine case definition.

While distinguishing between the two activities is important, there is no consensus on the ways to make the distinctions as partly shown in the discussion above on existing guidelines and regulations. Working towards this issue, Hodge et al. have proposed a comprehensive approach of a two-stage process. The first stage includes a checklist of essential characteristics of the two activities to make the distinctions. The second stage uses enhanced guidelines specifying additional factors for the distinctions. Although other approaches and even this approach may be unable to provide an absolute resolution, experts working in epidemic and public health have expressed

their agreement on the view that both activities should aim to provide ethical and timely responses to outbreak situations, and that activities should adhere to relevant legal and ethical norms (Hodge et al. 2004; WHO Meeting Report 2009).

Research ethics review

Rooted from historical precedents of unethical studies which caused great harm to research subjects, normal procedures established for obtaining ethical approval for research are increasingly perceived bureaucratic and inflexible (Slowther et al. 2006; WHO Meeting Report 2009; Lang et al. 2010). In the context of REEs, requirements for ethical review are further complicated by the nature of such epidemics. It is that the epidemic can geographically spread across regions and countries within a short period of time but also disappear quickly. Research into it accordingly requires the involvement of many institutions of afflicted areas and of international research community for infrastructure support, and rapid initiation. Normal research ethics review once applied to research in the setting of REEs has imposed many challenges and issues. First of all, research review might be constrained by the lack of time in responding to the emergency nature of epidemics. Research ethics committees (RECs) could face pressure to give rapid approval for proposed studies in order to quickly confront the epidemic. This pressure can come from researchers, sponsoring organization, or government agencies. For researchers and research institutions, the review procedure might become cumbersome due to the potentially large number of RECs involved. Submitting to multiple research ethics committees which may have differing responses may cause further delay (Emanuel et al. 2004; Muller et al. 2004; Farrar 2014). As evidenced from the case of SARS in Toronto in 2003 by Muller et al., within only 18 days delay from the onset of the outbreak to the receipt of ethics approval, there was a loss of 149 (60%) of 249 potential patients who could have been

enrolled into the study (Muller et al. 2004). In an analysis from Cancer Research UK reported by the Academy of Medical Sciences in 2011, there was an average of 621 days between launching a trial and recruiting the first patient (The Academy of Medical Sciences 2011). Such delays, however, in some cases are not in any way intended to enhance patient safety and benefit public health (Glasziou 2004; Farrar 2014).

To address these ethical concerns, research ethics review models have been proposed to allow flexibility for RECs and specifically adapted to the context of public health emergencies. The key points of these proposals are 1) to construct a model of centralized research ethics boards of area or region (Muller et al. 2004; Ezeome and Simon 2010), 2) to apply a certain form of expedited review or “fast-track” review, both of which are aimed to reduce some parts of usual procedures of a full review (Macklin and Cowan 2009; WHO Meeting Report 2009), and 3) to focus on proportionality which is mainly based on a guiding norm for research ethics review, proposed in The *Tri-Council Policy Statement*. According to this Statement, “Proportionate review is intended to reserve the most intense scrutiny, and correspondingly more protection, for the most ethically challenging research.” (Tri-Council Policy Statement TCPS 2 2010)

Other potential proposals target to a preparedness plan of building “model protocols” and/or obtaining in-principle ethics approval prior to the onset of outbreaks with ongoing supervision and periodic re-approval when necessary. In this model, collaboration between research institutions and researchers is required to build up model protocols. The purpose of this model is to speed up the process of protocol development and enable a faster review of research ethics boards, especially in cases

when the research ethics boards may be overloaded during the time of outbreaks (Muller et al. 2004; Macklin and Cowan 2009; Ezeome and Simon 2010).

c) Consent

Officially grounded in the very first principle of the Nuremberg Code, a representative backbone of research ethics, informed consent in the context of research has evolved and become central to the ethical conduct of research involving human subjects worldwide. Major international and national guidelines around informed consent which are widely accepted to have established the basic principles for requirements of informed consent include the Belmont Report, the Declaration of Helsinki, the Council for International Organizations for Medical Sciences (CIOMS) guidelines, and the guidelines produced by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use– Good Clinical Practice (ICH-GCP). The requirement of obtaining consent is based on the fundamental ethical principle of respect for patient autonomy¹ (Beauchamp 2009; Norman 2011). Following from this principle, three components must be met: disclosure, capacity and voluntariness (Etchells et al. 1996). Other main bases for informed consent are to protect patients and participants from harm (Eyal 2011), trust (O'Neill 2002) and self-ownership which stresses on proprietary rights over ourselves and our bodies (Archard 2008). While supported by strong rationales,

¹ In discussing about the relationship between autonomy and informed consent, Tom Beauchamp and James Childress argue that consent is needed to respect patients' autonomy, and autonomy here relates to autonomous choices (Beauchamp and Childress 2009, pg.100).

consent remains one of the most controversial topics due to complications caused by research context and research practice. This also applies to consent in the context of REEs. Issues in obtaining informed consent in REEs include the time limitation which might make obtaining direct consent from participants or their legally authorized representatives impossible. This may be due to subjects being in a critical condition, temporarily unconscious, or when there is a narrow window for therapeutic intervention, (Calain et al. 2009; Macklin and Cowan 2009; Ezeome and Simon 2010). To some extent, this is similar to the types of research conducted on critically ill patients with all of the characteristics of acute care setting (Andrew D. McRae, 2002). Added to this context as in the case of REEs is the intense public health practice for disease control and prevention, e.g. isolation, quarantine, overloaded healthcare infrastructure, and the implementation of triage process to healthcare services. Such contextual factors have been stated to subject prospective research subjects to potentially greater vulnerability which may significantly compromise their decision making or that of their family members. Coupled with emotional distress, desperate desire to get treatment and confusion between routine activities conducted for public health practice and those specifically for research, individuals may feel compelled to participate in the research without a thorough understanding of it (Ezeome and Simon 2010).

Therapeutic misconception² (Appelbaum et al. 1987; Lidz and Appelbaum 2002) is thus most likely to happen in such an emergency epidemic context (Ezeome and Simon 2010). Ensuring potential research participants or family members understand fully about the research whilst trying to avoid factors that might undermine their decision making, pose many challenges to researchers. Issues reported in the case of research on filoviruses, Marburg and Ebola, in the most remote and resource-poor areas of sub-Saharan Africa can be seen as an extreme examples of how the outbreak setting might affect clinical research and how contextual factors might compromise the relationship between research participants, communities and researchers (Bausch et al. 2007; Bausch et al. 2008; Calain et al. 2009). Some important factors that have been highlighted in this case are isolation facilities in hospitals, incompatibilities between universal healthcare standards and local culture, pre-existing distrust and hostility of communities toward outbreak control teams and foreign investigators, ostracism from the community of returned survivors (Boumandouki et al. 2005), extremely limited contacts with family members and anonymous interactions with medical providers through protective clothing, and constantly being on the verge of death. At the community level, clinical research in such settings might run the risk of being perceived as exploitation of vulnerable populations (Bausch et al. 2008).

Issues with obtaining consent also arise in research on clinical samples collected from antecedent studies or originally taken for public health purposes. The fact that there

² The ‘therapeutic misconception’: The therapeutic misconception occurs when a research subject fails to appreciate the distinction between the nature of clinical research and that of ordinary treatment, and therefore inaccurately attributes therapeutic intent to research procedures.

might have been no plan for the use of a certain type of data for future research at the time of collecting clinical samples, can lead to challenges for research which requires going back to sampled individuals to get consent for the use of these samples. This might be logistically difficult or even impossible in some cases in which samples have no identifying information or where it would be difficult to locate the individuals after quite a long period of time. In cases when researchers want to use collected samples without going back to participants to obtain consent, they are required to submit the protocol to relevant research ethics committee for the use of the samples or certain type of data extracted from the samples (Macklin and Cowan 2009). In acute epidemic settings when subsequent research including new plans to use certain types of data could only be conducted in sequence based upon results of previous research, and provided that research on these epidemics often involves large number of patients, the requirement of going back to individuals to obtain consent seems to be inapplicable.

The inadequacy of research ethics regulations concerning consent practice in REEs, has led to the proposal of a variety of consent models based upon the type of research, anticipated level of benefit and risk involved in research participation and the concept of ‘societal good’(Macklin and Cowan 2009; Cook et al. 2010), as shown in Figure 1.5. More specifically, a culturally sensitive, informed and verifiable process is desirable (Bausch et al. 2008; Ezeome and Simon 2010). This could be done through training research personnel to obtain consent based upon these three criteria, and public disclosure of research information shall be made to local communities prior to and following the completion of research to enhance the understanding of community about research and increase the ‘social appreciation’ of their role in research participation (Bausch et al. 2008; Macklin and Cowan 2009; Cook et al. 2010). While

public disclosure should arguably take place in any form of community consultation (FDA CFR 21 and 45US FDA 1996) (Formenty et al. 2003), in REEs there are particular challenges in identifying afflicted communities in advance due to the migratory nature of the epidemics and concern that community support for research might impose direct or indirect coercion on afflicted individuals (Macklin and Cowan 2009; Ezeome and Simon 2010).

Overall, the fundamental argument for consent in the setting of REE research is that be it in any form, consent should take into account the principle of beneficence whereby the research will benefit afflicted populations and the society as a whole, and prospective research participants stand a chance of survival or improved healthcare through investigational therapies or healthcare delivered in clinical studies (Tran et al. 2009; Calain et al. 2011). Strict adherence to consent procedures which are commonly regulated for research in normal research settings as a reflection of extreme interpretation of autonomy has shown to be put in conflict with beneficence, or the social value of research in the setting of REEs. As indicated in cases when researchers face the tension between beneficence and the duty to respect autonomy, a range of dubious solutions might include 1) research could be done in the neglect of autonomy (Calain et al. 2011), 2) “innovative therapy” has been used without benefiting from well-designed trials (Fost 1998), 3) research has been done in blurred boundary between public health practice and research (Hodge et al. 2004; Calain et al. 2009; WHO Meeting Report 2009).

Table 4. Recommendations for informed consent for clinical critical care research during the H1N1 pandemic

Registries, audits, retrospective chart reviews, and prospective observational studies regarding H1N1-related critical illness that do not influence patient care should use a waiver of consent
Randomized trials of treatments for H1N1 critical illness that are in widespread use (e.g., dose or duration of antivirals or use of corticosteroids) should use deferred consent or waived consent
Randomized trials of treatment with an established safety record but that are unproven for H1N1 (e.g., serum immune globulin) should use deferred or waived consent
Randomized trials of new H1N1 treatments without an established safety record that are unproven for H1N1 (e.g., ECMO) should use deferred consent
For patients with no existing surrogates or unavailable surrogates, alternate consent models should be considered, such as deferred consent (deferred from the patient, deferred from the surrogate), two-physician consent, a request for an "objection to participate," and waived consent
Verbal consent should be considered for surrogates who are illiterate; consent through translators should be considered for surrogates speaking different languages or dialects
Telephone consent should be considered for surrogates who are prohibited from coming to or unable to come to the hospital during a pandemic
Consent models should be predicated on the anticipated level of benefit and risk incurred by study participation
Hybrid consent models (e.g., different consent models for the same study) that acknowledge whether surrogates exist or are unavailable) should be encouraged, adapted to local norms and circumstances
Taxonomy of REB-approved H1N1-related studies into which patients may be enrolled without <i>a priori</i> written informed consent should be developed locally; public notification (by community consultation, print, audiovisual, or web media) should publicize enrollment as the default, akin to the assumption of consent for organ donation in some jurisdictions, with opportunities for the surrogates to opt out
Co-enrollment of patients in both H1N1-related treatment and observational studies and other unrelated studies should be allowed, adapted to local norms and circumstances

ECMO, extracorporeal membrane oxygenation.

Figure 1.5: Alternative consent models in H1N1 pandemic

(Source: Cook, D., K. Burns, et al. (2010). "Clinical research ethics for critically ill patients: a pandemic proposal." *Crit Care Med* 38(4 Suppl): e138-142)

d) Collaboration

Collaboration is one of prominent themes in the literature on the ethics conducting research in the outbreak of REEs. It is mostly mentioned in the form of solutions towards facilitating the timely and effective response of research conduct in the time of REEs. One example of this was mentioned above in section 1.2.2b in proposals is to increase the speed of research ethics review through establishing research collaboration among researchers in the field for a collection of model protocol. In the analysis of experiences learned from past occurrences of acute epidemics such as

Ebola, SARS or H1N1 pandemic influenza, while ineffective response is believed to be partly caused by such issues as delays in research ethics review, it also results from the lack of collaboration between various profiles of experts, and between research and public health practice (Calain et al. 2009; Tran et al. 2009). Reasons for the lack of such collaborations could include the divergence of research interests, prioritising patient care, lack of information on the pathogenesis and pathophysiology needed to inform public health practice (Calain et al. 2009; Tran et al. 2009; Ezeome and Simon 2010), and potential bad publicity caused by rumors and false information (Ezeome and Simon 2010).

Addressing these issues requires wide collaboration of various stakeholders including, but not limited to, clinicians, public health practitioners, and researchers of all groups of expertise, funders, research communities and the public. (Farrar 2007; Beigel 2009; Calain et al. 2009; Tran et al. 2009; Ezeome and Simon 2010). This can be conducted through the format of national and international collaborative research networks (Muller et al. 2004; Farrar 2007), and the involvement of research community, public and mass media (Tran et al. 2009; Ezeome and Simon 2010). Challenges in establishing these collaborations might be the rapid spread and migratory nature of REEs, resulting in spread to new research sites and communities, thus requiring new collaborations with further involved parties. As collaborations require time to be built and developed, research collaborations in the REE research context is therefore suggested to be planned and implemented prior to the outbreak events (Ezeome and Simon 2010).

e) Benefit sharing

Ethical issues in recent years have increasingly emphasized the importance of benefit and sharing and of the social value of research. Highlighted in international research context, it is claimed that ethical research must have social value and that to minimize exploitation in international health research in low and middle income countries, fair benefits to participants and their communities should be ensured (Participant 2002; Emanuel et al. 2004; Participant 2004). Benefits might include the information obtained from the study, medical treatment of participants during the study, availability of the proven intervention afterwards, or improvements in the health of the community through employment and training for community members to improve health-care services for the entire community (Emanuel et al. 2004; Participant 2004). However, reaching a fair level of research benefits between researchers, sponsors, study participants and their communities either within the scope of a research project or wider scope of society is complex, and difficult to translate into practice (Schulz-Baldes et al. 2007). Against this background, it is unsurprising that the question of benefit sharing should be discussed in relation to research in REE. Typical examples of conflicts arising in benefit sharing might be 1) the controversy over the distribution of H5N1 virus specimens through WHO networks broke out in 2007, and 2) the controversy over the access to the experimental drug ZMapp for the treatment of Ebola in West Africa in the outbreak of 2014. In the first case, controversy occurred due to the refusal of one country to share H5N1 virus specimens with WHO due to concerns that its strains of H5N1 would be used to make vaccines in high-income countries which would then be “resold” to lower income countries at what they considered to be unaffordable prices. There was also concern that scientists in high-income countries would be able to take out patents based in part

on these strains and sell back the vaccines at market prices. The sharing of virus samples is necessary because it allows researchers to track the evolution and spread of resistance, to evaluate the risk of a pandemic and allows for the development of vaccines (Enserink 2007). As Indonesia had more confirmed H5N1 human cases and deaths of any other country, its withdrawal from the network was particularly concerning, and posed a threat to global health security (The Lancet Infectious Diseases 2008). The second case of Ebola broke out from the access to an experimental drug cocktail called ZMapp given to two American missionaries who contracted the virus in West Africa, and this was the only possible treatment at the time. This drug, however, was not made available to any infected cases in the four afflicted countries in West Africa (Caplan 2014). These two cases have fostered debate on benefit sharing over which such questions have been posed as provided that there are some form of benefits from research or public health activities, who consists of potential beneficiaries, who should stand the most chance to gain the benefits, how to make the benefits accessible and maintain the trust between researchers, public health practitioners, and afflicted communities/countries.

In the anticipation of clinical trials to take place in the filovirus hemorrhagic fevers outbreaks in the near future, in the paper reporting experiences in the outbreak of Ebola published in 2009, Calain et al. proposed four essentially distinct categories of potentially affected groups, including: 1) rural communities in sub-Saharan Africa exposed to the risk of infection through natural reservoirs or intermediate hosts; 2) health care personnel exposed to the risk of sustained nosocomial transmission, typically in poorly equipped African hospitals; 3) laboratory researchers accidentally exposed to virus samples and 4) anticipated victims of bioterrorism acts (Calain et al. 2009). In this classification, “Potential beneficiaries of the results of clinical trials

would thus differ in the nature and legitimacy of their concerns (real versus alleged), in the intensity of risk to which they are exposed (sporadic versus sustained), in their freedom of choice toward exposure and in their likelihood of access to future preventive or curative technologies". These debates arising out of the two cases of H5N1 and Ebola demonstrate a new global dimension of benefit sharing between poor countries who donate 'natural resources' such as clinical samples and technologically advanced industrial groups or countries with private interests (Sedyaningsih et al. 2008). These events would also trigger new debates and attempts in determining which 'community' perspective at global-wide dimension should prevail (Calain et al. 2009).

One possible solution for issues in benefit sharing might be that specific categories of beneficiaries of research should be elicited when approaching communities affected by outbreaks (Calain et al. 2009). However, due to differences in the perception of benefits of involved parties and the level of trust towards each other, reaching a consensus on these categories appears to be very challenging.

f) Risks to researchers and concerns for global security

Due to their high transmissibility and in some cases high lethality like SARS or Ebola, REEs often place medical providers and researchers at risk through contacts with patients and contagious specimens. In the case of Ebola virus, there is a case report of a needle stick injury of a virologist on 12 March 2009. The syringe contained *Zaire ebolavirus* (ZEBOV). As a result, she was given an experimental vaccine which had not been previously used or tested in humans. At the time of the injury, there was no proven treatment or a post-exposure prophylaxis for Ebola haemorrhagic fever (Günther et al. 2011). Besides personal risk, researchers may also

become disease vectors, putting their patients, colleagues and institutions at risk accordingly (Muller et al. 2004). Reported in the case of SARS, Muller et al. have pointed out other challenges that researchers might confront in doing their work. Researchers and healthcare workers were quarantined; travelling between institutions was required to be restricted to reduce transmission risk (Muller et al. 2004).

The storage of biological specimens at laboratories also raises a number of considerations with respect to infectious disease agent. An example of this can be found in the case of infectious samples and strains of filoviruses which require maximum security laboratories. This may result in the de facto monopoly by a limited number of reference facilities tasked with the management of official repositories and decisions about sharing specimens (Calain et al. 2009). The issue can lead to the risks of illegal use of the infectious agents and bioterrorism which can put a threat to global security.

Various approaches have been proposed in order to manage these risks. First of all, clinical care and trials could be integrated so that it would help to reduce the number of patient visits and the need for additional sampling through sample sharing. Media tools for distance communication for example telephone, email, teleconference, etc. could be utilized for clinical management and study coordination across sites. This not only helps to eliminate the spread of the outbreak from direct exposure and travelling but also allows and facilitates the participation of multiple research sites in the research. Finally, a cautious approach for transmitting prevention and providing adequate training for researchers are generally suggested for risk management in research conduct (Muller et al. 2004). In regard to issues of bio-security, there is suggestion for an international agreement on bio- samples management to be

developed – but this raises practical ethics challenges of its own as well (Calain et al. 2009).

1.3 Conclusion: The need for empirical research to explore the practical ethical issues arising in research on REEs from the perspectives of stakeholders who have participated in such research

The focus of my research in this thesis is on the ethical issues arising in the context of research in the context of rapidly emerging epidemics. In this chapter I have reviewed the relevant research ethics guidelines and the literature relating to the ethics of research in this area. This review has highlighted some of the limitations of the current guidelines in their scope and interpretations to the specifics of research practice in the REE setting. It has also highlighted a number of ethical issues in major parts of research practice including scientific design and planning, research ethics governance, consent, research collaboration, benefit sharing and risks to researchers and global security.

Overall, my review of literature suggests that research ethics in rapidly evolving epidemics is insufficiently addressed in the development of guidelines and regulations. They are only limited to consent and research ethics review. Although research papers have laid out various ethical issues arising in the research context with specific solutions as mentioned above, the issues are only reflected through single-sided view and are not systematically investigated. Solutions proposed are accordingly broad for the most part without taking into account the dynamics of research fabric which includes many actors and even public with different perspectives and agenda. In particular, the issues are predominantly raised from the view of investigators and observers who were not participating in the research

practice. In comparison with normal research setting and other disease setting, ethics guidelines and ethical debates developed for the context of REE are infrequently discussed and not widely applied. What has been missed so far is the views of other key relevant stakeholders such as research participants, research sponsor, funders, research ethics committee who directly involve in and play a crucial part in the conduct of research. These groups of stakeholders have their own moral duties and legitimate interests that should be paid attention to and balanced if a research is to be effective and lead to effective and appropriate solutions for ethical issues arising in the research context. Perspectives from all relevant stakeholders consequently should be identified and understood in the real context to see how they interact and influence taking into account of other contextual factors in order to achieve a broad and richer account of ethical concerns and challenges that might arise in the studied research practice. It is increasingly recognized that empirical description and analysis of ethical issues through qualitative methods can bring about considerable relevance and benefit to philosophical debates and proposing solutions to matters at issue (Hoffmaster 1992). What I want to point out here is not the application of empirical research in ethics which I will provide further elaboration in the following chapter on Methodology. It is instead the recognition of the fact that the complexity of situational factors and the perceived nature of the problem contribute and dictate which principle(s) are used and applied in an ethical dispute. As Frohock observes in his study of treatment decisions in neonatal intensive care units:

“The cases themselves-their complexity, the severity of the problems-allow reasonable people to apply the same principles in different ways. This discretionary power, rather than disagreement on principle, is the main

source of disputes over therapy in the gray zone. . of treatment” (Frohock 1986, pg.51)

Some qualitative research investigating how healthcare workers and patients perceived ethical problems in clinical medicine also suggest that ethical issues and the importance of each of the issue are perceived differently within each member group (Gramelspacher et al. 1986; Dickert and Kass 2008).

What can be problematic from solely relying on the application of philosophical theories in identifying and resolving ethical problems or that in combination with the single sided view of the authors is that it might discount other important factors involved in the perception of a problem, or certain issues attached to the practice of each group of stakeholders, which might not be seen by ‘outsiders’, and especially some problems might be ‘problems’ to the authors or observers, but not to the people participating in the practice. Ethical principles which are “too general and vague to apply determinately to concrete situations” and sometimes conflicting might fail to help resolve issues concerned. As noted by Hoffmaster on the theory-driven approach of ethics to ethical problems that arise in health care:

“The substantive moral work occurs in determining how a principle might impinge upon a particular problem, but the resources for addressing that issue are external to the principles themselves”(Hoffmaster 1992, pg.1422).

In this vein, he has also called for a more contextual approach to ethics which integrates ethnographic studies and theory-centered philosophy to investigate moral

problems in health care and conception of moral theory which is more responsive to the empirical dimensions of those problems (Hoffmaster 1992).

The overall implication for empirical research to be implemented in ethics is that it may provide a deeper understanding of the nature of moral problems arising in a practice within a certain defined society, of how they are perceived and handled. Doing empirical research with a community, which in this case is a research community including key stakeholders directly participating in the research practice of REEs, is hoped to bring up valuable insights and a broad range of aspects of ethical considerations of the research community in their work. To issues that are already identified in the literature, this knowledge is expected to add richer description to the ethical phenomenon as well as a comprehensive view for any solution possible.

While there is not to date any empirical research identifying ethical issues through perspectives of key relevant stakeholders, I propose to conduct an empirical research to investigate the practical ethical issues arising in the context of research into REEs for key relevant stakeholders. My research aims to answer the questions: What issues arise in research on REEs? Who is involved in these issues? How are these issues experienced, understood and reasoned about? In my next chapter, I outline the methodology adopted.

Chapter 2 Methodology

2.1 Introduction

The intention of this chapter is to present the research strategy I developed to answer the research question: What are the practical ethical issues arising for key stakeholders in research on rapidly evolving epidemics? My outline of the research strategy covers questions relating to 1) which type of data need to be collected, 2) how the data are to be obtained in practice and 3) how the data should be analysed.

I begin by outlining the rationale for adopting an ‘empirical ethics’ approach which combines qualitative methods and ethical analysis. After having done this, I lay out relevant theoretical positions regarding the nature of the type of knowledge I want to achieve and the choice of qualitative research methodology to obtain the data most suited to the ethical analysis that I want to integrate in this research. This is followed by details of how I implemented the research strategy including sampling, data collection and analysis as an iterative process. The chapter will be concluded with an initial high-level summary of the core themes arising from my analysis of the data collected and an explanation of how the presentation of my empirical findings in subsequent chapters will be structured by these themes.

2.2 Rationale for choosing qualitative research and ethical analysis for this kind of study

The value of qualitative research methods for bioethics is its utility in understanding values, personal perspectives, experiences, and contextual circumstances (Hull et al. 2001). The value of qualitative research, especially, that which aims to identify and characterize ethical problems existing in concrete settings as an important contribution to research on ethics and medical ethics has been increasingly

emphasized (Birnbacher 1999; Musschenga 2005; Dunn et al. 2012; Salloch et al. 2013). In this type of research, qualitative data can not only investigate the broad range of concerns but is also able to capture the depth and complexity of ethical issues experienced by actors involved. In considering how a qualitative approach would fit my research based on what is known about the research subject and how we can answer the research question, there are three significant reasons why I chose this methodology. First, little is known about ethical issues in the practice of clinical research in emergency epidemics as well as their context and perspectives of key stakeholders involved. Second, there is a lack of systematically collected empirical data on this research setting. And third, whilst my aim is to better understand the nature of ethical considerations arising in emergency epidemic context through key stakeholders involving in the research practice, it is important to yield rich accounts of the research context and multiple perspectives from narratives. In addition to stakeholders' accounts, I, as a researcher, can provide my own account of ethical considerations based upon my reflection on the data collected and my understanding of the field.

In the next section, I will specify areas in which qualitative data can contribute in my research, and how these data can be related to ethics and to what extent.

2.3 The relationship between qualitative research and ethical analysis:

2.3.1 Criteria for empirical ethics

The combination of qualitative research, and ethical analysis is a feature of what has come to be known as the 'empirical turn' (Borry et al. 2005), e.g. descriptive ethics, morally relevant empirical research, or well-informed practical ethics (Musschenga 2005). The ultimate aim of empirical ethics is to improve the context-sensitivity of

ethics in an endeavor to make normative claims about practical solutions (Musschenga 2005; Dunn et al. 2012). With this aim, empirical ethics has gradually taken an important place in the field of medical ethics (Salloch et al. 2012) although there are still on-going debates around value and validity of this research approach to ethics (Garrard and Wilkinson 2005; Hedgecoe 2007; Hurst 2010).

An empirical ethics approach also appeals to me as a person with a background of law and clinical research coordination and is very interested in practical rules which can be translated from ethical principles or theories. Through years interpreting and applying these rules into relevant practice settings myself, I see the value of social research input is significant not only in the application of these principles but also in the phase of conceptualizing ethical principles and developing theories. Basic ethical principles once introduced to practice must be seen as relevant to be accepted by targeted societies. And in order to become ethically motivational, those principles should be achievable. The exploration and understanding of the whole context where ethical principles are operating has thus become an area of strong interest within ethical methodology; according to Sissela Bok:

“I believe that any method, to be of help, should originate with the actual choices people make. It should have to look at the actual excuses they give, to themselves and to others, the arguments by which they appeal to principles, and the means by which they evaluate such arguments when others make them. To take such a path will require a search for cases, examples, descriptions of what happens” (Bok 1999, pg.58).

If bioethicists do not take these contextual factors seriously, their ethical advice may be misguided, too general, or even presumptuous. An example for the need of consideration of operating context is the application of the concept of ‘autonomy’ in obtaining informed consent from research participants. This Western concept applied in research has been introduced to Viet Nam and other Asian countries during the globalization of clinical research in the last few decades. Its application, in which “moral weight is placed on an individual's ability to govern herself, independent of her place in a metaphysical order or her role in social structures and political institutions” (Christman 2011), has raised ethical challenges in Asian countries where people are highly likely to be traditionally family- and group-oriented (Pope et al. 1998; Uwe P. Gielen et al. 2008). Harmonization in communication and fatalism are the two salient characteristics in Asian societies, and these, in some occasions, especially in the medical setting, cause difficulties for a Western-styled consenting process (NBAC Report 2001; Lindegger and Bull 2002; Silverman 2005). This is where empirical information about ethical issues or challenges arising in the context or evaluation on existing measures applied in a particular context is most needed for a comprehensive contextual understanding which may lead to alternative judgments, and practical solutions.

There are a number of different models of empirical ethics research which connects the collection and analysis of empirical data and normative analysis. These can be divided variously based on the starting point adopted, i.e. empirically or philosophically-driven, or which part of applied ethics the empirical information can serve as crucial inputs to develop an account of solutions to deal with moral issues, i.e. explorative research or moral pragmatics (Dunn et al. 2012; Salloch et al. 2013). However, despite their differences these divisions all ultimately have in common the

goal to develop an account of a sound, coherent and convinced normative judgement/solution. In the light of this, many conceptual frameworks have been proposed regarding how to integrate empirical data with normative analysis in an attempt to bridge the gap between the 'is' and 'ought' on the basis of achieving a coherent account of facts and values or having a systematic combination between empirical data and normative analysis in order to develop and refine arguments.

2.3.2 Adopted approach

Having reviewed criteria for empirical ethics research and possible methodological frameworks, my chosen approach is to use qualitative research and ethical analysis as in the following schematic framework:

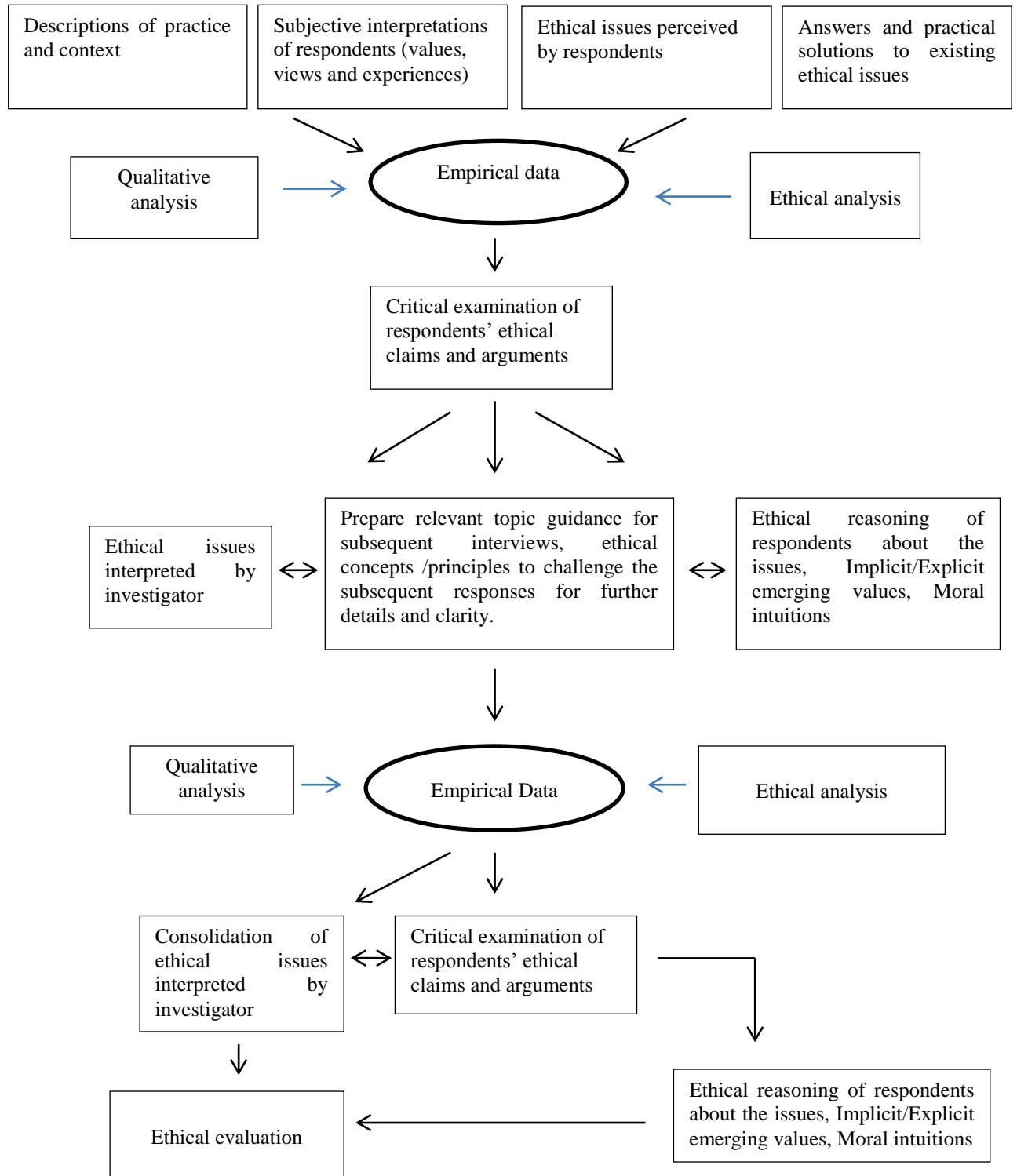


Figure 2.1 Schematic framework for qualitative and ethical analysis

In order to answer the key question of the present study i.e. What are the practical ethical issues arising for key stakeholders in research on rapidly evolving epidemics?, I propose to collect and analyse four types of information as follows:

1. Descriptions of relevant practice and context (objective circumstances)
2. Interpretations of respondents (the meaning making of a person as a result of impacts from complex and dynamic features embedded in a particular context and society)
3. Ethical issues and characteristics of the issues perceived by respondents
4. Solutions that have been applied or proposed to resolve existing ethical issues by respondents.

The main focus of the study is to achieve a good understanding of the moral context and ethical issues faced by stakeholders, and their views about possible solutions. Given this aim, I adopt an approach to my research exploring ethical problems perceived by stakeholders in their practice, which emphasizes the importance of *meaning*:

“In this worldview, individuals seek understanding of the world in which they live and work. They develop subjective meanings of their experiences – meanings directed towards certain objects or things. These meanings are varied and multiple, leading the researcher to look for the complexity of views rather than narrow meanings into a few categories or ideas. The goal of research, then, is to rely as much as possible on the participants’ views of the situation”(Creswell 2007)

In this manner, my research will be able to investigate a diversity of interpretations implicitly or explicitly expressing multiple manifestations of ethical problems, and acknowledge the existence of influences from events, participants and other sources to my construction of ethical issues.

As outlined in the framework above, after collection, data will be subjected to both qualitative analysis and ethical analysis. Qualitative analysis at this stage will proceed both inductively and deductively to produce descriptive accounts from respondents about what came up as ethical issues with their reasoning, relevant contextual features, and processes used for dealing with these issues. During this analysis, particular attention will be paid to ethical themes including vocabularies used, concepts and value emerged and ethical arguments. Findings from these analyses will be used to inform the design of topic guides for subsequent interview rounds. This step will help, first, to focus on core categories of issues and themes emerging from the initial set of interviews, and second, to identify other relevant stakeholders who may play a significant role in research practice and whose interests are important components of interviews in subsequent stages. In other words, at this stage, with the core categories of issues and themes narrowed down from an initial large pool of empirical data, further data will be collected in the direction of these categories. This phase can be repeated until it is determined that subsequent interviews are no longer bringing new information for the development of studied topics.

The second phase of analysis is the phase in which I will draw a consolidated set of ethical issues from the empirical data collected and preliminary analyses. In this phase, with the help of qualitative analysis, relevant empirical data will be brought together to create a larger coherent framework for any emerging relationship that might exist. Normative weight will be sought for the empirical data by discussing and

comparing them with other factors in a relevant argument. This step of ethical evaluation is aimed to extend the dimension of an ethical problem resulting in a compelling account of reasons for the consideration of giving a normative judgement.

2.3.3 Ethical dilemma or ethical problem

As the questions posed to respondents are going to be about what type of ethical issues they might have faced in their research practice, another important methodological concern is the terminology to be used in the interviews. Which terminology, e.g. 'ethical/moral problems/issues' or 'ethical/moral dilemmas' would be most likely to effectively evoke respondents' reflection about moral values and conflicts arising in moral values in their daily research practice, or in a broader sense, what they might feel went wrong or right in comparison with their own moral accounts? In common parlance, no great difference is raised between the two terms 'moral problems/issues' and 'ethical dilemmas'. Most bioethics texts suggest that moral problems usually involve conflict, choosing between equally desirable or undesirable alternatives, or balancing options (Braunack-Mayer 2001). However, ethical 'dilemmas' tend to be defined more narrowly as situations in which on moral grounds, persons ought both to do and not to do something. According to Beauchamp and Childress, moral dilemma can occur in at least two forms "(1) Some evidence indicates that act x is morally right, and some evidence indicates that act x is morally wrong, but the evidence on both sides is inconclusive. ... (2) An agent believes that, on moral grounds, he or she both ought and ought not to perform act x ... the reasons behind alternatives x and y are good and weighty, and neither set of reasons is dominant" (Beauchamp and Childress 1994, pg.11).

There are empirical studies on healthcare professionals' reasoning about situations which they see as morally problematic. The first study that needs to take into consideration here is the Nursing Dilemma Test developed by Crisham. It contains descriptions of six morally problematic situations derived from extensive interviews with nurses. In this test, Crisham has chosen situations which she and her respondents see as dilemmas (Crisham 1981). Another Canadian study on nurse's definition of ethical dilemma provides a clearer account of 4 different situations of ethical dilemmas perceived by nurses; 1) there are conflicts between the nurse's own principles and those of other professionals, 2) confusion arose when no obvious right or wrong choice existed, 3) situations where someone's conduct was considered emotionally instead of rationally based, or 4) there are specific dilemma situations, e.g., concerning the termination of treatment situations) (Davis 1981). In general, these results reveal that 'ethical dilemma' may be an indistinct concept to nurses in their common usage. Perception of moral problems of medical doctors has also been investigated in research. A qualitative research conducted with 15 general practitioners (GPs) in South Australia to identify the way in which moral problems were defined by lay views has suggested that the moral domain is perhaps wider and richer than mainstream bioethics would generally allow (Braunack-Mayer 2001). Through analysis of interviews with all GPs, the author found that while some of the views of the GPs about the nature of their ethical dilemmas accorded with the definition provided most of bioethics literature, i.e. based on the notion of conflict and choice between competing alternatives, other explanations of the ethical nature of their problems centered around the publicity associated with the issues under discussion which makes the issues become publicly contentious requiring doctors to

form a view on such issues, concerned about their relationships with patients, and anxiety about threats to their integrity and reputation.

In consideration of the theoretical disagreement on the nature of ethical dilemmas and the broad account of the terms given by healthcare professionals, Holm has suggested that, as a less contested concept, the term 'ethical problem' should be used as an approach in interviews. He argues that: 'a person faces an ethical problem in a situation in which ethical considerations are important for the choice of action' (Holm 1997). Given that his study purposes are 1) to provide a description of how healthcare professionals identify ethical problems, and 2) how they reason about the problems they have identified, he goes on to provide further description for one concept in the definition above, namely 'ethical considerations', while keeping other concepts including 'person', 'choice', 'action' in their common-sense meaning without any technical specification. Depending on each normative theory, 'ethical considerations' would entail different meanings and contents, e.g., consequentialism and deontology. And while wanting to encompass considerations that are ethically or morally relevant by both the consequentialist and deontologist as well as non-philosophers, Holm suggests three following categories of ethical considerations in his study. A consideration would be therefore classified as an ethical consideration if it: a) refers to a non-legal or not solely legal norm, duty, obligation or right; or b) refers to consequences (well-being, happiness, etc.); or c) refers to what kind of person one ought to be or what virtues one ought to have. These categories can serve as a guide for an investigator during the interview to consider what may be relevant for his/her topic and to probe more about it for further discussions with the respondents. I think these categories are useful in this research because while they are grounded by three widely adopted ethical theoretical approaches on consequentialism, rights and virtue,

the general concepts used here, for example, ‘obligation’ or ‘consequence’ are open enough for the research not to be bound by and confined to their particular theoretical specifications or arguments caused by other closely related theories. This would be, furthermore, advantageous in a later stage of normative analysis in relating practical ethical considerations grounded in these concepts to ultimate ethical principles and their specifications mentioned in the literature elsewhere. However, strict application of these categories would limit the account of moral issues raised by respondents. Another challenge in applying these categories would be that participants, especially in Viet Nam or other countries to whom these concepts are to some extent foreign, would find difficult to relate them to their practical setting and actual considerations. For these reasons, and as the purpose of this research is to identify a wide range of ethical considerations raised by stakeholders in the research practice of REEs, in other words to understand their view on the ethics of research in REEs, and based on all relevant accounts of what can be counted as ‘ethical problems’ as mentioned above, I chose to adopt a broad definition which is that ethics is about situations in which people have views about what is morally 'right or wrong' or where they face 'difficult decisions'. This definition will also be used as my probing guide in the interviews with participants.

2.3.4 Determination of the problem

It is also important to pay attention both in the interviews and in the analysis to the different ways in which terms such as ‘ethics’ and ‘morality’ may be used by respondents and by the researcher to identify and reflect upon ethical considerations. In this research I have understood the distinction between ethics and morality as follows. Firstly, while ethics is generally used to refer to ultimate abstract principles

of morality and human conduct, morality is connected with a variety of different specific standards and rules involved in the actual assessment of and dealing with actions of individuals or groups (Macklin 1999; Olatunji 2007). This reflects much ethnographic research, in which the moral is taken to consist of the actual commitments, compromises and practices by means of which social participants negotiate what is at stake locally (Kleinman 1995). Ethics, by contrast, is a step further from morality in a way that it can go beyond the scope of a particular moral norm recommended or approved by a society or a group of people as a result of intellectual reflection on those socially approved norms in attempt to provide justifications and answers to matters at issue (Olatunji 2007). These distinctions will help to clarify the roles with corresponding tasks between the investigator and respondents as well as moral sources used by the two. Specifically, on the one hand, respondents through their first hand experiences and by appealing to practical moral sources, i.e. cultural norms, social and professional practices or codes would speak from their perspective of particular ethical problems or considerations. The investigator, on the other hand, from her knowledge of abstract ethical principles would engage with the studied environment to gain empirical information with involved rules and principles to construct a rich description of the practice, and reflect on it more deeply by examining its coherence and appealing to abstract ethical principles. As a consequence, determination of what count as ethical problems would be to some extent different between the respondents and the investigator. However, acknowledging these two distinctions does not mean that I will use ‘morality’ and ‘ethics’ differently in the interviews talking with participants, for doing so would be mistakenly inferred that participants are people who are not capable of appealing to ethical principles in their reasoning. Using these two words interchangeably in

interviews and in the thesis, in addition, may help to avert confusion and efforts in differentiating between the two which is usually overlapped in their practical usage and common discussion. Another important point to note is that in Viet Nam, almost research ethics training uses the word ‘ethics’ or ‘ethical issues’ in English, and they are all generally translated into Vietnamese as the same word ‘đạo đức’, using the word ‘ethics’/’ethical issues’ would make the interview sound familiar to them.

In summary, at this point, I have laid out my general approach of how data on ethical problems should be collected and put into further data analysis. From what follows, I will present how I will situate and deploy this research approach into a more detailed methodological plan of selecting participants, defining methods for data collection and organizing the analysis.

2.3.5 General plan for sampling and data analysis

In this section, I will start by providing my overall plan for sampling and data analysis. This then will be followed by detailed descriptions of these steps in each interview round. By structuring this section like this, I attempt to elucidate the interaction between the overall plan and the practice of applying it. In other words, what I want to show is that this process is developed through my experience and reflection as the research progressed.

Sampling and recruitment

As there was no information available regarding the correlation between the perception of ethical considerations, types of ethical considerations and any demographic information of key stakeholder groups included in the research, for example, gender, age, employer and their role in clinical research that they participated, I chose to start with randomly sampling from a purposively selected but

diverse set of populations of stakeholders. The key stakeholder groups that I originally planned to recruit into this research included

- study staff (investigators, study doctors and study nurses, laboratory staff),
- local Institutional Review Board (IRB) members,
- study sponsors or funders,
- patients and family members.

These groups had been classified as the key stakeholders in my research because 1) they directly participated in clinical research on REEs; and 2) they make up primary groups in any clinical research – whose work and decisions contributes to the sustainment and eventually the success or failure of a clinical research. Approaching all of the groups of relevant stakeholders is aimed to elucidate and highlight variation and common themes from many perspectives on ethical problems raised in practice.

As the aim of the research is to explore a wide range of ethical considerations through research practice in the setting of REEs, and although generalization or representativeness is not a pursuit of this type of qualitative research, an ideal plan for this research would be to approach different research sites that potentially would yield a broad range of experiences of research practice and ethical problems that are specific to the studied setting of disease, rather than be confined to a particular place or a community. Common themes that emerge across research sites are especially sought to reflect characteristics and problems unique to the setting of REEs and commonly shared by stakeholders working in the setting. Overall, initial preliminary research sites to be included in the research have been put forward are as follows:

- 1) Phase 1 in Viet Nam: OUCRU-VN including OUCRU in Ho Chi Minh City (the South of Viet Nam) and in Ha Noi (the North of Viet Nam) and 2

hospitals in Viet Nam, namely, Hospital for Tropical Diseases – Ho Chi Minh City, National Hospital for Tropical Diseases – Ha Noi.

- 2) Phase 2: International experts based in other countries. These participants would be persons who have been involved in international collaborative research on REEs with OUCRU – Viet Nam.

Pilot interviews and official initial sampling would be conducted in OUCRU - Ho Chi Minh City and the Hospital for Tropical Diseases as a point of departure for a draft of possible practical problems experienced by stakeholders at the two sites.

Phase one aimed to focus on perspectives on biomedical research from Viet Nam during SARS, H5N1, H1N1, EV71 and other REEs. In this phase, perspectives and field experiences in biomedical research from key stakeholders directly involved in SARS, H5N1, H1N1, EV71 epidemics in Viet Nam have been examined with in-depth interviews. In phase two, major ethical themes drawn from phase one were subsequently examined in in-depth interviews with selected stakeholders directly involved in infectious disease epidemics outside of Viet Nam with an aim to identify ethical considerations in a broader scale – reflecting the international scale of epidemics and epidemic research. Key stakeholders to be invited to participate in this study included study investigators, study doctors, study nurses, representatives of study funders/sponsors, representatives of local/international ethical review boards, research participants and their families. The stakeholders were recruited by direct verbal/letter/email invitation from the institutions that have participated in research projects on REEs with OUCRU or collaborated and worked within the same international research networks with OUCRU. The whole interview process was divided into stages of suitable number of research participants in each of the groups

followed by interim analysis of these interviews to identify themes for subsequent rounds of interviews.

Sample size

While there are no clear rules to determine sample size, and scant discussion around issues of sample size in qualitative research (Patton 2002; Onwuegbuzie and Leech 2007), given considerations of how the data can be interpreted, analytic generalization for the studied setting (Maxwell 1992; Curtis et al. 2000), and the limited amount of time of a DPhil project, it is important to make it explicit a specific approach to guide an appropriate sample size for the study. In a summary done by Mason for common sample sizes in qualitative research, the number of sample size varies upon types of the qualitative research and methods of data collection (Mason 2010). Of all listed ranges mentioned, notably are recommendations from Green and Thorogood that "the experience of most qualitative researchers is that in interview studies little that is 'new' comes out of transcripts after you have interviewed 20 or so people" (Green and Thorogood 2004, pg.120), and according to Ritchie et al., qualitative samples often "lie under 50" (Ritchie et al. 2003, pg.84). Generally noted by Sandelowski, sample size in qualitative research should be neither too small that it is difficult to achieve data saturation, theoretical saturation, or informational redundancy, nor too large that it is difficult to undertake a deep, case-oriented analysis (Sandelowski 1995). Taking these into consideration, my strategy in determining the sample size of this research was to reach a point where the same patterns were reoccurring (Charmaz 2006, pg.102) while examining the codes developed from each interview round to assess at which point to stop sampling. This is aimed to keep the data analysis manageable. In the following paragraphs, I will describe methods of data collection, data analysis and the selection process at each research site.

2.3.6 Data collection methods:

Semi-structured interviews:

The semi-structured interview is an interview conducted based on groupings of topics or questions that are identified in advance of the interview but where the precise wording and the order of questions can be changed depending on the context and the characteristics of interviewees (Lindlof and Taylor 2002). The semi-structured interview was adopted because of the following distinct advantages for this research. Firstly, by contrast with a focus group, the individual interview would only happen within the context of a one-to-one established relationship, which means that respondents can feel free to talk and discuss about matters that are considered sensitive and confidential by them. This has been clearly expressed through my pilot interviews with colleagues in which privacy and intimacy of the interview setting were preferred by respondents for their sharing of thoughts and opinions. The general interview guide approach or the so called “semi-structured interview” allows respondents to describe their experiences of research practice and their insights of what might be viewed as ethical considerations in their own language, on the other hand, the interviews can be driven and become manageable, covering topics that the investigator wants to explore (Patton 2002, pg.349).

The second advantage of an individual semi-structured interview is that it would create opportunity for thoughtful reflection of respondent through a dialogue with the interviewer. The interviewer, in return, can have the opportunity to request further details or explanations from respondents and to challenge their responses when appropriate. Insofar as morality is socially constructed, by which it is conceived by social actors who are key stakeholders in this research through their social interaction,

their reflection on their own research practice, issues as ethical problems, and possible solutions for such problems would need to be encouraged by enquiry procedures in a social research. As Blaikie notes:

“Much of the activity of the social world is routine and is conducted in a taken-for-granted, unreflective manner [...] It is only when enquiries are made about their behaviour by others (such as social scientists) or when social life is disrupted, and/or ceases to be predictable, that social actors are forced to consciously search for or construct meanings and interpretations [...] Therefore, the social scientist may have to resort to procedures that encourage this reflection in order to discover the meaning and theories”
(Blaikie 2000, pg.116).

While interviewing participants who have been directly involved in clinical research on REEs would serve as the main and very valuable source of information for this research, it is important to acknowledge at this point that this type of data would represent perceptions of participants, rather “truths”; that is how true or accurate the events would be in their narratives (Patton 2002, pg.321). Given the aim of this research, their interpretations of ethical problems attached to the research practice and their perceptions of how things happen and possible solutions with relevant moral values play a key part in this research and thus are valued.

Document review:

In order to obtain a richer picture of the ethical issues arising during rapidly emerging epidemics, I decided to complement my individual interviews with document review in parallel with interviewing.

I conducted a document review before, during and after the research. Before carrying out the interviews, I reviewed existing guidelines, standard of operating procedures (SOPs) regulating the research practice at research sites, information of clinical research that had been undertaken in OUCRU and other potential collaborative research partners that I wanted to include in my research, correspondence of ethics committees and study notes regarding review and approval of research on the REEs which I chose to be the focus of my research, and study files relevant to job description of study staff. This information gave me a general understanding of regulations and principles applying for previous and on-going research practices, what sort of problems or considerations that were discussed about among groups of stakeholders and potential areas that I could use to prompt my research participants to reflect on ethical aspects of their research practice. Recognizing known considerations or problems would facilitate the interviews by allowing more focused questions and discussion. Furthermore, recognizing topics which were seemingly ignored would help me prompt participants in these areas.

During and after the interviews, document review has helped me to gain a deeper understanding of the findings, for example, differences in perceptions of people on what could be counted as ethical problems, why these differences existed, and what could be considered as possible solutions with moral values embedded.

2.3.7 General plan for data analysis

2.3.7.1 A review of data collected and data analysis of empirical research on ethical issues:

After reviewing and outlining which qualitative approach and methods of data collection are appropriate in addressing the research question, another equally important point to be considered is how the data should be analyzed and presented in order to capture the range of ethical issues in the interviews. A review of previous empirical ethics research carried out towards this aim would be of use in giving some direction of how the data should be collected, organized and analyzed. In a qualitative study by Hurst et al (Hurst et al. 2005) on how physicians face ethical difficulties, the authors used “coding and analytical elements of grounded theory” for their data analysis in which data from interviews with US hospital doctors was initially broadly classified codes into three categories “issues”, “processes”, and “values”, then reassembled according to relationships identified in the data and proceed to broaden newly grouped categories to capture their different aspects and associations. Another empirical study done by Braunack-Mayer (Braunack-Mayer 2001) as I have outlined above exploring how Australian general practitioners described what they viewed as moral problems in their practice has otherwise suggested three different approaches in the way practitioners in the interviews discussed their stories and issues. There were accordingly three levels of generality of issues drawn from the interviews: issues were described in general terms, followed by anecdotes or as particular stories without specifying them as of a particular type of issue. Drawing on these three levels, each interview was coded into three groups: 1) the ethical problems mentioned, 2) problems described in details and 3) discussions of why the problem was seen as ethical problem. Categories used for the analysis are built on the suggestion of

participants and explanatory concepts from the literature. Approaching a wider group including both doctors and nurses for empirical research, Uden et al (Uden et al. 1992) identified a notable difference in the construction of ethical problems between these two groups. Doctors tended to mention ethical problems prospectively – describing situations where they felt uncertain about how to decide while nurses mostly narrated the problems retrospectively - situations where they in opposite to doctors had felt certain to act but were restrained from acting in congruence with their judgement. Stories narrated by doctors and nurses were seen as texts interpreted for the representation of moral experience captured in the interviews. Open coding, condensing into themes, coding into themes and finally relating these themes to the interviews as a whole were applied in the analysis. The results were then summarized and reflected upon a narrative theory perspective proposed by Ricoeur and Tappan (Ricoeur 1976; Tappan 1990). What is shared in common among three studies and the study by Soren Holm aforementioned is that their initial questions used were straightforward yet broad, for example “Please tell me about an ethical problem you have encountered in your work as a general practitioner?” (Braunack-Mayer 2001). Data was accordingly coded based on how the problems were described. This interview approach, however, in my pilot interviews was ineffective in prompting participants to think about a broad range of areas involved in their research practice. As a result, the analysis may then be limited to what can be recalled in arbitrary by participants as problems in the interview. Referencing three other empirical studies aimed to identify ethical problems in the area of pharmacy, ethical problems were reported either with values involved or factual context of the situation (Hibbert et al. 2000; Chaar et al. 2005; Cooper et al. 2005). In terms of developing ethical problems

through the interviews and analysis, studies done by Hibber et al. and Cooper et al. have illustrated three possible ways:

- Through the area of pharmacy practice the problem originates in,
- How the problem is described by pharmacists,
- Through the analysis for themes and their concatenations in relation to the whole interview.

In what follows, I will present my experience of the studied context through the pilot interview and how it has informed me in shaping and refining my interview and data analysis approach in light of empirical methods that I have reviewed above and a broad definition of “ethical problems” that I am going to adopt in my research.

2.3.7.2 Pilot interview and general coding scheme:

Pilot interview:

Before beginning the main phase of my main project, I carried out 9 pilot interviews. This pilot interview round aimed to test 1) if the set of questions and wording could be understood by potential respondents and its acceptability, 2) if the structure of the set of questions would be able to direct the respondents to talk about their experience in their research practice, and 3) to provide me with a rough understanding of the research practice and potential groups of stakeholders. The interview questions focus on 4 key areas: 1) types of work that respondents were involved in clinical research on REEs, 2) difficulties/challenges/difficult decisions they encountered in such research on REEs in general and in each area of their work, 3) their solutions to the considerations raised and 4) which source that help them recognize or identify such considerations (refer to Appendix 3). Especially in the second area of questioning above, I also probed them in specific areas which I derived from my literature review and personal experience. However, these areas were asked in a neutral way, so as not to impose any pre-conceived concepts on respondents while allowing them to recall what happened in their practice and relate them to discussions around what they might think of as ethical problems or difficulties/challenges in general. I would not call data generated from this type of probing as a deductive process. Rather it is still inductively grounded on respondents' experiences as these questions are open and neutral enough for their narratives to be openly expressed and discussed in their experience and perspectives.

Participants in this pilot interview included a study doctor who was also a principal investigator, study nurses, laboratory specialists and technicians, study co-ordinator and study pharmacist. All were working on clinical research on REEs at OUCRU.

Pilot interviews with laboratory staff, study co-ordinator and study pharmacist showed that although these groups of people were directly involved in clinical research, their exposure to other groups of people working in research and practical research practice is limited and thus their experiences of research practice, awareness and understanding of ethical consideration was mostly confined to discrepancies in the working procedures of their own sphere. For example, in the group of laboratory staff, considerations were generally discussed around issues in the application of laboratory procedures, and in the group of study co-ordinator and pharmacist, considerations raised were mainly confined to logistics (administrative procedures involved) and dealing with involved parties to get things done as planned. On reflection on these issues, it appears to me that experiences of these groups of respondents lacked the insight of an entire picture of practical research practice, leading to a circumscribed knowledge of ethical considerations to stimulate further ethical thought and debate. As a result, I decided to exclude these three types of participants from the subsequent interview rounds.

A disadvantage of the approach used in this pilot interview, which was to ask respondents about their work and try to relate this to ethical considerations, is that respondents only listed some general main tasks that they had worked in clinical research on REEs. Some could not remember clearly what happened in their research practice. Others had worked for the research under many roles such as principal investigator and study doctor, for example, and as such recalling and listing all the work seemed to be impossible in these cases. Therefore, a new approach was designed to prompt their memories and reflection on their research practice. This approach was to divide sets of appropriate questions around three main stages of research: pre-study/research, during the study and post-study. These questions would

generally cover main procedures conducted in research. In answering these questions, respondents would be able to relate them to their actual work and that they might have been involved in. Discussions around advantages and disadvantages in respondents' actual research practice could then be taken forward based on their memory and reflection of what happened in the practice.

Coding scheme

Drawing on my review of previous empirical research as I have outlined above on their interview and data analysis techniques, a broad account of what may be taken into moral perspectives of participants in practice and experience drawn from coding the pilot interviews, collected data was analyzed and organized into three broad categories:

- Characteristics of the REE context
- Patterns of research practice in light of areas where ethical problems were raised
- Ethical considerations with concepts and values involved in each of the problems raised by respondents.

In general, with thematic analysis, I would carry out 6 basic phases with the data. These include: familiarizing self with the data, generating initial codes, searching for themes, reviewing themes, defining and naming themes and producing the report of what have been found in the data in its relation to my research question (Braun and Clarke 2008). Following from my draft coding of the pilot interviews, data were first organized and coded into each group of stakeholders. This helped me in a later stage of comparing codes and themes and developing more generalized core themes and categories of patterns and ethical considerations.

Data were inductively coded through a simultaneous and iterative process of data collection and analysis. Initial data were collected and analyzed to develop provisional broad categories and concepts. Further data were subsequently collected to illuminate and strengthen categories. At the same time, interim data analyses let me realize areas to further explore in following data collection. This approach can be illustrated in the schema below:

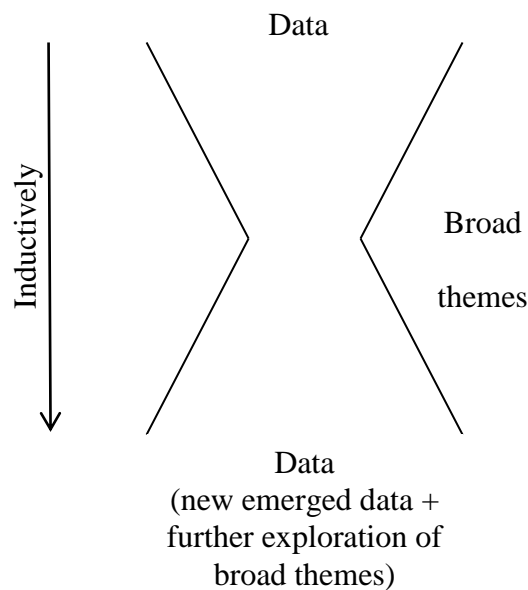


Figure 2.2: Schema for data coding

2.4 Empirical data collection:

Based on experience derived from my pilot interviews and the planned methodology, I decided to conduct two main interview phases. The first phase focuses on perspectives from Viet Nam. The second phase - informed by the findings of phase one – was to engage stakeholders from regions outside of Viet Nam to explore the issues identified in Phase 1 in a global perspective. Interim analyses are conducted to inform subsequent interview rounds. Detailed plan of each phase is in what follows.

2.4.1 Phase 1: Viet Nam

The first phase is conducted in 5 research sites in Viet Nam including Oxford University Clinical Research Units (OUCRU) in both Ha Noi and Ho Chi Minh City, the Hospital for Tropical Diseases (HTD) in Ho Chi Minh City, the Children's Hospital Number 2 (CH2) in Ho Chi Minh City, and the National Hospital of Tropical Diseases (NHTD) in Ha Noi. Interviews were carried out in 3 rounds with interim analyses conducted after each round. Before going into details the characteristics of each of the research site, I will begin by giving an overview of Viet Nam where the majority of my interviewees were based.

Located in Southeast Asia, sharing borders with the Gulf of Thailand, Gulf of Tonkin, South China Sea and countries including China, Laos, and Cambodia, Viet Nam has the population of around 89.7 million. Becoming a developing middle income country, over the past decades, Viet Nam has achieved important successes in economic, social and health sectors. Of countries sharing the same GDP per capita, Viet Nam has improving health outcomes, demonstrated through indicators such as the significant increase in the life expectancy at birth (from 71.3 years in 2006 to 75.8 in 2011) and the reduction of infant mortality rate (from 36.7 per 1000 live births in 2000 to 20.9 in 2011) (Oanh et al. 2009). Key reasons for these achievements are attributed to such factors as economic growth, stable socio-political environment, strong commitment of the government to achieve development and socioeconomic goals, including health goals, and the strategy on poverty reduction and hunger eradication (Oanh et al. 2009).

Population	89,708,900 (2013)
Total adult literacy rate	93.4 (2013)
GDP per capita	US\$1,911 (2013)
Health indicators	
Hospital bed density (2012)	2.49 beds/1,000 inhabitant (<i>Excluding private establishments</i>)
Physician density (2008)	1.22 physicians/1,000 population (2008)
Total expenditure on health	6.6% of GDP (2012)
Total expenditure on health per capita	US\$234 (2012)
Life expectancy at birth (total, years)	75.8 (2011)
Infant mortality rate/1000 live births	20.9 (2011)
Neonatal mortality rate/1000 live births	12.4 (2012)

Figure 2.3: Vietnamese key social, economic and health indicators

(Source: World Development Indicators Online (World Bank 2013); World Health Organization; U.S Central Intelligence Agency, The World Factbook online, website: <https://www.cia.gov/library/publications/the-world-factbook/geos/vm.html>)

2.4.1.1 The first interview round

a. Research sites:

The first two sites that I decided to start the research are the Oxford University Clinical Research Unit (OUCRU) and the Hospital for Tropical Diseases (HTD).



Figure 2.4: Map of Viet Nam and the location of OUCRU in Ha Noi and Ho Chi Minh City (HCMC), and the Hospital for Tropical Diseases in Ho Chi Minh City (OUCRU – HCMC locates within the hospital campus

Source: Health Research in Viet Nam: The Vietnam Research Programme and Oxford University Clinical Research Unit. Viet Nam, OUCRU (Wellcome Trust 2012)

Both of these sites are based in Ho Chi Minh City, Viet Nam. The two sites were purposively chosen due to 2 following reasons:

- i) The Oxford University Clinical Research Unit (OUCRU), an international non-profit organization established as part of the Oxford Centre for Tropical Medicine of the Oxford Centre for Tropical Medicine, has conducted and involved in many local and international collaborative clinical research projects on rapidly emerging

epidemics including major emergency epidemics occurring across countries and regions such as SARS, H5N1, H1N1 influenza pandemic, Ebola epidemic and Hand, Foot, Mouth epidemic. After nearly two decades operating in Viet Nam, OUCRU has developed strong links not only with HTD, but also other hospitals in Ho Chi Minh City, Hanoi and other regions of Vietnam as well as many international research and health organizations. With its large sources of experiences about emergency epidemics and scientists that could be approached for the present research, the involvement of OUCRU in the project ensured the feasibility of the investigation as originally planned. The present study was conducted with stakeholders working at and in collaboration with the Oxford University Clinical Research Unit (OUCRU) through the Viet Nam Research Programme. The Programme is initiated in 1991 in Ho Chi Minh City and Ha Noi in 2006 with an aim to address national health problems and improve the prevention, diagnosis and treatment of infectious and non-infectious diseases, many of which are also of global health problems (Wellcome Trust 2012). The Programme, in the South (HCMC), is hosted by the Hospital for Tropical Diseases as part of efforts to bring a close integration between local and international researchers based in OUCRU and local clinicians working at collaborative hospitals. With strong support from the Vietnamese government and the Wellcome Trust, the Programme was expanded in 2002 to develop as an Institute for Clinical Research dedicated to build research capacity and conduct essential clinical research of local priorities. The unit in the North (Hanoi) has close links with Vietnamese government ministries and health departments. It is hosted by the National Hospital for Tropical Diseases (NHTD) and works closely with the National Institute of Hygiene and Epidemiology and the National Hospital for

Paediatrics, and others research institutions in the North of Viet Nam. On a global scale, The Programme collaborates widely across Vietnam and with research groups in Cambodia, China, Indonesia, Malaysia, the Philippines, Nepal, Singapore and Latin America with a diverse portfolio of funders. The Oxford University Clinical Research Unit also coordinates the South East Asia Infectious Disease Clinical Research Network (SEAICRN) as mentioned above. This multinational research group is an attempt to advance scientific knowledge and clinical management of infectious disease through integrated and collaborative clinical research. In regard to research of diseases relevant to local populations, OUCRU implement a multi-disciplinary approach to integrate clinical research with epidemiological and laboratory studies. OUCRU’s main research areas include malaria, dengue, enteric fevers, tuberculosis, central nervous system infections and zoonosis with a wide range of investigational approaches such as clinical trials, genetics, and public health as demonstrated in the chart below:

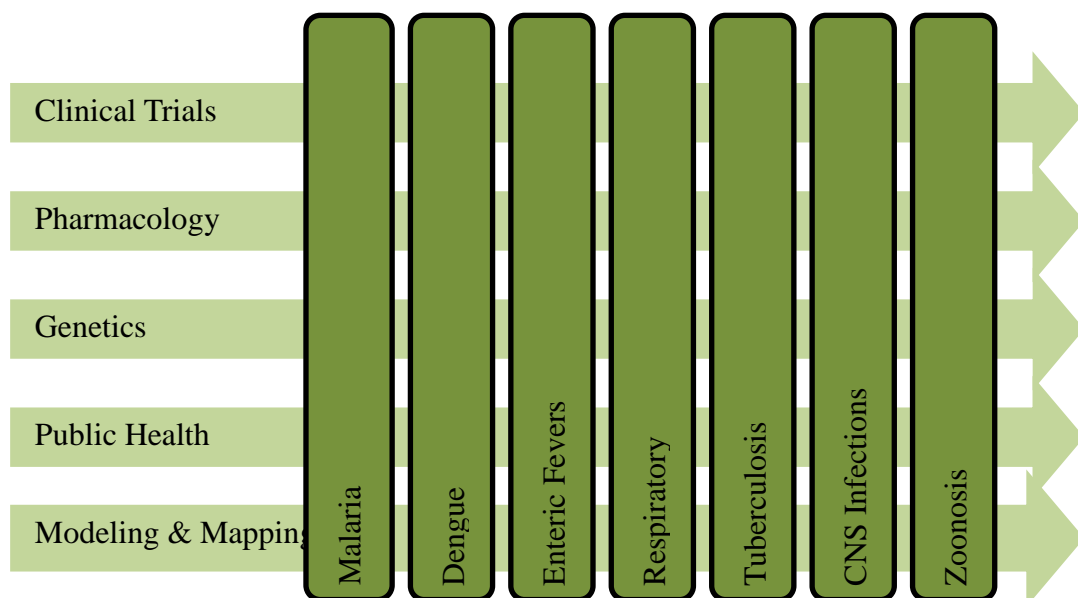


Figure 2.5: Main research areas and targeted diseases in OUCRU – Viet Nam

(Source: Baker, S. (2011). Presentation: Research at the Oxford University Clinical Research Unit (OUCRU): Activities, Organization, Experience, Process)

In line with the significant growth of research collaboration after time, the number of collaborative projects is accordingly increased as illustrated in the table below for studies conducted in recent years, from 2009 onwards:

Research	Completed in 2009-2010	Active 2011	In Development for 2012
Controlled Clinical Trials	9	8	5
Observational Research Studies	16	45	24

(Source: Baker, S. (2011). Presentation: Research at the Oxford University Clinical Research Unit (OUCRU): Activities, Organization, Experience, Process (Baker 2011))

These research projects are both hospital and community based. There are large cohort studies that have been done in collaboration with local Preventive Medicine Centres across the country on influenza, dengue and malaria. Along the same line carrying out these research community based projects, activities of public engagement in science recently have been deployed in targeted communities. The purpose of this public engagement project is to engage the Vietnamese public with biomedical science to raise awareness of research conducted at OUCRU.

Equally important, the Hospital for Tropical Diseases (HTD) in Ho Chi Minh City is the main referral hospital for infectious diseases in southern Vietnam serving a population of 38 million in Southern Viet Nam (Torok et al. 2008). Through extensive collaborative links with international and local research partners, HTD has built a very strong research capacity covering a wide range of research areas on infectious diseases. Not only having so much experiences as a local research

institution in epidemics, but also a possible access to patients and family members who have participated in emergency epidemic research makes HTD a crucial site for my research.

- ii) Before doing this research, I have worked for more than 3 years at OUCRU as a study-coordinator of which my role is to support clinical research conducted at OUCRU and other research sites and to liaise with relevant research partners regarding regulatory documents. Choosing the two sites that I have experience working with and have some existing relationships with study staff working at both sites provided me further insights about the practice, context and people involved in the research, hence somehow make the collaboration and engaging at a later stage through interviews favourable and advantageous. Above all, the understanding of and the familiarity with the research context, in my view, is one of significant criteria for selecting research site in this type of empirical ethics research in which the investigator can make participants feel comfortable and assured with his/her presence so that they are willing to participate in the study, then the investigator can make the most of the interviews. In some cases, questions in the interview about ethical issues would require participants tell about bad practices, violation of rules or principles in doing clinical research of their own or other people that they know about, and an established relationship between the investigator and participants would facilitate the interview process when the participants feel they can trust the investigator, and accordingly want to share the information with him/her.

b. Sampling and recruitment:

At the time the research officially commenced, all clinical research on REEs at OUCRU and HTD had been completed, so I had to choose those to retrospectively

interview. Clinical research that I prioritized for this interview round was research that met two criteria: finished closest to the time of my research, and different types of research. Three clinical studies on influenza epidemics were chosen: SEA032¹ and SEA034² completed in September and October 2010 respectively. With respect to the types of research, SEA032 is interventional while SEA034 is an observational study. In each group, I made a list of people who were listed as study staff in the Delegation Log archived in study binders at sites. Also noted in the delegation log is information of roles and job description of each member. Based on these types of information, I could learn more about their research participating background for the preparation for interviewing.

Participants in this phase include study staff (expatriate and local investigators, study doctors and study nurses), local IRB members, patients/family members and study sponsors/funders. The interview process was divided into stages of suitable number of research participants in each of the groups followed by interim analysis of these interviews to identify themes for subsequent rounds of interviews. Approaching all of the groups of relevant stakeholders aimed to elucidate a wide range of ethical considerations from many perspectives.

For participants as patients and family members, a study-coordinator based at HTD was asked to help the investigator in contacting potential participants for the interview based on patient/family member list provided by the investigator.

¹ SEA032: Antiviral Treatment in Adults and Children With Novel Influenza A (H1N1) Respiratory Tract Infection - a Clinical, Virological and Pharmacokinetic Study

² SEA034: Clinical Validation of the Point-of-Care MStudy doctor Influenza Test in Asia

Participants	Affiliation	Number of interviews
Principal Investigator/Co-investigator	OUCRU	4 (men)
Study doctor	HTD	4 (3 men, 1 woman)
Study nurse	HTD	3 (women)
IRB member	HTD	2 (1 man, 1 woman)
Study sponsor	OUCRU	1 (woman)
Research subjects ³	Admitted to HTD	3 (men)
Family member	Having family member admitted to HTD	3 (2 men, 1 woman)
Total number of interviews		20

Table 2.1: Number of interviewees in OUCRU - HCMC and HTD

c. Structure of interview and interview guide:

Participants were informed of the purpose of the interview, i.e. to identify ethical considerations that they and their study team have encountered and to know how they have addressed or would address these issues during research conducted in rapidly evolving epidemics, e.g. SARS, H5N1, H1N1, EV71, etc. This step aimed to serve as a reminder for interviewees of the scope of the interview, and to prepare them to relate the experience to ethical issues/considerations.

Interviews were begun by open questions about working experience and processes which they have been through in their participation of emergency research projects. Participants would describe their experiences and relate these experiences to other

³ One female participant came to the interview but withdrew afterwards as she did not want to be audio-recorded.

research settings. Experience and description provided at this stage could be general experience about the processes they had been involved in during the research.

Interviewees were later prompted on topics which were raised by them during the interview and by the interviewer.

Experience of interviewees was organised into 3 types of information of 3 basic stages of a clinical research: pre-study, during the study and post study:

- Description of processes which the interviewees have involved in their role
- Their experience of difficulties/challenges and advantages through those processes, and their ethical considerations from these difficulties and advantages. The investigator probed interviewees about ethical concepts out of their general description of difficulties and advantages such as rights, duties, or generally about:
 - ✓ What things they think should or shouldn't have been done,
 - ✓ Any lesson they had learned from participating research on emergency research
 - ✓ Suggestions as to how we can improve the research on emergency research)

Topic guides were designed based on general provisional themes and topics identified from pilot interviews and interim analyses as an aid tool for the investigator during the interview. Topic guides contained set of questions, topics and subtopics to be covered during the interview, the basic structure of the interview, and how questions should be worded. Each interview group had a set of corresponding topics. Covering topics from the investigator were probed by open questions about their experience of the processes. If the interviewees were involved in and knew about such processes, more follow-up questions were posed.

After several first interviews when I had collected accounts of experiences and perspectives of respondents on certain areas, for example, their practice of obtaining consent from patients and family members or how some IRB members might react on their review of research projects on REEs, I used these to build up illustrative examples in questions for further interviews. The advantages of using illustrative examples to my interviews are 1) enabling me to drive the conversations to important areas, 2) provoking deeper thoughts and reflection on moral topics, and 3) keeping the neutrality of the interview; that is my stance towards the content of what a respondent might say (Patton 2002, pg.365). It is especially crucial in cases in which after generally open questions like “What is your experience in planning research on rapidly evolving epidemics in terms of ethical considerations?” or “Do you have suggestions to resolve the issues with respect to the nature of the evolving situation in an epidemic?”, illustrative examples including all possible options that already happened, e.g. both negative and positive perspectives/actions towards a topic at issue would help respondents recall what happened, their experiences of those events and encourage them to be more open in their answers. Also by this method, as Patton has pointed out in what follows:

“...When phrasing questions in this way I want to let the person I’m interviewing know that I’ve pretty much heard it all - the bad things and the good – and so I’m not interested in something that is particularly sensational, particularly negative, or especially positive. I’m really only interested in what that person’s genuine experience has been like” (Patton 2002, pg.366).

Throughout the interviews, such illustrative examples for each of corresponding topics have helped me obtain a rich and relatively consistent account of the research practice and moral topics at issue raised by respondents.

2.4.1.2 Second interview round

a. Research site:

The second interview round was conducted based on the interim analysis of the first interview round. A children hospital was included in the second interview round due to several interviews with the Paediatrics Ward in HTD, in which difficulties and challenges were particularly raised around obtaining consent for children to participate in clinical research. Themes such as “collective decision making” accompanied by “kinship”, the status of a child in a Vietnamese family and factors that might affect obtaining consent for children needed to be further explored with stakeholders participating in this practice. While HTD has a Paediatrics Ward, the amount of clinical research on REEs were also dispersedly conducted in collaboration with Children hospitals in Ho Chi Minh City. Children hospital Number 2 (CH2) is one of the main children hospitals in HCMC and has a long term established research collaboration with OUCRU and other local and international research partners. Sharing similar clinical research context and situation with OUCRU and HTD by being in the same research collaborative network, expanding the present research to CH2 would help to extend the diversity of ethical considerations identified in the research practice in children population as well as further explore and confirm general themes generated in the first interview round.



Figure 2.6: Children’s Hospital Number 2 in Ho Chi Minh City and High Quality Service Examination Room in CH2 where I conducted some interviews with family members.

(Source: Website of Children’s Hospital Number 2, available at: <http://www.benhviennhi.org.vn/>)

b. Sampling and recruitment:

From the first interview round, there were two factors identified as bearing certain effect to the richness of the information provided by the respondents. These included:

- The partnership between the investigator (the interviewer) and interviewees

In the case of study staff, obtaining consent to interview, time available for the interview and the richness of information depended on the partnership which was built in advance between the interviewer and interviewees. Some interviewees who had an established partnership with the interviewer were willing to give consent to the interview and openly talk about their research practice, ethical issues/considerations which they had faced during their research. They also gave as much time as the interview required to rethink about what happened and provide more information. Another thing to note is that interviewees who held multiple posts or specialized in a certain task

assigned in the research, e.g. obtaining consent from research participants, managing staff, involving in discussing research plan, writing protocol, etc. could give more reflection on what they have experienced, either on a variety of research tasks or on a specific task. The more tasks they were involved in, the more information of a variety of topics they could provide.

As a result, with potential participants at CH2, I prioritized participants who I had had a partnership with or known already and who were involved in types of work that could possibly give information about more topics. To do this, based on the job description I compiled a list of all potential interviewees from the list of study staff archived in each study binder to make a list of potential interviewees to be approached for the interview. Participants with pre-established partnership and who involve in much work were also chosen to approach first.

- In the group of patients and family members, it was shown from the first interview round that occupation affected the openness and activeness of interviewees to the interview. It was also possibly caused by the educational level and/or by gender. However as information related to occupation and educational level was not recorded in patient files, sampling was, as a result, done in random, yet in an attempt to make a relative balance in gender and living places to ensure the diversity of opinions from respondents.

A study-coordinator appointed by CH2 was in charge of contacting all potential participants for the interview based on the study staff list and patient/family member list provided by the investigator.

Participants	Affiliation	Number of interviews
Study doctor	CH2	4 (1 men, 3 women)
Study nurse	CH2	2 (women)
IRB member	CH2	3 (all men)
Family member	Having family member admitted to CH2	7 (3 men, 4 women)
Total number of interviews		16

Table 2.2 Number of interviewees in CH2.

c. Interview guide:

Interview guides for all the relevant groups remained as same as the first round. However, key common areas which had emerged from the first round were listed out in topic guides for each of the interview group for probing and further follow-up with respondents. This was to ensure the openness of interview questions while keeping the interviews relatively focused to key areas for exploring further details, e.g. similarities and differences, relevant examples and above all relevant themes that cut across all of the groups and unique for the studied setting.

2.4.1.3 Third interview round

a. Research sites:

The third interview round took place in OUCRU- Ha Noi and the National Hospital for Tropical Diseases (NHTD) in Ha Noi, Northern Viet Nam. As outlined in the general plan, interviews conducted at these two sites aimed to gain a wider view on ethical considerations raised by participants based in the North of Viet Nam through their research practice in the context of REEs. NHTD is the host of OUCRU in Ha Noi. NHTD is the tertiary referral hospital specialized for infectious diseases. Being placed under the direct control of the Vietnamese Ministry of Health (MOH), NHTD

therefore has a strong rapport with the MOH. In rapidly evolving epidemics breaking out in the North of Viet Nam, NHTD and OUCRU in association with other local and international research networks and research partners have collaboratively carried out a wider range of research on such epidemics.



Figure 2.7: The National Hospital for Tropical Diseases in Ha Noi, OUCRU – Ha Noi locates within the hospital building.

b. Sampling and recruitment:

Similar to previous interview rounds, participants in these two sites were invited for interview based on the study staff list and patient/family list.

A study-coordinator appointed by NHTD was in charge of contacting all potential participants of the hospital including hospital staff, patient/family members for the interview based on the study staff list and patient/family member list provided by the investigator.

<i>Participants</i>	<i>Affiliation</i>	<i>Number of interviews</i>
Principal Investigator/Co-investigator	OUCRU, NHTD (NHTD: 1, OUCRU: 3)	4 (3 men, 1 woman)
Study doctor	NHTD	3 (1 man, 2 women)
Study nurse	NHTD	3 (women)
IRB member	NHTD	2 (men)
Research subjects	Admitted to NHTD	4 (2 men, 2 women)
Family member	Having family member admitted to NHTD	2 (women)
Total number of interviews		18

Table 2.3: Number of interviewees in NHTD and OUCRU – Ha Noi

c. Interview guide:

Interview guides for all interviewees based these two research sites were similar to the format used for the two previous interview rounds. However, illustrative examples drawn from those two interviews, especially typical patterns of ethical problems and research practice that were commonly shared by all research sites in the South were used for prompting respondents based in these two Northern sites to highlight commonalities and differences.

2.4.2 Phase 2: Interview international experts

Data from the first interview round and from a literature review show that international collaboration is essential for clinical research in rapidly evolving epidemics. Such work needs to be conducted in a concerted, integrated way in order to prevent epidemics and respond to such events when they inevitably occur. This is particularly true in resource-limited countries like Viet Nam, which is in need of

scientific research facilities, modern techniques, well trained scientist and research funding. Interestingly, international research collaboration is one of the elements considered by Vietnamese IRBs when reviewing a research project, and study doctors when taking part in the research. While many clinical trials are conducted by the pharmaceutical industry on new medicinal products, clinical studies initiated and driven by academic researchers from governmental and non-governmental organizations (NGOs) for non-commercial purposes make up a substantial and critical part of medical research contributing to the evaluation of various diagnostic and treatment strategies and options within real conditions of the health system as a basis for developing rational therapeutic guidelines and governmental policies (Delisle et al. 2005). The role of NGOs in clinical research, especially, has been highlighted in global health research for development by contributing at all stages of the research cycle, fostering the relevance and effectiveness of the research, priority setting, and knowledge translation to action (Delisle et al. 2005).

In Viet Nam, research projects conducted in collaboration with international research organizations including Centre for Disease Control USA (CDC), Oxford University Clinical Research Unit Viet Nam (OUCRU-VN), and DANIDA are considered by local ethics committees' members and scientists to be of a higher standard than those conducted by Vietnamese experts in terms of having clear objectives, definite research duration and outcomes, better conditions of research sample storage, the capability of meeting the appropriate standards required for a clinical research. They are also typically better funded. These features are thought to help limit the disease burden, i.e. reduce economic costs, provide better healthcare and reduce the risks of unethical acts caused by the lack of funding and limitations of research capacity. Some of these international organizations are characterized by a long-term

relationship with local Vietnamese hospitals whereby trust and understanding are built up over time and thus they are able to react quickly in response to the emergency setting of rapidly evolving epidemics whereas almost none of any pharmaceutical companies could take on at the time.

My literature review of ethical considerations raised by international experts who are based at international research organizations and have been involved in clinical research in the setting of rapidly evolving epidemics has identified a number of references to the challenges in applying international normative and regulatory guidelines into local practice and in the context of evolving epidemics, of different cultural perceptions which need to be taken into account to make research ethical, and the dynamics of international collaboration. This suggests that, the perspectives of international experts who have been through recent epidemics with their hands-on experience in dealing with the issues and challenges have the potential to provide more insights into ethical considerations from different aspects of the epidemic research setting. Interviews with international investigators based at OUCRU show that ethical considerations were raised around topics of conflicts between local and international ethics review boards. In particular concerns were raised about how to interpret different ethical requirements and put these into local practice in harmony and despite the lack of an evidence base for many of the existing therapies used in the local setting. Other issues raised included engagement with the staff at sites, power balance and decision making, inter-cultural relations, communicative ‘soft skills’, and external influence placed by international research partners upon local institutions and researchers. These themes are reinforced with the local perspectives expressed by hospital-based study doctors and co-investigators in which full involvement of local staff and incorporation of their intellectual input, opinions and recommendations in

research design and planning. These are considered crucial and prerequisite for any research to be carried out successfully and to meet local regulations, cultures, politics and moral norms.

Data from these two groups in combination raised the need to further explore ethical considerations identified by a group of international experts who have been directly involved in research in rapidly evolving epidemics. Such a group, by way of their experience of being involved in the research work conducted in multiple research sites in many countries, or by establishing collaborations or funding limited resource countries affected by epidemics, would be able to provide important insights and/or different perspectives about the issues above. These data would help, firstly, to give a better understanding about Vietnamese research situation in the setting of rapidly evolving epidemics, and secondly, to add a more comprehensive overview of the ethical issues and their underlying patterns in the studied context. It was therefore necessary to carry out a small number of additional interviews with international experts to complement and add value to the data already collected in Viet Nam.

a. Sampling and recruitment:

International experts who were invited for this interview round included people involving in international collaborative research and directly worked with Vietnamese partners or who have been part of a collaboration with OUCRU Viet Nam as part of the same research project irrespective of whether they have been in Viet Nam and worked directly with Vietnamese partners.

1. Investigators who were based at international governmental or non-governmental organizations
2. Representatives of study sponsors

3. Representatives of international ethics review boards or ethics advisors who have directly reviewed or involved in consulting ethical aspects in the studied research setting
4. Policy makers who involved in the making of policies in response to rapidly evolving epidemics.

Participants were conveniently sampled based on existing working connections of supervisors and the location of the participants.

<i>Participants</i>	<i>Affiliation</i>	<i>Number of interviews</i>
Expert in public health and research on infectious diseases	WHO	2 (women)
Study sponsor	Wellcome Trust, UK	1 (man)
Policy maker	UK Health Protection Agency	1 (man)
Investigator/Ethics committee member/Ethics consultant	UK (2), China (Beijing, Hongkong (2)), Canada (1), Australia (1)	6 (5 men, 1 woman)
Total number of interviews		10

Table 2.4 Number of interviewed international experts

b. Interview guide:

Interview guides and topic guides were developed for 4 types of participants outlined above. Each set of questions are composed of key areas identified from the three interview rounds in Viet Nam and literature review of research practice and potential ethical problems arising in the setting of international collaborative research on REEs. There was a connection between themes identified by local people based in Viet Nam with research practice of people based in other countries and I wanted to further explore these and other themes from my literature review. Furthermore, combining

preliminary themes and literature review helped me to compose and categorize some topic areas specific for each of respondent groups according to their job. However, initial questions remained general so that any thoughts or perspectives of respondents could be freely expressed.

Due to the fact that international experts are people undertaking multiple work in research at the same time or during their research career, and that in some cases their working positions did totally fit into my participant categories, for example, Head of Intensive care unit who both does the job of an investigator and of a member or ethics advisor of ethics committees, I read their background profile to understand what was involved in their work. I then used this knowledge to pick appropriate questions from the interview guides for 4 types of participants for each person that I was going to interview. Illustrative examples were also prepared based on their work for the interview.

2.5 Data management and analysis

Overall, I conducted 64 interviews with all key stakeholders (Appendix 1). All interviews with Vietnamese people were carried out in Vietnamese and those with non-Vietnamese participants were in English. All interviews were digitally recorded, verbatim transcribed and imported to NVivo software for analysis. Pilot interviews and interviews of the first round in Vietnamese were translated in English. Subsequent interviews in Vietnamese were kept in Vietnamese for the analysis and only encoded paragraphs were translated into English. For the analysis of data, NVivo software helped me organize and archive all the data, allowing me to make notes throughout the analysis and to create models derived from the data (Bazeley 2007). In my research, models consist of associations of themes in describing a pattern and

processes. Some examples of the models that I developed are process of obtaining consent or level of difficulty in obtaining consent.

Following 9 pilot interviews with participants from OUCRU – HCMC in September 2010, I conducted a preliminary analysis with the data. This analytic step was partly assisted by NVivo software. I began by sorting out all of the interviews into specific group of participants, and then reading through each of the interview and field notes that I had written during the interview and after the interviews to get a sense of core contents of what had been discussed in the interviews. What appeared to me in these pilot interviews was that participants in discussing about what they had seen as advantages and problems provided descriptions of what happened in their practice, their perceptions towards the situation from general to specific level of a case such as characteristics of the REEs and how they had responded in its reality. So first of all, I decided to classify and code the data into three main categories including descriptions of the research setting of REEs, descriptions of particular research practice including its advantages and what participants raised as issues in their research practice. In the analysis of this step, I realized that the micro-analysis, widely known by word-by-word and line-by-line analysis of text, has a drawback in analyzing my data to address the research questions. That is by immersing into individual words the focus of analysis was sometimes lost. I was at times confused at which pieces of information I should encode from massive data, not to mention that “ethical problems” and many other research practices involved were not always typical of the REE setting that I aimed to explore for my findings. In other words, understanding and “seeing occurrences” spread through the data while identifying themes/patterns that are unique to the studied setting and search for their relationships in the overall picture is important in answering the research question. This type of disadvantage of micro-

analysis is also mentioned in a paper on critique of using grounded theory as a research method by George Allan (Allan 2003). Instead, he proposed another method to handle qualitative data in a more focused and manageable way; that is identifying key points which are seen as important to the research and concentrating the analysis on these points. This method is considered to be in line with qualitative coding analysis (Miles and Huberman 1984) as a protection against data overload (Allan 2003). However, it is not meant to replace entirely the micro analysis. Once the key points are identified, codes within each key point are then analyzed by labelling chunks of interview text with words or phrases capturing the meaning of the data. Applying this method in my data analysis, I first focused on key meanings of what was described as “problems” or “difficulties/disadvantages” and their embedded research practices. Choosing these accounts as my key points, I then looked deeper into the content of each key point for coding what I see as important or notable occurring. Codes that were related to a common theme were grouped together. However, as it was necessary for the analysis of these pilot interviews not to be refined too early to a neatly clear-defined account of themes or categories, I only tried to make a summary of what I have founded from the pilot for my further understanding of and familiarity with the research context to prepare for the following official interview phases. This summary of issues and other general findings derived from the pilot interview round and some of these coded transcripts were circulated and discussed with my supervisors and advisor in Oxford. In this step, my supervisors and advisor have independently looked at my sample coded interview transcripts and given their own perspectives. We then compared our analysis and discussed on the consistency of the analysis, meanings of key points and themes identified and which points that I might have missed in the analysis.

Entering the main data collection stage, I kept writing field notes during and after the interviews. This was done almost in each of the interview to record my observation of notable facts, e.g. attitudes of participants in answering some of the questions, surrounding interview environment that I supposed to bring some effect to respondents, key points or concepts that participants raised and repeated during the interview, and some of my thoughts and impressions over the interviews. In between the analysis of each interview round, these field notes have helped me to recall main points to follow up and to build up illustrative examples in following interviews. In the stage of data analysis, these field notes have been used in checking the consistence of my interpretation at the time of analysis against the time of writing the field notes and provide me further insights to the interpretation and the analysis as a whole; that is to move from particularities to a general understanding.

Data were analyzed after about 10 interviews. This was to ensure that I still had sufficiently fresh memory to look at the data and that I would not be overloaded at the end of each interview round. During the data analysis, memos were electronically made in the analytic software in codes when necessary. These memos were generally about my ideas or queries about the meanings of themes or particular codes/categories, or issues for further interviews.

As mentioned above in the section on integrated approach in developing themes, what I applied in my data analysis is to set up an appropriate organizing framework of code types. Based on the preliminary general categories including three types of information as I have outlined above for my pilot interview, at the first level, I divided data into 2 main categories consisting characteristics of REE and a group of stakeholder categories for each type of participants (in total I have 9 categories for 9 groups of stakeholders). In each of the stakeholder category, I then applied the key

point analysis method to look for patterns – descriptive findings and themes/concepts – a more categorical or topical form (Patton 2002, pg.453). This method is applied for both identifying sociological process of research practices and what is viewed as “ethical problem”. However, in “ethical problem”, I also coded embedded concepts falling into a separate domain of ethics or morality. These concepts include moral concepts and moral values in discussion or interpreted from the data. Later on, I move to comparing these themes to build up a more inclusive common level of concepts and even broader categories. So in each of the stakeholder category, essentially there are categories of patterns of the research practices that each of them has involved in, categories of incidents of ethical problems, and categories of perspectives towards an event. The key in the whole process is that I have used key points as “ethical problems” as a departure for further exploration of relevant codes. This helped me not to lose my focus but enable me to systematically organize and develop themes.

2.6 Ethical analysis

As I have outlined in the section on places for the input of ethical analysis, the aim of this stage is to make a mutual reference between empirical data and ethical principles/debates of relevance. Specifically, accounts of ethical problems with values and debates emerged from the data are specified. These accounts are then brought for a further ethical evaluation whereby in discussing with relevant normative debates and/or elaboration and in appealing to ethical principles/theories, normative weight of the empirical findings can be sought in relation to their actual situations and contexts. While values and debates of ethical problems are elaborated throughout each chapter as a rich descriptive and explanatory account for such problems, I will also present emerging values in the Discussion section at the end of each of the chapter. Emerging

values will include moral values that are recognized and/or shared across key stakeholders in discussing about ethical problems. They are looked forward to shed light on the perception of key stakeholders on what might be viewed as ethical problems, arguments around the issues and what might come up as solutions in addressing these problems. This will be elaborated in section on emerging values in the discussion at the end of each chapter. Emerging values will then be taken forward to further ethical discussions of relevance converging to my own account of arguments and recommendations in looking at dimension of ethical problems under investigation and approaches in which solutions for these problems can be developed, argued and justified. In general, there are 2 parts that my ethical analysis aims to produce in this research:

- Provide discussions on moral perspectives based on moral values and normative weight elicited from narratives of stakeholders and relevant debates of such problems mentioned elsewhere in literature of empirical findings and philosophical arguments.
- Drawing on the empirical data on the research practice under investigation and moral perspectives of respondents raised around ethical problems in their practice and moral values upheld, by examining their coherence and literature of relevance to develop an account of my own view of what could be “ethical problems” in the studied context.

2.7 Scientific and ethical approval

This study was reviewed and approved by the Oxford Tropical Research Ethics Committee (OXTREC 33-11) and all three institutional ethics review boards at the three research sites including the Hospital for Tropical Diseases – Ho Chi Minh City

(Decision No.663/QĐ-BV.BNĐ), Children's Hospital Number 2 – Ho Chi Minh City (Decision No.519/QĐ-NĐ2) and the National Hospital for Tropical Diseases – Ha Noi (Decision No.32/HĐĐĐ-NĐTU).

2.8 Chapter summary

This chapter has provided a description of how I have approached my subject of study in an attempt to systematically identify ethical problems and more broadly characterize moral perspectives of all involved key stakeholders about their research practice in the context of REEs, and described how I have used these accounts for the ethical reflection interwoven in addressing the research question. For the overall structure of data and findings presentation in this thesis, ethical problems are developed revolving key broad areas of research practice in their relation. Additional themes and patterns of factual research practice and moral values identified in the data are concurrently analyzed within these key headings. Concatenations across narrated ethical problems, emerged patterns and themes are also considered for an explanatory account of their possible relationships.

In this light upon my completion of data analysis, I have identified a relationship framework at which ethical problems are related to and constructed in all the interviews. This relationship framework is emerged at three levels: international collaboration, research ethics review and consent, and it structurally connects all the core themes identified from my interviews. Drawing on this relationship framework, I will structure my empirical chapters as follows:

- Chapter 3 - Collaboration: I will present an overview of the international and the Vietnamese local context of research collaborations, and examine issues

arising in international collaborative research projects in the setting of REEs. This serves as a presentation of research collaboration at its macro level.

- Chapter 4 – IRB review: As a meso level of research collaboration delegating down to specific research institutions, I will provide a descriptive account of the general structure of Vietnamese IRB system, its operation and elements that might affect the local IRB review and determination. Following from that factual account will be ethical problems encountered by involved stakeholders in the local IRB review together with corresponding solutions for those problems in the setting of REEs.
- Chapter 5 – Consent: Focusing on the micro level relationship between research subjects/family members and study doctors/research organizations, I will present consent practice with its primary domain in the Vietnamese research setting and particularly in REEs, and an account of stakeholders' perspectives of concerns and challenges they have confronted during their research practice.
- These empirical chapters are followed by Chapter 6 in which I will provide my critical evaluation and reflection on the narrated account of ethical problems and solutions raised by all key stakeholders and explore their possible implications for ethical accounts taken as argumentative basis to develop a deeper understanding of ethical problems with contextual insights and solutions for what can be established as good ethical practice in the studied context.

Chapter 3 International research collaboration

As introduced in Chapter 1, collaboration between various stakeholders in research on REEs is crucial in making the research happen and contributing to an effective response to the setting. International collaboration was one of the main themes identified by my interviewees when discussing requirements and challenges in the research conduct in REEs. As highlighted in the literature, the requirement for collaboration may come from the need for expertise, research infrastructure or regulatory bodies, and the challenges of collaboration occur in the interaction of participating stakeholders.

In this chapter, I present an overview of international research collaboration in the context of REEs worldwide and in Viet Nam with findings of stakeholders' views of the nature of international research collaboration. Concerns and challenges in the international research collaboration are then introduced as identified by my interviewees as being ethically problematic. Against this background, my interviewees suggested solutions in addressing the problems/challenges and improving the research response. The chapter is finally concluded with emerged values shared across respondents and my reflection on the findings of the chapter.

3.1 The context of international research collaboration on REEs:

3.1.1 An overview of international context:

The burden of infectious diseases disproportionately affects people in developing countries and this includes newly emerging and re-emerging infectious diseases. In the 2003 outbreak of Severe Acute Respiratory Syndrome (SARS), the estimated cost to the Asian economy was between \$11 and \$18 billion, and a GDP loss of between

0.5% and 2% (U.S Department of State 2011). Pandemic influenza soon after is estimated to have caused a higher burden of global infection and cost to the economy, with a disproportion of mortality rate in Africa and Southeast Asia (Dawood et al. 2012). Globalization with an increased mobility in addition to climate change is bringing about a shift in disease burden (Arguin et al. 2009), and increasing the risk of rapid spread of epidemics across the world.

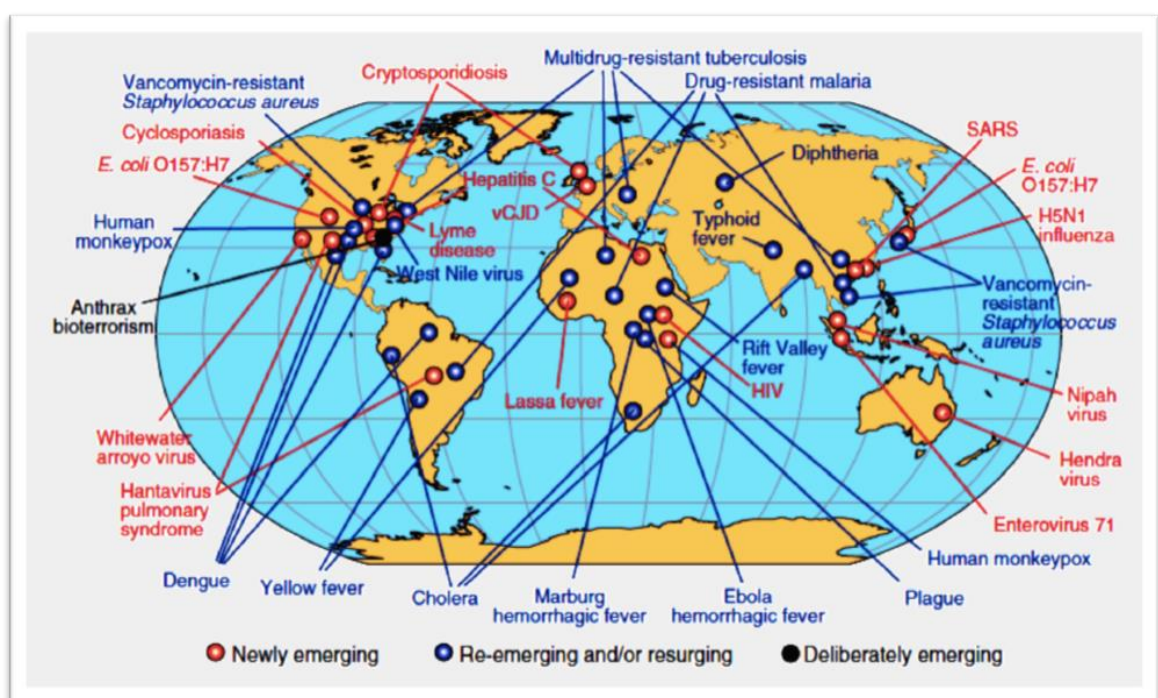


Figure 3.1: Global examples of emerging and re-emerging diseases

(Source: Morens, D. M., G. K. Folkers, et al. (2004). "The challenge of emerging and re-emerging infectious diseases." *Nature* **430**(6996): 242-249. (Morens et al. 2004))

Rapidly evolving infectious diseases require concerted efforts in disease control and prevention at both national and international levels. In REEs scientific research can play an important part in reducing the burden of infectious diseases, for example SARS-CoV, highly pathogenic avian influenza A (H5N1) virus, EV71, Ebola virus, and the 2009 influenza pandemic (Fauci 2005; Ippolito et al. 2009; Abelin et al.

2011). In these cases it is striking that collaboration across research sites and countries produced research giving new insights on the epidemiologic, clinical and therapeutic aspects of diseases. Understanding REEs involves collaboration at many levels within and between countries. In low and middle income countries, there is an urgent need to conduct high quality research to address local health problems, and in high income countries there is a need to be prepared for a global threat. REEs thus require scientific capacity-building where necessary infrastructure, funding, and scientists are put in place. This was raised by the International Conference on Health Research for Development (COHRED 1990) and subsequent reports of the Ad Hoc Committee on Health Research (1996) and the Council on Health Research for Development (COHRED 2000) who called for action towards a more equitable development in health through establishing effective research support systems to, both address the local needs of afflicted countries and, also to help prevent global spread. So far there have been many international collaborative initiatives set up in response to outbreaks, for example The Global Outbreak Alert and Response Network (GOARN, 2000) coordinated by the World Health Organization (WHO), South East Asia Infectious Disease Clinical Research Network (SEAICRN, 2005), The Asia Partnership on Emerging Infectious Diseases Research (APEIR, 2006), International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC, 2011). Such international networks aim 1) to share research resources to facilitate a rapid and effective response to emerging diseases, 2) to plan and conduct joint research projects by involving different stakeholders, and 3) to advocate research result dissemination and consultations among various health partners.

3.1.2 International research collaborations in the local context of Viet Nam:

3.1.2.1 Health research system in Viet Nam:

The focus of my research is on Vietnam. In order to have a clear sense of how international research collaborations happen in Viet Nam, particularly on REEs, it is necessary to first of all provide a brief outline of how the health research system is organized in Viet Nam. As shown in Figure 3-2, the structure of the Vietnamese healthcare service is administratively divided in three basic levels: central level (Ministry of Health (MOH)), provincial (provincial health departments (PHD) or sometimes referred to as provincial health offices or provincial health bureaus) and district level (district health offices (DHO)). Health service delivery is established at four levels: central (central and regional hospitals managed directly by the MOH), provincial, district managed by the PHD, and commune level managed by the DHO (Figure 3.2). The system is organized on the principle of double coordination of professional management authorities and geographically administrative management authorities (central government, people's committees at provincial, district and commune level). In other words, a professional department is under control of two authorities in parallel: its professional management authority and geographically administrative management of the department's location. This organizational principle is established and required in areas in which the combination of professional benefits and community's benefits is crucial (Ministry of Justice and Institute of Legal Science 2006, pg.433). This structure indicates that studies which need to be implemented at certain level and place are required to have been approved by corresponding professional departments and administrative authorities before being submitted to the central level. The decision at the central level - in cases where this is required - is final. However, in practice, this decision is essentially made from

opinions and suggestions of relevant subordinates in collaboration. This hierarchical organization of the health administrative and delivery system is the one in which decisions about research collaboration and management are made.

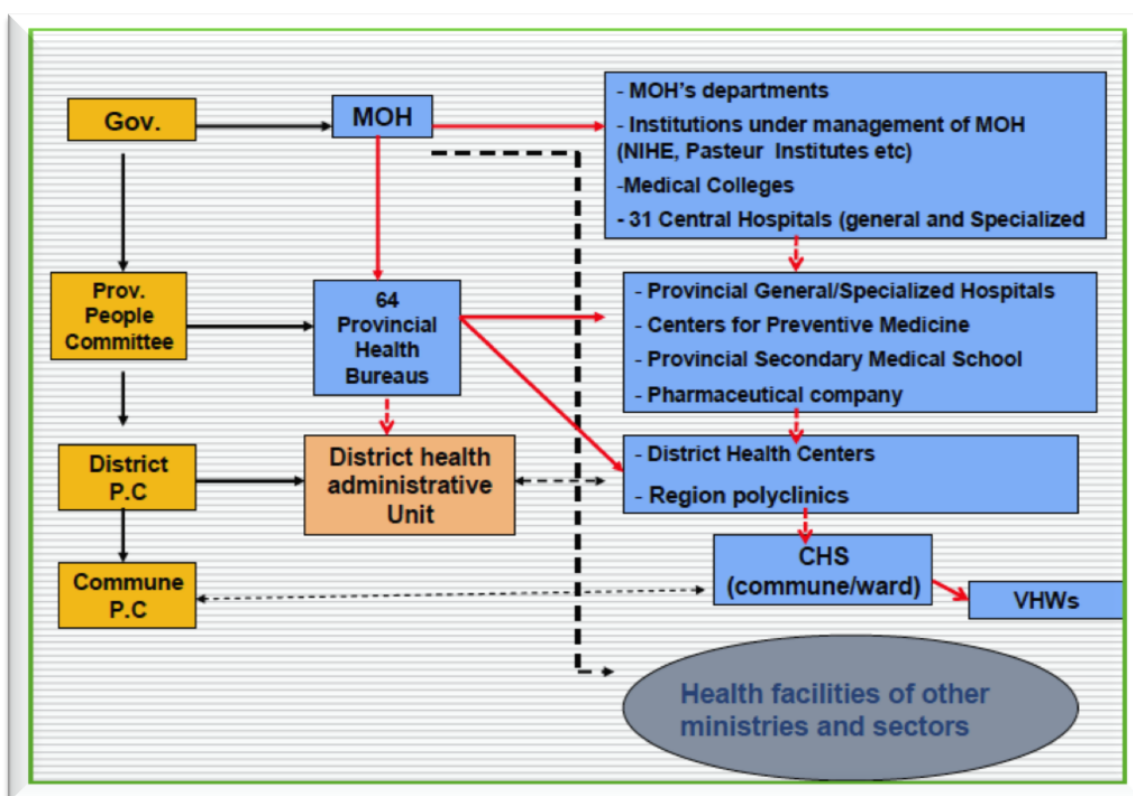


Figure 3.2: Structure of public health care system in Viet Nam

(Source: Oanh, T. T. M., T. V. Tien, et al. (2009). Assessing provincial health systems in Viet Nam: Lessons from two provinces. Bethesda, MD: Health Systems 20/20 project, Abt Associates Inc (Oanh et al. 2009))

In the case of hospital-based studies, research collaboration can be set up directly with the hospitals involved. However, with community-based studies, collaboration would have to go through relevant administrative and professional authorities before approaching the community. These authorities include the People's Committees and Preventive Medicine Centres responsible for the area. Until the study has been approved by these authorities, it cannot be carried out by local research staff at the Preventive Medicine Centre based at the community. Such centres have connection

with the community, appropriate administrative authorities and function to carry out community-based studies, e.g., human resources, expertise and necessary facilities. In community-based studies, working with community is thus not simply a single encounter between scientists and individuals in community, but also includes administrative bodies, local medical providers and community leaders. This happens partly due to requirements of administrative procedures and partly due to the Vietnamese culture of making decisions collectively and respecting other people (Nguyen 1985; Gordon et al. 2009) . This background context was an important factor in my interviewees' experience. As an expatriate researcher based in Viet Nam said:

“No because so far all our research has been hospital based, so I planned to do during the beginning of the pandemic I wanted to do swabbing and bleeding of children in schools and Binh Thuan province and when we wanted to do that I went first to the Department of Preventive Medicine and then to the People's committee to talk about it and they would take care of talking to the whole community so they went to sub departments of the people's committee and talked to the community at the people's committee level. So they would talk to their, what they call their community leaders, yeah so they would talk to them and they would go to the schools and we wrote patient information sheets for, for all the teachers in the schools, for all the children in the schools and their parents, even before we went to do the study so that everybody knew about it already...In that sense the structure of Vietnam is really created, everything is virtually divided into provinces and then into districts and then communities and then into communes so you know you go to the main people's committee and they make sure it gets to all the subs and they go to

their subs and then the community leaders talk to the community” (Principal Investigator 4, Expatriate).

3.1.2.2 Overview of international research collaborations in research in Viet

Nam:

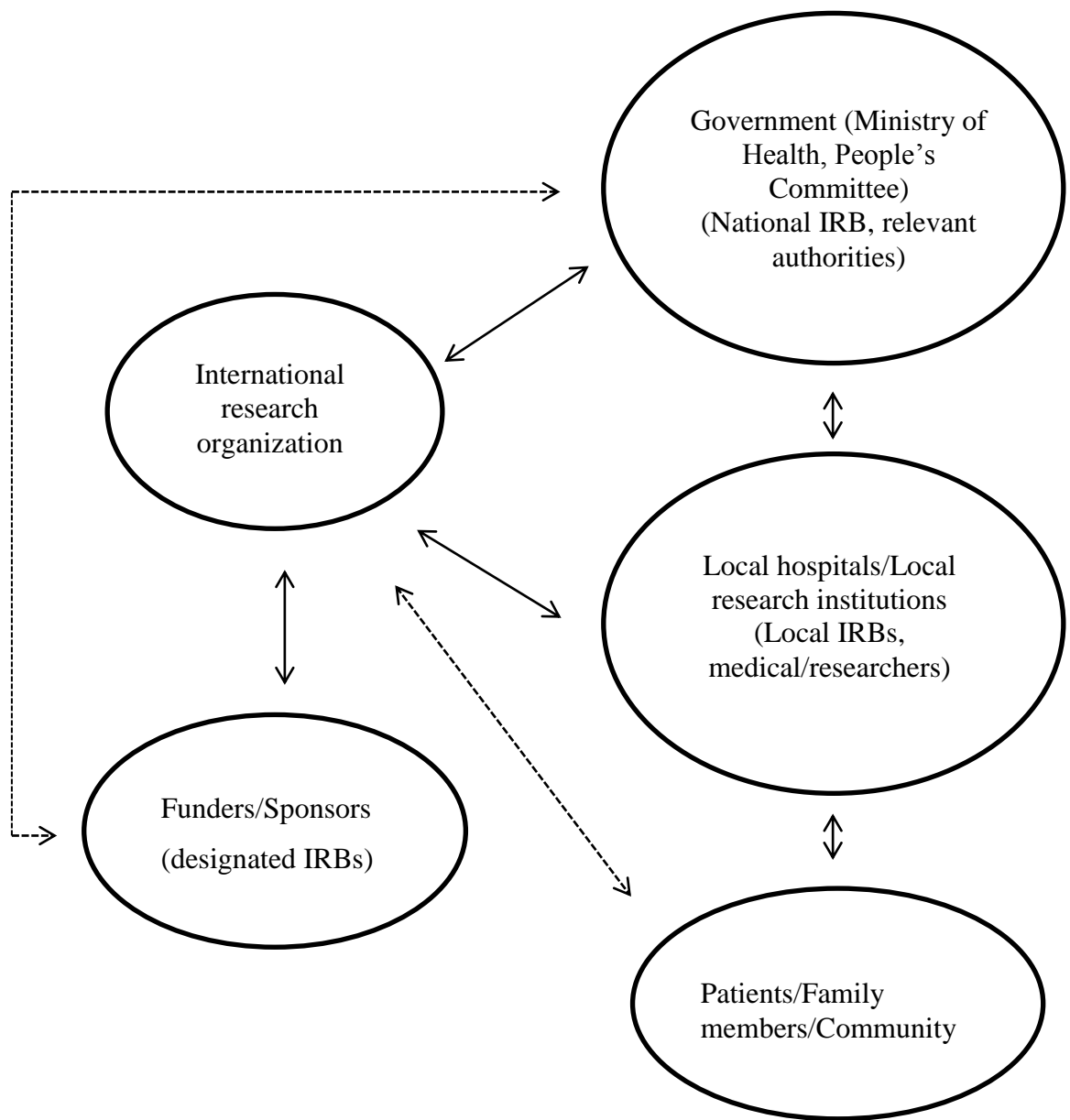
Although there are changes in disease pattern in Viet Nam with declines in the share of morbidity from communicable diseases and an increase from non-communicable diseases, accidents and injuries, the country is still enduring a double burden of disease because the morbidity rate from communicable diseases remains high. HIV/AIDS, typhoid fever, dengue fever and malaria continue to have high prevalence, while tuberculosis, in 2013, is reported to be the second cause of death in people with infectious diseases in Vietnam (Hinh and Minh 2013). In addition, some newly emerging or re-emerging diseases have also broken out recently such as SARS, Avian influenza A/H5N1, and pandemic influenza A/H1N1. The importance of conducting research to address these health issues is recognized by Vietnamese public health sectors and the government. This is evident through examples of collaborations of local hospitals and institutions across the country and to international research partners in concerted efforts to address issues of global health emergencies such as ISARIC, SEAICRN, and APEIR.

An assessment on Vietnamese health research system in 2006 (Anh 2011), showed that internationally funded research was significantly greater than that funded by the national budget. This funding was mainly provided by international organizations including non-government organizations, bilateral or multilateral committees, foundations and councils. In terms of collaboration in research, at the time the assessment was released, networks within the health research system in Viet Nam

were limited, and it was argued that research institutions in the country could not collaborate effectively. Several policies have been issued to promote and improve research activities inside Viet Nam, for example, decision No. 171/2004/QĐ issued by the MOH approving the “Proposal on the reform of the science and technology management mechanism” of the Ministry of Science and Technology (MOST). The MOST also announced “Directions, objectives and key science and technology tasks for the five-year period (2006 – 2010). There has yet to be an official update on this subject.

a) The nature of research collaboration in the studied context:

Drawing on my working experience, document review and the analysis of my interviews, it can be argued that research conducted by international research organizations in Viet Nam can best be understood in terms of three levels of collaboration: micro, meso and macro. At micro level, this is collaboration between individual research participants/family members and local study staff/international research organization. At meso level, it is the collaboration between research ethics committees or Institutional Review Boards (IRBs) with each other, researchers, research institutions and patients/family members. At a macro level, it is the collaboration between international research institutions and local hospitals/research institutions/communities, or funders/sponsors. Collaborations involved in this kind of research can be illustrated in the chart below:



- ↔ Two-way, direct relationship
- ↔ Two-way, indirect relationship

As can be seen in the chart, collaborations between an international research organization (IRO) with other local partners occurs in an institutional context, not between individuals. There are studies done in the collaboration between an IRO and the local government (national research projects) through delegated subordinate local hospitals/research institutions, and between an IRO with local hospitals/research institutions. Within the governmental system and local hospitals/research institutions,

there are IRBs operating under the governorship of the institutions. Collaboration with local institutions would imply a connection with local IRBs based within the institutions, and local IRBs cannot be seen as being detached from their governing institutions. Relationships with local study staff, IRBs, study funders, and sponsors are generally bound by constitutional relationships in which close links are created through research activities, especially in long term research collaborations. It is revealed in this present study that these collaborative relationships are crucial when proactive research planning needs to be discussed and agreed by parties for a rapid response during REEs.

In my research, I have only investigated issues rising in the relationships between OUCRU and partners in hospital-based studies. This includes collaborations between individual research participants/family members and local study staff/international research organization at micro level; between international research institutions and local hospitals, and between international research institutions and funders/sponsors at macro level. In addition, there are some additional experiences of foreign investigators involved in community-based research in community. However, these data do not include perspectives from community or local researchers involved in direct community-based studies.

In my analysis of the interviews conducted with local and international stakeholders, it became clear that the nature of the research collaborations in which they were engaged in was important to them in relating to their general experiences in the research projects and problems confronted. That is to say, on one hand, their involvement in the collaboration presents concerns or day-to-day challenges in collaborative research projects. And on the other, such collaborations and the prospect

of it elicited the possibility of solutions in addressing those problems in the research conduct in REEs.

b) Relationships between Vietnamese and international research institutions, between research institutions and communities: collaboration at a macro institutional level

The importance of collaborative relationships between local and international research institutions and rationale for international collaboration in research on REEs:

At the institutional level, establishing scientific research collaborations involves considering characteristics of an institution, what contribution each collaborator can make as an institutional entity and what all involved parties can produce together. Collaborative research generally increases the capacity of individual scientists to make significant advances. In biomedical research, collaborations become crucial for mobilizing intellectual and technical resources which lead to scientific discovery of direct benefit to society (Macrina 1995). Collaborations in research on REEs have dramatically grown in recent years. One important reason for collaborations in research on REEs is demand from developing countries who lack the necessary resources to deal with issues of public health emergencies. It is also recognized as the responsibility of both afflicted states and international organizations to encourage health development and protect people in epidemics (Global Forum for Health Research 2004). Secondly, modern research often demands large amounts of clinical data in order to produce statistically meaningful results, and using data from diverse populations makes research results more widely generalizable (Parker 2014).

Similarly, these reasons are raised by my interviewees when they spoke of international research collaboration in REEs. In this case, OUCRU is seen by Vietnamese research partners as an international group versus “them” as local group even though OUCRU has been based in the country for a long time and the majority of employees are Vietnamese. This might be explained through different objectives, political perspectives, working practices, interests and values held by the two groups. Coming out from the interviews are other aspects that collaborations would be built from and bring benefits to, not just the benefits of science. First of all, research can be supportive to public health services by identifying new pathogens and finding ways to tackle it. In addition, it is the urgency of epidemic situations drives formation of collaborations. An expatriate investigator said:

“Yes so a sense of urgency, people are on top of it, they’re eager, the director [of the hospital] wants to know so he orders them so it’s very quick, urgent so that’s the good thing about outbreaks is there’s always a sense of urgency, people want to know, Ministry of Health wants to know, the director wants to know, the doctors want to know what’s going on and we’re there to help them to do something with the sample” (Principal Investigator 5, Expatriate).

In this setting, Vietnamese hospitals are the main providers of clinical cases and existing human resources to support clinical studies, and foreign research organizations like OUCRU often provide funds and research facilities in compliance with international standards. This financial support of research has been raised as a primary reason for establishing international collaborations. As a Vietnamese investigator argues:

“We want international collaborations because we want them to support us the funding. I think that the main reason. For example, my hospital, in my hospital, we can do research on our own. In the past, we were incompetent at writing up a research protocol, however, at the moment, there are people studying abroad coming back to the hospital. I am an example. After coming back, they are capable of writing research protocols after taking some courses in public health. But when we want to carry out the research, we need money for everything. So it gets stuck. That’s the reason why, I think, in most cases, what we primarily need from foreign countries is funding. Especially in cases of epidemics, you need laboratories. There must be laboratories, and it requires lots of money which we can’t afford” (Local Principal Investigator 13).

Giving a general comment on the nature of international research collaborations, a local IRB member has stated:

“To be frank, in terms of doing scientific research, Vietnamese funding is very limited, so we have to rely on foreign organizations, non-governmental organization to conduct research. With our own fund, Viet Nam can’t do anything. We can only do that through the aids of those organizations. Both parties get benefits. It is a matter of course that both sides get benefits so that they agree to invest money in. But it also benefits our people so we just do it. There is not any problem” (CH2: IRB member 3).

As suggested in the comment of the IRB, in overall, collaborating with foreign organizations in doing research is a type of collaboration whereby all involved parties can receive benefits. And the benefits for local people are most considered.

In general, local investigators and IRB members shared the same view that local research sites have more benefits than harms in doing research with foreign parties. Another benefit is a chance to gain experience in large scale clinical studies. While there was no such large scale research with guidance from the Vietnamese Ministry of Health at that time, international collaboration presented learning opportunities. This was described by a Vietnamese investigator with the specific example of SEA001 study on influenza:

“So I think, in general, in terms of benefits and harms, there exists both harms and benefits, but the benefits are outweighed. At least we can learn a lot from them. If there is not their involvement, we can never have large scale studies, and we have nothing to learn. For example, if there’s not SEA001, not such large studies, I believe, there would be many doctors who wouldn’t know about SEA network. Of course, we would apply in compliance with guidance from the Ministry of Health, and we had waited for the Ministry. The Ministry has only applied the same research model and deployed in large hospitals for 1 or 2 years recently” (Local Principal Investigator 13).

By involving local study staff and coordinating all research activities in an international research network, not only has research practice been standardised, but ethical aspects and procedures are more likely to be met due to training on good

international research practices and obtaining ethical review from IRBs at all relevant levels. These in combination improve the whole quality of research:

“I have done 3 studies: one study on hand, foot, mouth disease (HFMD) at state level, one study on HFMD with Pasteur, and one with OUCRU, 14CN study. I’ve just joined this study, and I’ve heard that studies in collaboration with OUCRU are generally better than national ones. Such aspects in research as methods of archiving samples and diagnostic techniques are more accurate than ours. So if I see a study doing with OUCRU, I feel more secured” (CH2: Study doctor 1).

“You know Wellcome, they have to follow international standards, and their protocols have to be approved by local IRBs and international IRBs, many IRBs and the IRB in the Ministry of Health so basically, that’s our advantage because it follows standards” (HTD: IRB member 2).

“I think the auditing, typically in the last pandemic influenza, I appreciate it very highly. I assume that is one of methodical, standard. To be fair, from my individual experience of doing many studies, it is really difficult to implement the same system like that. Difficult!” (NHTD: IRB member 2).

The reputation of international research organizations is highly valued by local partners, and in some cases, it is set in the mind of local investigators and local research institutions that research protocols from international organizations are already standardized across multiple sites, and therefore there is no need to give more comments on scientific aspects. Sharing his experience working with the US CDC, a local investigator said:

“Influenza, there has been a surveillance system since 1998 when there was an outbreak of H5N1. It is a long time ago. At that time, in my hospital, although we had the scientific review board, no one paid attention to...because that was international collaboration, in our mind, we thought it is already standardized. There would be no point in giving our comments on it, because it’s standardized” (Local Principal Investigator 13).

When considering funding provided by international collaborations, two types of collaborations are distinguished: international non-profit research organizations and pharmaceutical companies. On comparing between these two types of collaborators, a local investigator has said:

“If that is the collaboration with a non-profit organization, firstly, in terms of their financial funding, because it’s not really abundant, sometimes it’s not enough to pay for medical doctors for their efforts made in research. Sometimes because, as I said, it is a duty, and although being paid low, doctors in the hospital still have to join the research. But with pharmaceutical companies, they have advantages that all that can’t be done by a non-profit organization can be done by pharmaceutical companies. Secondly, they can pay corresponding to the doctors’ time and efforts, and so the doctors feel deserving. Thirdly, in terms of types of studies, their research purpose is quite different from that of a non-profit organization. While pharmaceutical companies primarily focus on clinical trials with drugs, non-profit

organizations can focus on doing clinical research and epidemiological studies” (NHTD: Study doctor 2).

As indicated in the quote above, there are two fundamental differences: the amount of funding and types of clinical studies that can be done by these two collaborative entities. Limitations in research funding and capacity to implement broader types of clinical research are raised as characteristics of international non-profit organizations in comparison with pharmaceutical companies.

However in further discussions with local IRB members about their opinions on collaborating with pharmaceutical companies in doing research on REEs, it seems that local hospitals did not receive proposals to carry out a research on REEs from pharmaceutical companies, perhaps as the pursuit of commercial interests constrains their involvement in other studies. As explained by an IRB member:

“That is why I feel a bit sad when there are emergency disease outbreaks and pharmaceutical companies – they are likely to run after commercial interests. Even in collaborating with foreign pharmaceutical companies, they just collaborate with us in order to obtain a visa for their drugs to come to Viet Nam” (CH2: IRB member 1).

My interviews with international experts also suggest some worries in establishing research collaboration with pharmaceutical companies on REEs in terms of the trust and openness necessary to respond rapidly and mount an effective response. Talking about doing research with pharmaceutical company, an international expert shared that:

“Well I, you know I, and this is not, I mean this is just my particular bias is that I don’t, I’m uneasy about the pharmaceutical company funded protocols in pandemic research because I think there is, there has to be a level of trust, openness, in the research process to, because you do have to in a sense move quickly and you’ve got to rely, you’ve got to have confidence in the people you’re working with. And that’s often difficult with commercial things, they don’t necessarily want you to know what the pharmacology of their drug is or if you’re doing studies they don’t necessarily want you to see the data, that kind of thing” (Principal Investigator 6).

On the side of expatriate experts based in Viet Nam, they share their overall experience of collaboration with Vietnamese partners as a mutual support in which OUCRU contribute research resources such as good laboratories and expertise to produce results desired by local partners. Vietnamese partners, in return, have access to research participants and samples that can make projects feasible. On the basis of these, local research sites are seen as equal partners in this collaboration:

“It starts with a patient comes in and then a second and a third with something similar or something a lot, it’s either a lot or something small but unexpected and quite severe. So then if that happens because we have good laboratories, we have a lot of tests so we find something and then the partners, Vietnamese partners either NIHE or here or National Paediatrics Hospital, they appreciate that so we give them an answer to what is causing their problem. And after it becomes quite easy because we can help them, we can do the tests for them, so

we don't only talk and give them a lot of work we can also provide them some diagnostic service, and diagnosis of the disease they didn't know they had before. And then you talk together, so everybody, because then you're really equal partner, we are strong because we can give something, they're strong because they have the patient and access and everything and these, so then we decide on a project, we discuss, often so many things are in Vietnamese so I have to always make sure somebody translates generally" (Principal Investigator 5, Expatriate).

Elaborating more on this, the benefits of collaborating with local partners include the benefit of local advice in making research appropriate and feasible, and also academic benefits resulting from the research:

"For epidemics absolutely, and I would say even especially more than something else because the primary experience of an epidemic lies in those doctors who see it first hand and they're the first ones to see it. You know we did the diagnostics, the laboratory stuff pretty much for most of Vietnam for epidemics but we don't know the disease, we don't practice on the ward so as soon as hand, foot and mouth disease started to get out of hand we'd call everybody in to come and we had meetings about you know what we do about this, what do we treat it, H1N1 same thing. It started, that was a little different, it started in the HTD because of Vietnam's containment policies but you know we just, we called everybody, who are you seeing, what's happening, so I would say site engagement is more imperative for epidemic

research partly because of their experience and partly because of the nature of that research (Study Sponsor 1, Expatriate).

“And they will become co PIs or co researchers and we will do the publication together so we all have named persons working together” (Principal Investigator 4, Expatriate).

In doing research in REEs, local advice given by front-line clinicians may be particularly significant to allow international experts to better understand the clinical situation in the area and to tailor response quickly to the setting.

Through long-term collaboration with and close contact with Health Departments and the Ministry of Health, an expatriate expert has also mentioned the positive role of OUCRU in leading to the policy change:

“So many things here because we’re in the north, also lead to the policy change so we have close contact with the Ministry of Health” (Principal Investigator 5, Expatriate).

The importance of relationships between research institutions and communities

The term community in this section refers to communities where the research occurs. It is defined by interviews with stakeholders describing community-based studies. Experiences shared by investigators and international experts in doing community based studies partly reflect the process of going through the relevant authorities described above. As they do not directly approach the community, organizations running this type of study all state that the collaboration between the research institution and communities takes the form of indirect communication supported by authorized community administrative departments. In this process, investigators

engage community leaders such as People's Committees and Preventive Medicine Centres to discuss research proposals. These bodies can then disseminate information to their community, and enable their staff to work alongside investigators.

“So far all our research has been hospital based, so I planned to do during the beginning of the pandemic I wanted to do swabbing and bleeding of children in schools and Binh Thuan province and when we wanted to do that I went first to the Department of Preventive Medicine and then to the People's committee to talk about it and they would take care of talking to the whole community so they went to sub departments of the people's committee and talked to the community at the people's committee level. So they would talk to their, what they call their community leaders, yeah so they would talk to them and they would go to the schools and we wrote patient information sheets for, for all the teachers in the schools, for all the children in the schools and their parents, even before we went to do the study so that everybody knew about it already” (Principal Investigator 4, Expatriate).

“R: Yeah, yeah so sort of indirect experience around you know going into the community for sero epidemiological studies so.... really you know that comes back to engagement with public health authorities because you know in this setting we don't, we're not really able to go into the community and ask, knock on patients' doors, that's something needs to be done through preventative medicine or you know other authorities. So it's a different set of stakeholders to engage with....ah... who in, you know in the context of an

emerging disease are going to have other priorities, they're going to be focused on public health.

Interviewer: Engage with authorities?

R: Yeah, yeah I think if you want to get it done you, you know that's the only, they have to do it for you and you have to justify why it's important" (Principal Investigator 8, Expatriate).

As confirmed by an expatriate investigator based in the South in the quote above, this exercise is defined as "engaging with authorities" rather engaging the community.

Similar patterns can be found in community based studies on influenza taken place in the North of Viet Nam. As explained by an expatriate based in a Northern research site:

"Interviewer: So it means that when you want to establish a collaboration or want to carry out a research in a certain area so the first thing we have to engage with the leaders?

A: Yes the first thing you have to convince the people's committee or the women's union or something you know that it's worthwhile engaging on an issue until you've done that you can't really go into community. I mean that's different for hospital patients obviously it's more of an individual thing but when we do community studies then that's important" (Principal Investigator 1, Expatriate).

3.1.2.3 On what account scientific research collaboration is established?

Interviews with local and international stakeholders provided an account of the key factors considered at the time of establishing research collaborations and the factors that contribute to the success of collaboration. In what follows, I present these two groups of factors shared by relevant stakeholders directly involved in the process of setting up research collaborations with international research partners.

Drawing on experience in working with a wide range of collaborators such as pharmaceutical companies, other Vietnamese research institutions, and international research institutions, Vietnamese investigators and study staff in the interviews suggested factors that they considered important when reviewing a research partner. These included reputation, research capacity, funding, expertise, and previous research collaboration with that partner:

“Yes, we do. It is something like if we have good impression with whom we have collaborated, things would be easier. For example, there will be some aspects when you hear about a research partner, firstly, if it has good reputation, secondly, if its research resources are strong or not, and thirdly, our history of doing research with it until now, if it’s smooth. Take the example of doing research on HFMD. If working with OUCRU, I think that I would have to be more careful because the research partner is very detailed and careful.”

(CH2: Study doctor 2).

A previous collaboration or the reputation of a prospective research partner enabled local researchers to know more about the working methods and manner of the

prospective partner. Previous collaborations were also counted as an advantage in setting up new projects. As shared by a local study doctor:

“Who the research partner we are going to collaborate with is important to make the decision because, for example, if we work with them for a long time, we very much understand each other, or to big pharmaceutical companies like Novartis, I would easily accept it right at the beginning and we agree to read their research proposal right away. But to some companies who first come or research organizations first come and work, they have to go through a process so that we can review if they are licensed to do research, how about their reputation, how they have done research. We will get to know those information before we receive their research protocol. To organizations who we’ve already had experience with them or we have collaborated with them before, we usually receive and read their research protocol immediately and give comments on it without inquiring more information about their reputation and their research capacity” (NTHD: Study doctor 1).

Such requirements from Vietnamese research partners put OUCRU in a unique situation in which with its long-term base in HTD and NHTD, where research on REEs could be quickly initiated compared to other organizations. An IRB member noted this:

“No, pharmaceutical companies can’t embark on research on emergency epidemics immediately. They have to go through an intermediary. But especially to emergency epidemics, there is not any pharma company to ask to

collaborate with us so that we can carry out research immediately. OUCRU is the quickest one because it already locates in here. You see, research on influenza or other epidemics could be implemented immediately, so was the PCR testing. We had the PRC result while Viet Nam still hadn't finished it. It's already here so we don't have to look for elsewhere. That's the convenience" (HTD: IRB member 2).

The presence of on-site research facilities was stated by a Vietnamese IRB member as a specific advantage in the influenza pandemic which required modern scientific techniques. If these facilities and collaborations hadn't been set up in, it would be hard to have any research initiative to be quickly made in response to such REEs.

a. Familiarity and trust

My interviews show that familiarity and trust are key factors in successful collaboration. In discussing OUCRU's relationship with Vietnamese hospitals and research institutions, a study sponsor described further on what account collaboration is based:

"Execution-wise I think that OUCRU is in a unique situation of collaboration, trust and experience and that combination doesn't put up huge barriers...I think that those discussions happen quickly, I think that the sites we work with are very responsive and I think that they understand the severity of it. So again we have very established relationships with these sites, we have very senior Vietnamese researchers who are very trusted in this community on site, so even if it's in Nha Be or Binh Thuan, no I would say those discussions

happen very quickly. And the Department of Animal Health call Dr A as soon as something happens they call her and she's out there on a Saturday helping them. So for us that's not a barrier. I could see that as a barrier in other situations but just not in this context" (Study Sponsor 1, Expatriate).

This close relationship and trust that have been built with local sites, means local sites support OUCRU and are responsive to discussions and issues around research conduct.

Expatriate experts of OUCRU based in Ha Noi Unit also shared their experiences in creating familiarity with local research sites through collaborations and site visits. By doing this, expatriate experts can understand situations at local sites and other sites where they may want to establish collaboration in the future. These prospective and current research sites would also become familiar with them when if there is any problem, local sites can quickly contact them:

"When there's an outbreak, because we don't see the patients, there's an outbreak it's because we do the patient rounds and we find out, see the patient, or some hospital doctor comes to us like we have a problem, can you help us or can I send a sample. So it's just by being here, doing your clinical rounds actually by having local presence and by going around, seeing the partners, so we...sometimes we are at paediatric hospitals and there is the one Oh here's something new or Ah, maybe we should test the specimen, and I think it may be good so I'll test" (Principal Investigator 5, Expatriate).

Discussing further with expatriate researchers and the study sponsor based at OUCRU about what “trust” consisted of in this setting, it was suggested that one component was Vietnamese partners’ trust of OUCRU’s research capacity such as applying international standards, and OUCRU’s research experience in general:

“...things are so steady, we have such good relationships with the sites and they trust us and to be honest with you they don’t, they have a lot of experience of us, they don’t have a lot of independent experience at this quality level of research so if we come in we say there’s the SOPs (Standard Operating Procedures), they say great, thanks for it” (Study Sponsor 1, Expatriate).

Speaking of her experience working with OUCRU, a local study doctor said:

“I’ve heard that doing research in collaboration with OUCRU is better than national ones. Their research questions, laboratory techniques and sample archive method are more accurate than ours, so if I see the study done with OUCRU, I feel more assured” (CH2: Study doctor 1).

Trust in another case is equated with “faith” by the respondent in the sense that it does not require some evidence or a clear understanding as a ground for the trust. An expatriate investigator noted:

“B: Sometimes I get the feeling that they think that what we’re doing is not really worthwhile and yet they still support it. So I don’t really, I sometimes

think that they don't really sort of believe or understand it, to think it's, you know to decide whether it's worthwhile doing.

Interviewer: So that's how you had to convince them?

B: We usually don't have to spare much time convincing, it's usually they'll just have faith. I don't know if it's just because Oxford as a good reputation and maybe that's why, yeah maybe they are more critical of other studies” (Principal Investigator 3, Expatriate).

These quotes above suggest the confidence of local researchers in working with OUCRU. It is manifested in a way that local research partners are confident about the quality of OUCRU's work although in some cases they may not necessarily to clearly understand and feel worthwhile of the work done.

In other cases, it is supposed to be the mutual understanding to maintain the collaboration. Expectations of all parties are thus shared and there is an understanding of what would be required:

“Yeah I agree that it doesn't necessarily mean that you trust them implicitly yeah. Yeah I think it's just more that it's comfortable because you know what their expectations are and you know you don't, you get to a level where you understand what they'll require from you if a study is going to go ahead. So that's, because if you don't have that already it takes a long time of negotiating back and forward and who's responsible for what, what you will provide in the study, what they'll provide and the quality that you require and yeah” (Principal Investigator 3, Expatriate).

In general, according to accounts of both Vietnamese and expatriate experts based at OUCRU, familiarity and trust is seen as a cornerstone in establishing research collaboration. These are also key factors any research initiative on REEs as without prior establishment the amount of time required to build a research paradigm satisfactory to all collaborators would risk the whole research enterprise. Commenting on these factors, an international expert based in Australia said:

“If it’s someone that we know well, whom we have worked with before, who we liked and we trust we would have no hesitation in sharing everything with them. If it’s someone who we’ve worked with previously and we came away from that relationship dissatisfied in some way we probably wouldn’t be particularly enthusiastic about sharing with them. If it was someone new we would almost certainly give them the benefit of the doubt to start with. It helps that the information that was collected by these sorts of studies had no great financial or intellectual property value, it was just information that was going to be useful to try and help improve the clinical and public health response to this outbreak” (Principal Investigator 15).

b. Academic pressure

Collaborations in research on REEs are driven by pressures from the national and international community. Interviewees talked specifically about the academic pressure leading to communities taking part in the research:

“Internationally I, no I don’t then it’s pressure from OUCRU, I think it’s peer pressure, it’s a reputational pressure, it’s an academic pressure. I think that

there is academic pressure to collaborate with international research. Now some people don't care, the old Minister of Health in Indonesia didn't care, she shut off the scientific community. Other people do care and other people are progressive enough to understand the importance of it. So yes I think there's academic pressure for communities to engage, scientific communities to engage in pandemic research" (Study Sponsor 1, Expatriate).

c. Willingness to collaborate

Another important factor in establishing research collaboration as well as maintaining the collaboration is the willingness to collaborate from all parties. In the context of REEs, the need to understand the disease is a major factor determining willingness to collaborate. An expatriate investigator when asked to give his general view about research collaborations with Vietnamese partners said:

"Yes I think there's willingness from the sites to do whatever was possible..."
(Principal Investigator 8, Expatriate).

The willingness is also recognized as a basis for effective collaborations by the international experts I interviewed. Interviews suggested that when people were willing, they were enthusiastic about sharing experience and knowledge, and achieving consensus:

"So the dynamics are fantastic. There's, at least amongst the intensive care unit (ICU) networks there's an enormous willingness to share experience and knowledge, share case report forms and data dictionaries so that new studies

can be conducted much more efficiently than if they had to invent everything from scratch... So there was very extensive collaboration amongst researchers who know each other well and have worked together on multiple other projects previously” (Principal Investigator 15, Australian).

What I have presented above are the key components that are taken into consideration at the time of establishing research collaborations and factors that make such initiatives happen effectively, especially in the setting of REEs. Moving beyond the initial decisions about forming collaborations is the question of how to maintain the collaboration. According to my interviews with expatriate based in OUCRU, it is clear that the sustainability of effective collaborative relationships between local research sites and international organizations depends upon respect for the opinions of local partners, a degree of “give and take” in the relationship, and an emphasis on accountability and transparency in research work. These principles play an important role in maintaining the relationship:

“Poor recruitment or sometimes we have some protocol violations but generally this is, SEA projects, FHI sometimes results that the hospitals are unhappy to be..... some false positive results from the lab, causing confusion and we have to really make sure we explain what happened, keep the trust that everything is okay and sorted, some new staff did something wrong...[laugh]” (Principal Investigator 5, Expatriate).

“So that’s important that there’s give and take with the relationship. So it’s important to keep that in mind and not just to say the study is done and that’s

it, or relationship is finished because it probably isn't" (Principal Investigator 3, Expatriate).

d. Influences from both parties:

Through the description above about relationships between local Vietnamese research partners including researchers and IRB members and international partners there are mutual influences that both parties place upon each other.

Influences from local partners to foreign research partners

As corroborated by local partners and international partners, it is the practical experience of local researchers as front line medical staff dealing with epidemics that plays an important role in the planning of local research initiatives. A study sponsor based at a local site has explained:

"For epidemics absolutely, and I would say even especially more than something else because the primary experience of an epidemic lies in those doctors who see it first hand and they're the first ones to see it. You know we did the diagnostics, the laboratory stuff pretty much for most of Vietnam for epidemics but we don't know the disease, we don't practice on the ward so as soon as hand, foot and mouth disease started to get out of hand we'd call everybody in to come and we had meetings about you know what we do about this, what do we treat it, H1N1 same thing" (Study Sponsor 1, Expatriate).

Not only providing advice on treatment and routine care in general, it is about what can be feasibly done in the practice and what is considered culturally acceptable in the area:

“The collaborators, their role in the, yeah for the H1N1 very important role in advising about what was acceptable in, you know how much blood you can take and how many times you can visit, very, they’re very definite about those aspects and about what treatment should be given” (Principal Investigator 3, Expatriate).

Influences from foreign research partners to local partners

It may be possible for local partners to become more active in the collaboration, and influential to the hierarchical working system in Viet Nam. As an expatriate investigator stated:

“I think that’s true for trials but it is not because we don’t have they.... because they’re often just passive because of the hierarchy structure in Vietnam so the director is always too busy and the ones that can do it they say I have to wait for the director, I don’t, there you go, so it’s not in the Vietnamese culture or doctors not directly.... director can take initiative to go and then they’re very passive and because we’re the foreigners it’s easier for us to push and get things approved” (Principal Investigator 5, Expatriate).

International partners also affect the local system through the acknowledgment of groups that are often considered as marginalized in the local working system:

“Oh I see okay, we always ask all our collaborations which should be, we always ask the, we ask the head of the collaborating group, they have to tell us

what staff should be included and so it's not our choice. So we don't have trouble with that because then you know how it is in Vietnamese groups it's very hierarchical so it's what the person in charge says. So we stick we that, although sometimes we'll add somebody else if we know they did a lot of work and the head person hasn't included them, we just include them and we'll show that we include them and it's never a problem to include others. So I sometimes put nurses on, because I know they did a lot of the work and the director won't put them on" (Principal Investigator 3, Expatriate).

3.2 Concerns and challenges in international research collaboration:

Issues presented in this section arise out of narratives of international collaborations. The majority of them are drawn from collaborations between OUCRU and Vietnamese research institutions. Collaborations between Vietnamese local research institutions in research projects on REEs included in the interviews are legally bound by the order of the Ministry of Health, and thus they do not call themselves as "collaborators". There was however no issue reported in such local type of collaborations.

3.2.1 "Research executor"

While being seen by international research partners as "being equal" in research contributions, some local Vietnamese researchers do not perceive their role in the same way, specifically, the level of involvement of the research work that they can have in doing the research. This issue was raised among some local Vietnamese researchers when they perceived themselves as a "research executor" in doing research in collaboration with foreign partners. As expressed through the interviews,

local researchers felt that they were limited in their involvement of setting up and planning research projects. They argued that they had had less chance to give their own suggestions with regard to research planning, and by accepting and carrying out the research as already arranged by the study sponsor (in this case is OUCRU), local researchers saw themselves as people who just executed the study:

“Study doctor 2:[laugh] Everything was done carefully so I have nothing more to talk about. In general, we could give more suggestions if we were in that committee.

Interviewer: The project committee or the sponsor?

Study doctor 2: The sponsor. We are only investigators who execute the study”(HTD: Study doctor 2).

Perceived the same issue as being a “worker” who went and got samples for foreign research partners, a local study doctor saw their role as only supporting foreign partners to complete the study:

“Uhm, when doing a research, of course we want that we can do everything from the start, not just...., currently, we are just like supporting people to finish the research. In fact, our research at...at the ward, we also do our own studies here, but because we don't have enough capacity and facilities to do some assays. We don't have conditions to do. For example, if we need to generate things like cytokine, assays, etc. nowhere could do it. OUCRU can do it, but when we give the idea, they write the whole research protocol. So by doing that, they also encourage us into developing that research protocol, or we

could do a PhD or jointly do something. So those are good directions. What I want is to do separate research for the hospital, for the hospital itself, for the department, not just like acting as a worker to get samples for people” (CH2: Study doctor 4).

Here in this case, he suggested a full completion of all necessary procedures in doing a research by and the ownership over the research of the department and the institution where he based as a sign of not being a supportive role or a “worker” who work for someone else in the fulfillment of someone else’s overall work.

Giving comment on research collaborations with foreign partners, another local investigator suggested a state of coming to rely on foreign partners of local researchers in this venture:

“So I think, I think...Actually it was good in previous years because in fact, our Viet Nam haven’t....Maybe we become dependent. I mean, up to now, we haven’t got money, so we can never generate big ideas. We never dare to think about it, and so we just focus on the routine. So that is the bad thing if we are just dependent on them. We just think like “Ah, so you wrote it already, I don’t need to rack my brain. Just give it to me and I’ll do it, I will do whatever you want me to do” (Local Principal Investigator 13).

As indicated in the quote above, it is due to the lack of financial supports which partly results in the habit of scientific thinking in routine, local researchers are getting to be dependent on foreign collaborators in putting forward research ideas and planning.

A different opinion was expressed by a local study doctor cum IRB member stressing the importance of local contribution and the cooperative attitude of foreign partners on listening and being open to local advice:

“I don’t see any problem here regarding this because actually in international collaborations, they do the research very....when we...we can’t afford such...Honestly, I hold a slightly different view about this compared with other people. Firstly, I don’t think we are inferior to them. It is their own thoughts through the interaction that make them feel like they are inferior. For example, foreign partners can give us financial supports. We can’t deny the fact that, international research organizations, they have many capacities, for example, finance, research facilities for diagnosis, etc. and they even write research protocols very well. We don’t have any person to write such good research protocols. Let’s say if we can write such a good protocol and have that much money to do it, then we can become the owner. But if we can’t, we will have to co-work with them. And when you jointly work with them, why should you have such a thought like, for example, when they finish the research protocol, they say this this this, and we just do it and we think we’re just like mercenary. It is actually not like that. We are collaborating and they need us. So giving an example, they have money, but they can’t access to clinical samples and have certain good credits in local communities like us. So to some extent, to them, we shouldn’t think that person who has money control everything. It’s not like that. So I think it is okay for us to collaborate to do work on research like that. I act as a study coordinator in 14CN study, and I see everything is good. There is not any problem. In fact, they can

require us to fill in many study documents, and how to fill them in. We, in return, put forward our suggestions if we see the research protocols have some points unsuitable to the clinical setting, for example, if we can say to them “This makes hard on our patients. It would be difficult to obtain samples”, something like that, we suggest to modify, change it, and they are very cooperative. So I think that’s normal” (CH2: Study doctor 2).

Continuing to explain that local staff may feel limited in their involvement in collaborative research projects, the study doctor indicates that the local hierarchical working pattern could play a role in this perception. Senior doctors holding managerial positions are involved in the process of designing research projects, and when the work is delegated to subordinates, they lack of the general sense of how things being discussed and arranged in upper levels. This will be further elaborated in the following section.

In general, what all these data suggest is that there is a sense among some local researchers of having less involvement in the whole research process and that this leads to them perceive themselves as “executor” or “mercenary”. While this may not suggest a perception of self-devaluing, there are implications of a passive, mechanical role and the desire to actively contributing to research collaboration with intellectual input such as giving ideas for research, writing research protocols, and carrying out the research by themselves.

In an interview with an international expert in Britain, he also expressed the concept of “sample monkey” about himself whereby despite being a researcher, his role was only limited to collecting samples. There is a need to be more involved in research by being able to analyze the data that he contributively collected for the research. This

intellectual contribution is seen as a reward to him as a researcher and make him feel being placed in a proper role of a researcher: doing the science:

“It’s like well yeah but we all need publications, we’re all career scientists how had we decide authorship, how do we decide who gets to the do work, I don’t want to just be, they call me the sample monkey here because I just go round collecting samples sometimes and I don’t want to be a sample monkey, I want to be someone who’s doing the science. I love the clinical side of it and I think it’s underestimated and to do it well is actually quite challenging and that’s why I love working with OUCRU because you know they just get on and do it and it’s done to a good standard and I like that energy. But after I’ve collected all the samples successfully I want to be analysing them and looking at the data myself, otherwise there’s no, there’s no great reward” (Principal Investigator 2).

3.2.2 Hierarchical system:

As briefly laid out in the preceding section on the limited role of researchers in international collaborative research projects, this may result from the hierarchical working system in Viet Nam. There is a clear division in the work and when the work is delegated to each of department, study staff are bound both by legal and institutional regulations to take on the work assigned:

“Interviewer: So you didn't take part in work like meetings for discussion about patient recruitment that when patients would be admitted to Ward D or something like that?

B: That's what I've just told you. They held the meeting, discussed with each other then they asked us if their plan is okay or not, and we have only one option; that is nodding our head in agreement or not” (HTD: Study doctor 2).

Being asked about the fact that Vietnamese researchers' perception of taking a passive role in research in collaboration with international partners like OUCRU, an expatriate investigator based in OUCRU – Ha Noi has confirmed this fact and given further explanation to this. He pointed out to the hierarchy medical governing structure in Viet Nam as a reason for how the research should be implemented and be divided into levels according to leaders of local research sites:

“Interviewer: Yes so again with the collaboration during the previous interviews there's one issue that's raised from the local partners, I mean from Vietnamese side saying that so they just feel like they're the one that you know have a very passive role where they're just involved in taking samples and then you now execute the research procedures that have been established or designed by research foreigners. So how do you think about it?

A: I think that's true for trials but it is not because we don't have they.... because they're often just passive because of the hierarchy structure in Vietnam so the director is always too busy and the ones that can do it they say I have to wait for the director, I don't, there you go, so it's not in the Vietnamese culture or doctors not directly.... director can take initiative to go

and then they're very passive and because we're the foreigners it's easier for us to push and get things approved. But if they've no solutions because we are always asking for ideas and projects, we're still waiting. So they don't come, we come let's see. And when there's an outbreak and if they want a study then they we come to us and okay if you put it like this and come back with a proposal and sometimes it's difficult to finish or what to do" (Principal Investigator 5, Expatriate).

This hierarchical structure may cause unnecessary delay in planning research in an outbreak setting when everything needs to be reviewed and agreed by the leaders of local research sites. This structure can place not only local researchers but also foreign research partners in a passive state whereby any research must wait for decisions of local leaders.

3.2.3 Benefit sharing:

As is clear from the account above of the relationships of involved parties and rationales for international collaborations in research, there are mutual benefits that involved parties receive through their collaborations. However, benefits from taking part in the research in general and, how they should be shared are perceived differently. In this section, I will present concerns and challenges caused by different perceptions of and demands on benefits that are expected by involved stakeholders.

a. Benefits from research participation for research participants and research communities:

My interviews suggested that there were expectations of direct individual benefits such as access to better healthcare, financial supports for hospital fee, drugs, and that these were the primary motivation of almost all participants interviewed. Commenting on this wish for direct benefits, interviewed researchers expressed a clear sense of local people expecting individual benefits from their research participation and in the interview below this seemed even more important in REEs:

“A: Yes I know that’s the thing, they were very pushing about benefits and we would say, we kept on wanting to put in the thing that there’s no individual benefits, that it’s only of benefit to the understanding and to the, you know to the control of Dengue in the community but it’s not an individual benefit.

Interviewer: But do you think that in the outbreak there’s more chance for you to recruit more patients?

A: Yes, well it depends what your study involves but there is likely to be more individual benefit yeah. I mean for us for instance we provided oseltamivir and masks and things so yeah there’s clearly a benefit other than the reimbursement” (Principal Investigator 3, Expatriate).

Reimbursement and incentives were considered together with other direct benefits of treatment as general “gaining part” for research participants in Viet Nam:

“We just use money as a gaining part, for example the research offers them 100%, then 50% is the money, they’ll agree. That means money is important,

but the treatment is also important. For example, we say to them in general "This research...when you participate, they will monitor your health, treat you like normal, but they will monitor you very closely, your health condition, your disease, and part of that, your hospital fee can be reduced, for example, everytime when you go for follow-up, the fee can be reduced". We have to say in a way that suits them. The disease is monitored well in a long time, even by international experts, they can have investigational drug which is not available in the market. This drug is good, new. That's right?! It also suits them. Their hospital fee can be reduced...everytime going for follow-up...travel fee is quite comfortable, they are offered a one-day labour cost...quite comfortable. If it's really reasonable, they will agree. There's nothing here called inducement" (HTD: Study nurse 1).

In the interviews, these two concepts of "reimbursement" or so-called "compensation" and "incentives" are used interchangeable to mean any financial supports, compensation or other incentives in form of material gifts. The use of compensation or incentives is mentioned as a means to motivate research participants in participating in a research. While issues with the use of incentives in clinical research such as undue inducement or coercive inducement (Grant and Sugarman 2004) are not raised, issues with compensation are raised as a conflict in the perceptions between local researchers and foreign researchers based at research sites. Through all the interviews with local researchers, there appears a common perception about "compensation" that they share. It is used with the meaning as a financial payment to make up for any possible losses from research participation and any other expenses generated directly related to the research participation:

“B: Or another issue is, for example, I have just submitted a study sponsored by WHO. They asked me that why I paid patients 10USD/day which is high to the living standard in Vietnam.

Interviewer: Ah, I have heard about this.

B: I explained to them that patients would have to pay for transportation from Dak O to Phuoc Long Province, hospital fees, eating, lab tests, and IV fluids if necessary, especially they are always accompanied by their family such as wife and children. They don't come to hospital alone like we do in the city. So all the fees added are over 10USD in total, but we only require 10USD. People just rely on theories and living standard while the practice is totally different in each place. You can see that in order to take care one acute patient, there are about 3-4 relatives staying in the hospital with the patient. So if we require a prolonged hospitalization for the patient, who will be in charge of all the fees for relatives to remain in the hospital with the patient? Therefore, if the Principal Investigator doesn't have a careful investigation on the context, it will be difficult. In general, expenses are sensitive matter. If we can pay for study devices, machines, we also take expenses for human into consideration” (Local Principal Investigator 11).

As in the quote above extracted from the interview with a local Vietnamese investigator who was also an IRB member, the compensation which he suggested to the WHO to be paid for research participants would even include all possible costs incurred from the caring of research participants. Similarly, local researchers

suggested that the compensation for research participants should be equivalent to their costs and efforts made to research:

“Uhm. Just general. And for example, when they come for follow-up visit, we take their blood, we should offer a rate that deserves them. That's why sometimes there are studies that are not successful. Why? Money is important, isn't it?! Some studies are difficult but they're successful because they have much money. And there are studies that are simple but people quit the follow-up visit. Because they think their efforts that have been made to come to follow-up visit doesn't deserve the time lost. For example, if they live in Thu Duc, they have to come here by "xe ôm", they have to spend hundreds of thousand dong, for example, and then the research only reimbursed them 50 thousand dong; "50 thousand dong is not enough for me to to pay "xe ôm", then why should I spend time and effort to go to follow-up visit?! That's not to mention that I will lose one day labour wage". For a normal work, for example, 150 thousand dong is a normal rate for one-day labour wage, and now if they participate in our research, they're only paid 50-70 thousand dong, then why should they waste their labour. That's why our research can't gain high efficiency” (HTD: Study nurse 1).

Compensation is commonly understood by local researchers and local IRB members to make up for all the losses related to research participation and their efforts in participating. A reasonable rate of compensation may motivate people to participate in the research. Local researchers' understanding about “compensation” in my research is similar to general understanding as outlined by Grant and Sugarman in

differentiating differences between incentives and compensation (Grant and Sugarman 2004). What makes the compensation problematic in this setting, as indicated in those quotes above, is a nonequivalent rate of the compensation according to differences in caring practices and practical scale of related costs. And once the compensation is not given at reasonable rate, it would make people consider the possible losses incurred in their research participation in comparison with what they could do from not participating and thus not be willing or committed to be in the research. In other words, insufficient compensation may decrease the recruitment to clinical studies. In developing countries like Viet Nam whereby personal income is low, wage loss during the time participating in a research may be an important consideration for research participants and family members.

Discussing further about this problem in the setting of an influenza pandemic in which patients were isolated in the hospitals, hospitalization could, accordingly, place more financial burden on patients. The question in this case would be whether compensation should be paid by the study sponsor as the isolation of the patient would consequent to public health policy rather than research protocol:

“I don’t know, I guess it’s you know should we pay for a patient to stay in hospital when they’re under containment and they’re forced to stay there anyway? That’s a good question, I think that’s unique to Vietnam, there are very few countries with enforced containment laws. What else, I guess there’s additional financial burden on the hospitals in epidemics” (Study Sponsor 1, Expatriate).

Arguments about which standards to be subjected to for the payment of compensation continue to disagreements in the rate being applied:

“Well you know, you know very well what we do, we just give a ridiculously high transportation fee, we reimburse their transportation costs but we give them much more than they actually pay for it. (Principal Investigator 4, Expatriate).

There is however a concern that overpayment would place investigators in a state of “bordering on being a conflict” whereby it can lead to “coercion”:

“On being a conflict right so when you, when you go a little bit further and you say well we give the patients \$10 and it’s a very poor farmer from, I don’t know wherever, Dong Nai, and \$10 is a lot of money and he doesn’t really want to be in a study but if he does he then he can eat for four days, that’s coercion” (Principal Investigator 4, Expatriate).

The “coercion”⁶ that this foreign investigator based at local research site implies is when the overpayment of compensation can affect the decision of potential participants who initially have an aversion to participating in the research.

⁶ For the sake of discussing about the nature of issues raised, rather than trying to distinguish or criticizing the use of concepts like “undue inducement” or “coercion” by participants in the interviews, in this part, I would choose to describe the content of their uses to elucidate the problems raised.

Citing the same issue but labelling it “undue inducement” which is also resulted by the overpayment of compensation in comparison with local living standard, another expatriate investigator, through this issue, has shared his disagreement with the view of local Vietnamese investigators in how to pay the compensation:

“A: This is a, so reimbursement just needs to be judged against inducement so if you’re offering someone a million dong to participate in our research and they earn 1 million dong per month the outside world would see that as inducement you know, it’s out of proportion to other existing studies, you know you’re providing an undue inducement to participate in the research. In Vietnam there’s a view amongst Vietnamese, senior Vietnamese doctors that if you take 50mls of blood from a patient you should pay them more. The risk is exactly the same but there is a view that you should pay them more

Interviewer: Yes so how can you explain about the views, the view like that?

A: I don’t understand it. There’s very smart senior doctors in the hospital who think you should pay per ml of blood and that’s wrong.

...

A: I mean yeah of course the only way you should pay more yeah. But I think that there’s like, there’s a different point of view from the investigators’ point of view and then the study nurse or I mean the local investigator point of view yeah just want to make clear why you think that we should pay more and release the burdens?” (Principal Investigator 8, Expatriate).

In the quote above, the foreign investigator also gave an example of a suggestion from local study doctors that research participants should be paid more for the extra amount

of blood taken for research, and this view to him is wrong on the basis that the risk involved in taking that extra amount blood and other costs for research participation are the same. What appears to be the conflict in the viewpoints of foreign researchers and local researchers is a set of criteria to be counted on for the compensation. While in the view of local researchers, payment for research participants should be included any related practical costs in the caring of research participants and payment for what research participants give to the research, e.g. blood, this view is not shared by expatriates based at local research sites. Over-compensating or providing direct benefits in general could be even seen as problematic when it might affect the decision of research participants and to put foreign researchers in a conflict with their research practice regulated by international IRBs and other international guidelines:

“No doubt, I know for sure. Another thing about it, the benefit for patients which sometimes leads to small conflicts of interest is that on the one hand often we need to get the Vietnamese institution on board say you need to give the patient something, especially with children you need to give them a present or something but Oxford Ethics says we cannot coerce patients into a study, you see the conflict?” (Principal Investigator 4, Expatriate).

b. Benefits from research participation for researchers: differences in perceived benefits

At individual level, besides the overloaded work in patient care and treatment and high risks of infection in contacting with infected patients in their routine medical task, and while doing research generally is not bringing much income for medical staff based at the hospitals, working on research projects on REEs with diminished

academic benefits is stated by the study sponsor based at local research sites not to be of interest of Vietnamese medical staff:

“But then I think what we’re lacking is an education in terms of the research and especially in terms of epidemic research and in establishing good epidemic research and I don’t think that that education gets filtered down to the people who really, really do the work. You know there’s a lot of very intelligent doctors but they didn’t get it, they may not necessarily want to do it and if they leave for a private practice you know they can’t stay to wait for our study. And then when we do research in this context there’s a lot of different sites involved so the academic benefits are not always clear, you know is your name going to get on the paper, is it not, I mean 001 has 87 authors, great so you’re author 86, thanks you know. I think that those can be compromised in epidemic situations because and by definition it’s an outbreak right, there’s lots of people, there’s lots of communities, lots of hospital going to be involved and the academic benefit is diminished so the research staff don’t necessarily gain any benefit from research. Okay we pay a little bit of money, that’s not a benefit, that’s just for their time and the resources that we use but staff we train them, whether or not they considered other benefit I don’t know, the scientific community does, the medical community does so that’s good but I don’t know if the staff are happy about it” (Study Sponsor 1, Expatriate).

So in the situation where many people from many sites are involved in research on REEs, academic credit in research publication is shared between the many participants, thus making these credits less clear.

Differences in the interest of doing research also bring about difficulties in establishing collaborations for there might be skepticism over motivations of collaborators. Sharing his experience about foreign research partners, an international expert said:

“Yes I mean again it’s interesting isn’t it, it’s very, there are lot of cultural differences and political differences and differences in the political set up between different countries. And yeah you know my experience so far of working with country A is that they don’t give up a lot of information or samples or data willingly, it’s quite a struggle to get, to work with them. And that maybe because they’re very, they’re very skeptical about the interest of outsiders and quite rightly because you know everyone is crawling all over them trying to ‘help them’. Again I sit back and I think are you really helping or are you really trying to get that New England Journal paper?” (Principal Investigator 2).

In sum, there are differences in the account of benefits expected from international research collaborations. In the interviews, these interests are expressed from both the micro level of individual researchers to macro level of institutions. Different perceived benefits and contributions affect the decision of researchers to join and their commitment to remain in the collaboration.

3.2.4 Tension between doing research and providing medical services

Another concern raised by foreign researchers in collaborative working is the possibility of imposing financial coercion on medical staff, which is not necessarily benefiting local medical staff at individual level. As shared by an expatriate investigator:

“I guess, I guess when working in a developing country, even though Vietnam is now middle income country but still Oxford and Wellcome Trust have more money than most Vietnamese hospitals, I think there’s always the thing you need to think about that you shouldn’t coerce patients but you also shouldn’t coerce doctors to do research. So that, I think that’s always an ethical consideration when working in a developing country” (Principal Investigator 4, Expatriate).

While research on REEs requires more resources and efforts to be made to provide a quick response, and these local medical staff are already overloaded with routine medical task, imposing a research agenda on them may call upon a consideration of whether or not to make the research happen in the tension between the good of doing research and the tense of resources in the local setting:

“Yeah I think there’s quality considerations when staff are dealing with an epidemic you know research of course requires a lot of attention, a lot of detail, we need to monitor stuff, we need to do it twice. In an epidemic situation you just can’t do that, there’s so many patients, there’s such a rush and there’s no pool of human resources to pull from to feed those situations or

meet those demands so people just end up working all the time and they're over worked and they're over tired and that's what happens in pandemics, there's a doctor's struggle to deliver basic health care and never mind the research. If we try to impose the research you know like it's questionable I guess, should we even be doing research in those situations because we don't have the resources for it?...I think a lot of research, not even epidemic research but a lot of research there's a PI who will decide or a director at the hospital decides it's going to get done. They don't do it, it's only research staff who have to do it, research staff don't necessarily want to do it. Ideally we pay them a little bit and it makes them happy enough to do it but probably if you took a survey of all of our collaborating sites at all, if you took a delegation log of every study in OUCRU and surveyed those people would you rather do research or not do research? I bet it would come back way in favour of not do research" (Study Sponsor 1, Expatriate).

Taking resources which are already constrained in the outbreaks of epidemics for research should be the case to be taken into account, confirmed by a representative of an international funder based in UK:

"And if you don't include it from the beginning then it's very difficult because it's then seen that you're taking people away from their main job of treating patients or digging them out or whatever, or whatever it might be, you're taking them away to do something that's seen as a bit of a luxury in terms of research" (Funder 1).

3.2.5 The disconnection between clinical research and public health activities

While there is a significant overlap in activities in epidemics, for example, collecting clinical samples, implementing diagnostic tests, and producing generalizable knowledge, public health activities and clinical research are often viewed as and implemented in two separate strands. This is raised as an issue when there is a lack of evidence to inform public health policy and medical practice, and poor quality of sample taken by the public health. Illustrating the issue of the lack of evidence to guide the medical practice in the event of REEs, a local study doctor has talked about the practice of treatment of HFMD as an example:

“We will also have to record its effectiveness and side effects. For example, the IV Globulin, it has been used from the past until now. The Ministry of Health actually just follows after. It actually is decided to use first by physicians. The Ministry of Health only works on paperwork, how they can really know how it works. So when physicians use this drug, people see it effective and they continue to use it. In addition, there are opinions from experts saying it is effective. As we don't have any evidence, we only have one option of relying on experts' advices. Just like in evidence based medicine, it has an assessment scale in which there are scales such as A, B, C, D and the last is expert opinion.

....

Because...No, but it's up to our tongue, how we talk and explain to them. For example, Intravenous Globulin, as a researcher, according to our knowledge, we say to them that it is still unsure if the drug is beneficial to patients or not beneficial in terms of finance. That's the matter. But no. The problem is when

the government fully pays for the drug, patients ask us that why we don't use it for them, and if not using like that, that's a violation in terms of medical ethics. (HTD: Study doctor 1).

There suggests a discount of the role of clinical research in the development of public health policy and medical practice. This lack of collaboration between the two sectors might lead to uninformed policy and medical practice, giving clinicians a dilemma between giving treatment and constraining necessary clinical research activities or even the charge of being unethical for withdrawing what is perceived as treatment benefits of patients.

Regarding clinical sampling, an expatriate investigator has raised an issue of wasting local resources if poor quality samples are taken and thrown away while if collaborating with researchers based at the site, sampling methods can be standardized and samples can be systematically collected and archived for any further purpose of studying more about the disease:

“So in Europe blood samples are kept, as a routine care you're not throwing everything away. And I think if something interesting is going on everybody here is about throwing away it's very difficult to convince the local partners like we don't have permission but just keep it for now until I have approval and then later we can test. But they just, it's very difficult to have people store samples, everything, so a lot of valuable things are thrown away where it's quite easy because we have freezers, we can buy them” (Principal Investigator 5, Expatriate).

Commenting on the fact that with the support of public health in funding and access to patients, clinical research could generate better result than the routine pathway applied in public health, an international expert based in Australia said:

“We had, I can comment on that experience. Our public health authorities collect data on notifiable infections and influenza A was a notifiable infection so there’s a legal requirement to collect information. But the quality and timeliness of information that was collected by the public health authorities was poor, it was little more than a count of the number of patients that were in intensive care, there was nothing collected in terms of risk factors, treatment, outcome, there was nothing that could be packaged together in a way that was useful in terms of providing information to clinicians or public health authorities in other countries that were yet to be affected by the pandemic. Our research occurred completely separately as a research project and so its approval was via ethics committees. But the quality of our data became known to the public health authorities in Australia towards the end of the pandemic and indeed they provided funding to assist us to collect the data and part of that was making our raw data available to their statistician and epidemiologist to analyse for their purpose and they were able to make substantial use of our information and found it vastly superior to the information that they were being provided through their own pathways. (Principal Investigator 15).

3.2.6 “Each country has its own ethics”: too many standards to follow

In my interviews, international collaborations are mentioned with a wide spectrum including collaborations with local and international IRBs, with a various profiles of study sponsors and funders. Adhering to standards set up by involved research partners is inevitable in any international collaborative research project. This reportedly becomes challenging in the setting of REEs as dealing with these procedures may result in significant delay. I will discuss in detail issues raised particularly in the relationship with IRBs in a separate chapter (chapter 4). In this current chapter, I will focus on challenges faced by local and international researchers in the relationship to working in collaborative groups.

Drawing on experiences working with different research partners regulated by their own set of rules driven by their perceptions of benefits, cultural and political setting, an expatriate researcher has stated an overview of differences among the research partners:

“Apart from that international collaboration, each country has its own ethics, America is very special in that sense they have much, much more rules than anyone else. Other countries that it would be tricky to do research which with would be the Myanmar or North Korea because they have an entirely different view of anything. So considerations of how countries that you work in are governed, how people work there” (Principal Investigator 4, Expatriate).

In the quote above, “ethics” is used to imply general rules governing research and research setting rather than the pure generally understood meaning of “ethics”, that is

about what is to be wrong or right. Depending on which party is involved, there are different requirements, as explained by a study sponsor based in Viet Nam:

“Now that’s just one of our funders, we have other funders who fund us directly, maybe have their own requirements for the regulations that we have to follow. Like some of our, Roche for example is an IND study so we follow all the US rules on definitely ethics, all that stuff. And the SEAICRN is funded by the NIH, we had to follow all the US rules, they don’t, and then whatever local requirements there are” (Study Sponsor 1, Expatriate).

With respect to funding and funding governance, there are many rules for funders, study sponsors and researchers in terms of operation and accountability. Research in REEs requires flexibility due to many associated uncertainties:

“So for hand, foot and mouth disease the decision went like this is a problem, we need to do something, find funding and let’s do it. I guess the biggest constraint in respect to sponsors and funding academic research is just availability of funds and the governance of those funds. And most institutions have all these rules and regulations and checks and balances that you have to follow. For example the NIH when we were doing influenza research with the NIH there was a contract and you can’t spend any money on a contract that’s not approved six months in advance. Or even you know you want to fly somewhere, your travel, international travel has to be approved six weeks in advance. So I remember Mr.X at some point in time, three years ago just said to them this doesn’t work, you can’t do flu research like this because you

don't know six months in advance and by the time you do and get it approved it's gone. So that was a big restraint on our ability, our flexibility to do anything..." (Study Sponsor 1, Expatriate).

Commenting on international collaboration in doing research with foreign partners, particularly with OUCRU and the Wellcome Trust, a local IRB member has stated the having to comply with many standards may restrain research initiatives in emergency epidemics:

"Honestly, there are not many issues as our research is often collaborated with Wellcome. You know Wellcome, they have to follow international standards, and their protocols have to be approved by local IRBs and international IRBs, many IRBs and the IRB in the Ministry of Health so basically, that's our advantage because it follows standards. However, as they have to comply with many standards, they become slow. Too careful makes us slow. And if being slow, we can't well respond to the urgent nature of the epidemic. That's the problem" (HTD: IRB Member 2).

3.2.7 External pressure on collaboration

External pressures can also affect the success of research collaborations. At the macro level between international research organizations and governments, competing research agendas may risk international collaborative research projects at institutional level. Said an expatriate investigator:

“A: But at the same time, you know as we’ve seen with hand, foot and mouth there will be perhaps a research agenda being driven from here and then from this hospital and in parallel, almost in duplication, there will be another research agenda driven from above from the Ministry of Health that’s flying down to Pasteur who are asking perhaps you need preventative medicine to go and do a community based hand, foot and mouth that almost replicates the plans coming from here. So duplication of effort is a risk when you’ve got a high capacity site like this with a hospital for a disease that’s all over, you know all over Southern Vietnam. With H5 it was you know mainly, only this hospital, so there was no real sort of duplication. So how you, how you harmonise research efforts for community based work for something like hand, foot and mouth is difficult. And maybe it doesn’t have to be harmonised, maybe you know good research often involves competing studies and that actually having two or three studies done in the same setting with similar results or some differences here and differences there is actually better science, you know you actually learn more.

Interviewer: But what kind of risk in that kind of duplications, can you tell me more specifically about the risk of carrying out many research similar to...?

[interrupted]

A: Yes some of the risks are obviously that Ministry of Health found that we are doing a very similar study, they will just say stop it” (Principal Investigator 8, Expatriate).

Harmonizing research efforts is also a challenge in such a duplication of research efforts on the disease in community- wide studies. However, competing studies are supposed to bring better science by generating a better body of evidence.

Cultural and political differences also put pressure on research collaboration between countries, an international investigator in UK has said:

“But even then you know within a region there can be such animosity and political differences between two neighbouring countries, you know India and Pakistan for example can I really see them working collaboratively on a new virus together, possibly not. You know they’d both want to have excellent labs, they wouldn’t want to, they’d argue over who, if they were to have a regional lab who should host it, India or Pakistan, it would be a nightmare to try and sort out” (Principal Investigator 2).

As indicated, animosity and political differences among countries could cause challenges in reaching an agreement among them on a shared scheme of research collaboration. Again, competition at a macro national level might turn out as an obstacle in setting up research initiatives. While differences in interests and boundaries are yet to be negotiated and eliminated, communications among possible partners would not be encouraged and research collaboration is unlikely:

“...Then again I haven’t shared any samples yet but we are part of a new consortia, through ISARIC mainly but also through the Repare [can’t hear the name of the study] study where it’s all very positive, it’s all very altruistic, it’s all for the good of global health but we never really discuss in great detail

about sample sharing. So you know if there's a global outbreak, a pandemic, and there are some samples in Holland that I'm interested in, do I get access to those or not and likewise do they get access to my samples? And there are people who are just as competent at doing a certain type of study analysis that I would be, or that probably even better than I am so then it's well who gets to do this work and then you've also got issues about the compatibility of the results because we use different machines, you know if you split the work between two countries maybe we're using different machines, different assays, how do we compare those results... It's all about communication and I try and encourage everybody in the consortium to talk about these things. It comes across as being quite negative when in the early days I think, because everyone is hugging each other and you know saying isn't this wonderful what we're doing. It's like well yeah but we all need publications, we're all career scientists how had we decide authorship, how do we decide who gets to do the work..." (Principal Investigator 2).

As shown from the extract research on REEs needs multiple collaborations to produce an effective response. And "the good of global health" is principled in these collaborations.

Disputes over issues around sample sharing give a strong base for this principle. For example the Indonesian government's refusal to share its H5N1 virus samples with WHO (Sedyaningsih et al. 2008) or Dutch scientists patenting a novel coronavirus (Bennett 2013). In cases where the government or researchers initiate research collaborations which appear to impede progress in public health, in the interests of

protecting global health these collaborations are assumed to be over-ridden. A recent speech of WHO Director-General, Dr. Margaret Chan illustrates this:

“Please, I’m very strong on this,” she said. “Making deals between scientists because they want to take out IP and be the first to publish in scientific journals, we cannot allow that. No intellectual property should stand in the way of you protecting your people. Do you agree or not?” (Bennett 2013)

3.3 Suggested solutions by stakeholders:

In the previous section I have described the practical ethical issues arising in research collaborations on REEs identified by my interviewees. In this section I outline the suggestions regarding solutions they made. .

3.3.1 Communication

The first solution proposed by my interviewees was related to communication. This includes the following activities.

3.3.1.1 Information dissemination

In addressing the general issue of reporting to the public, an international expert based in Australia suggested:

“So my view, I think it’s very difficult to place yourself in that situation because there would be very, an enormous number of very powerful forces that would need to be balanced and taken into account. My personal opinion in a hypothetical situation which is very different to how it would be in reality

is that in general knowledge has intrinsic value and that we as a society should never be afraid of new knowledge and that it should be reported with great honesty and integrity, even if the results cause distress or panic. What is important I think is that interpretation of those results is allowed to rest with people who are appropriately qualified to provide that interpretation and that the management of that interpretation shouldn't be placed in the hands of people who have a range of agendas that are not necessarily well aligned with the public health interest" (Principal Investigator 15).

Dissemination of scientific information, from his perspective, was defended by the intrinsic value of knowledge and the honest manner in which the public were informed.

3.3.1.2 To be listened and being transparent:

With regard to the concerns of unfairness in the evaluation of workload between study nurses and study doctors as outlined above, representatives of study nurses based in research sites in both the North and South of Viet Nam proposed that they should be informed and involved in related discussions with international partners, upon which their voice is raised and acknowledged:

"...she should have informed the ward of that and asked if the ward agree or not" (HTD: Study nurse 1).

And while this issue is also pervasive in other study staff groups, for example, pharmacist, study doctors, principal investigators, a local principal investigator

explicitly raised issues related to fairness and transparency, and how they might affect the participation of medical staff in research and collaboration:

“Ah, if they feel unfair, they would not participate in the research. It is right. Say if you were in that situation, although you wouldn’t care about money, you recognized “Oh, why I also directly do the work, and that man only needs to sign, I agree that he would deserve a share because he is the person who would be responsible, but for example, if there is 2 million, he gets 300-500, and I should thus get 300 or so. If he can get 500 but I only get 50, I can’t agree with that.

...

In general, the majority, I think they think about the benefits for patients. They also think about their benefits, for example, what they can gain, learn from the research. More specifically, when there is a research, whether or not they can have opportunities to learn something from it? That is the most important. Of course, money...many people would think, because....The problem is they know there is money paid, and if they can’t get it, they would be pressing on that. If right at the beginning, we get clear on the fact that: Ah, this is a collaborative research, and we only support” (Local Principal Investigator 13).

Another suggestion was to try to reach a balance between benefits and extra research work. Research should not be seen as a burden to local study staff who are already overloaded by routine medical tasks. Stated by a local investigator, the balance would help to encourage them to join into the research:

“R8: Uhm...They can't fulfill all the work. So we have to find out a way to balance.

When they see that doing research can bring them benefits in terms of knowledge, material, they will be eager for it. If doing research is like a burden to them, they'll never like doing it. So if we can't resolve this problem, it would be very difficult for us.

Interviewer: B: So in your opinion, salary payment for doing research is still inappropriate?

R8: Yes. For example, an average salary of a doctor is about 200-300USD for their main job in the hospital. Now a study sponsor says that you can't ask for 1,000USD for doing research while you're only paid 200-300USD for your main job, and that we only pay you equivalent to the average rate which is much less than actual income of some doctors. You see, if they have to do more than their routine work in the hospital when taking part in research, but they are only paid such amount of money equivalent to the average rate, they prefer to work in their own medical practices so that they can earn much more money than that, and do not care about doing research. This is a very sensitive issue, and Vietnamese doctors don't want to say it out because this is our Vietnamese culture. Asian people don't like to talk openly about money. But if we don't say it out to the study sponsor, they don't understand, and this causes conflict. One thinks if they are only paid just a small amount of money like that, they don't need to do it. The other side thinks why these doctors require much more than the current rate they're paid” (Local Principal Investigator 11).

Understanding context is necessary to address these issues, according to this local investigator.

In addition an expatriate investigator has suggested “opening lines of communication” in which involved parties can inform each other and clarify issues of joint endeavours:

“But we could have done a better job of at least finding, at least perhaps opening lines of communication better. So I think one of those things, you know I’ve seen other projects now, not necessarily in emerging outbreaks but actually having someone dedicated to communications and whose role it is actually is to make sure every step of the way there’s clear communication between both side and sometimes the risk is you know in this building and now the ward in the hospitals just over there that you get, you know you just get very focused and very narrow on the science and push along and you forget to bring along the partner” (Principal Investigator 8).

3.3.1.3 Sensitisation and consensus building

In responding to emergency epidemics, in the view of an international funder, there is a need to make local countries recognize the situation in terms of what needs to be done and the responsibilities of involved parties so that consensus between partners can be achieved:

“So there needs to be this sort of consensus and agreement and I think to get there there probably does need to be some more sensitisation and consensus building that goes on to say this is a valuable thing to do because at the

moment I think if you only think about it at the time the emergency happens then it's very hard to do" (Funder 1).

Sensitization here is described to be done at a comprehensive level. It includes informing people in communities ahead of time about the progress of epidemics and different research methods to better understand their possible contribution to research:

"So you know if we decide, if we find out in China that this influenza has become person to person spread and it looks like it is going to spread all over the place okay there is still time for hospitals in Vietnam to sensitise the communities in various different ways, visits, posters, radio, television, that these things are happening, so they know that something will be happening when they come to hospital" (Funder 1).

As indicated in the quote above, compared to unpredictable events of natural disasters, in REEs there is a short window of opportunity to inform people of possibilities of a wide spread and planned research. At the upper level of sensitization, it is suggested to set up some resources in advance for research initiatives in REEs. While research might not be counted as a part of epidemic response, there should be plans to make resources available for research. These plans would be discussed, and agreements of involved parties reached in advance:

"Yes, I mean imagine if you're working in a hospital and it becomes overwhelmed by flu cases, if there's two or three or four or five people who are sitting there, not helping, waiting for patients to come in who they can

randomise into their study that's not going to be very popular if they're doing that and they're not participating in the response more generally. So I think there has to be some sort agreement about how you're actually going to do the research at the time of that emergency. You know is everybody going to take part in it, are they going to be specific people whose responsibility it is to do it. If there's specific people does the rest of the hospital staff accept that these are people that are doing research and not part of the response. That needs to be discussed and agreed in advance so they're recognized" (Funder 1).

3.3.1.4 Engaging stakeholders:

In parallel with the idea of sensitization and consensus building described above, which stresses the importance of prior dissemination of information, it was suggested that a wider range of stakeholders should be included. This aims to connect people involved in research through discussions especially around the ethics of research practice. An expatriate investigator has stated:

“A: I think sort of the stakeholder engagement is probably one that would be the first priority and about making everyone feel part of the team and part of the ethics and ongoing communications between the stakeholders before, during and after.

Interviewer: So who do you think that should be the stakeholders?

A: I think you know it depends what you want to do but if, H5N1 came along tomorrow you know the hospital, Department of Health of HCMC, even the Ministry of Health. You may not be asking for permission, you may be advising them, letting them know. I think often we're actually not bad at that

part prior to getting the study going. I think when the study is going then after the study is finished we tend not to do so much, we don't give you know a quarterly update to the hospital of the overall success of the study or failure. Some studies are doing it better now, O5TB for example does a good job of updating all the investigators. Yeah so I think the soft, no not so much the hard, the scientific part or the clinical part but the soft skills around" (Principal Investigator 8).

As indicated in the extract above, stakeholders might include all researchers, local hospitals, and in the case of an emergency epidemic, national public health authorities. Involving the public health authorities in any research initiatives on REEs by proactively disseminating information about the situation including a research plan as a part of an overall response to the epidemic would help these national public health authorities better understand the research planning and thus be a partner in the planning and implementation of research.

This view is supported by opinions of other international experts based in UK and Australia when they continue to stress on the importance role of engaging national public health authorities, researchers and communities where research are being taken place so that responsibilities can be defined and everybody involved can recognize their roles in the overall response:

"Yes, I mean imagine if you're working in a hospital and it becomes overwhelmed by flu cases, if there's two or three or four or five people who are sitting there, not helping, waiting for patients to come in who they can randomise into their study that's not going to be very popular if they're doing

that and they're not participating in the response more generally. So I think there has to be some sort agreement about how you're actually going to do the research at the time of that emergency. You know is everybody going to take part in it, are they going to be specific people whose responsibility it is to do it. If there's specific people does the rest of the hospital staff accept that these are people that are doing research and not part of the response. That needs to be discussed and agreed in advance so they're recognized" (Funder 1).

And while the ethics of the research practice is seen as important in the research planning, the involvement of local and international IRBs, ethicists, anthropologists who can help researchers to gain more insights of local culture and practice, is deemed valuable:

"And again we've met with verbally a very positive response to the point where the national lead actually would consider it as good practice to try and have these protocols prepared and approved in advance of an outbreak and was willing to consider how the flexibility around them being generic could be considered by the ethicists" (Principal Investigator 7).

"So the clinical research certainly has to be ready before outbreaks and it has to be tested in between the outbreaks. So that's what ISARAC, led by [A] and WHO are now working really on to have the basic results protocol ready before the outbreak and it has to be used inter pandemically and new epidemic situations. And then we like to make sure that we address all the major ethical issues, so what we did was to bring to WHO ethics committee, to make sure

the ethics and human rights issue have been already addressed and then already solved before bringing them to a country. And then I think if those important issues are really sorted then we believe that it can expedite the local clearance from local IRBs” (Principal Investigator 14).

The involvement of ethics committees as expressed above would help to identify and address major ethical issues in research on REE in advance.

Community participation is also seen as an important component of planning for epidemic research to give a local view on the appropriateness of research projects:

“Going forward in a prospective way I think it’s really important that the work that ISARIC is leading in terms of the proposals for pre-approval of research projects at different tiers of complexity and risk, should be, should stimulate a broad and wide community discussion so that if and when a pandemic turns up the researchers and the public health authorities and doctors who want to benefit from the research have got the opportunity to say that anyone who might disagree with what’s going on that we have actually engaged the community before a pandemic occurred and the broad consensus in the community was that what was being planned and approved was appropriate and as such the opportunity to influence it was when it was under discussion and not when a pandemic turns up. So I think that, I think the attitude to community engagement and building community support are different when the research is being planned prospectively for future pandemics” (Principal Investigator 15).

While the “community” is not clearly defined in this case in terms of who should be included, their role as advisory and advocator is explicitly pointed out in this case. Elsewhere in normal research settings, community members might serve as advising researchers on community issues and concerns and as decision makers in all project activities (Koné et al. 2000), it is especial in the setting of REEs that the broad consensus of community on research planning would serve as a strong rationales over concerns related to the deployment of pre-planned and approved activities at the time when the epidemics break out.

Finally, to resolve the inflexibility of funding for academic research during the outbreaks of epidemics, one of the issues outlined in the preceding section on concerns and challenges above, it is recognized that there should be links to set up with a variety of funders with their disease priorities prior to the outbreaks. This would help to secure available funds and commitments for any research initiatives. In fact, this idea has been actualized through the establishment of ISARIC at the time of this present study was implemented. Specifically, by the existence of ISARIC in which networks and individuals worldwide involved in research related to the outbreaks of diseases are put together in the commitment to facilitate a rapid response to emerging diseases, relationships with funders are to be built through familiarity and trust:

“So they want to break down those funding barriers by creating these relationships with the funders and creating an entity that the funders are familiar with and trust” (Study sponsor 1, Expatriate).

“But I think they’re, frustrating as it is you have to work within that well established ethical framework and you just have to accept it and try and

anticipate it ahead of time. So how do you do that, I think from using, so ideally from experience, so one of the reasons we have joined ISARIC is because we want to contribute like the Vietnamese, like OUCRU does, their wisdom and experience, what worked, what didn't work, what was done well, what could have been done better, so that they're not reinventing the wheel the next time they set up an outbreak study. So one of the things that you have to look at is working with people who regulate ethics and funding and all these issues beforehand appreciate that those things will have to stay in place, that there will always be red tape, but how can we make the process more efficient when the outbreak does actually happen. And we're still working on that and we haven't got it quite right yet but to me that would be one of the, if ISARAC can help with that it would be one of the biggest successes" (Principal Investigator 2).

In brief, suggestions and opinions expressed in my interviews pointed out a group of stakeholders who are seen especially important to be included in research on REEs. They include local and international researchers and research organizations, local and international IRBs, national public health authorities, funders, and communities where the research is going to take place. All these relationships should be established prior to the outbreaks of emerging infectious diseases in order to generate a quick response within the short window of the epidemics. The aim is to create channels of communication between researchers and other partners whereby all can improve understanding of the situation, raise their awareness of responsibilities, advocate research activities and maintain the relationships. However, a clear account of how

this engagement should be conducted with each of these different stakeholders and to what extent it has been and should be is not clearly defined.

3.3.2 Open collaboration

In addition to improved communication, my interviewees also stressed the importance of openness in collaborations. While collaborations are recognized as crucial to successful research in the context of an epidemic, effective collaborations also have characteristics of an “open collaboration”:

“I think that should be mandatory, I think there really needs to be an agreement to data sharing, sample sharing, open collaboration at every level of the study. Yeah I don’t think, you can’t have people that have a separate interest from the, from the common interest simply because the risk is that it’s going to jeopardise the more important question” (Principal Investigator 6).

In this “open collaboration”, respondents from expatriate and international expert groups share their ideas about global collaborations in which supplementary role between partners, rather seeing each other as competitors, and the shared common interest that is to contribute to the knowledge of the disease for the public good through sharing data and samples:

“....and we never saw them as competitive, we just saw them as complementary and trying to contribute to expanding knowledge of this important new disease as quickly as possible” (Principal Investigator 5, Expatriate).

“But number 1 I think we need to develop the potential for global collaborations, they need to be collegial, they need to be open, open access to data collection, commitment to open data sharing and that sort of thing” (Principal Investigator 6).

3.3.3 Oversight mechanism:

In addition to effective communication and open collaboration, interviewees argued that a third element of successful collaboration was effective oversight. On top of all research related activities planned and implemented, representative of an international research funder has recommended a mechanism for independent ethical oversight to be put in place. This can occur in the form of an independent community representative, overseeing the research practices undertaken and maintaining fairness:

“R: Yes so it’s actually a Swedish word [“ombudsman”] that’s been imported to English and it’s like, it’s an independent person and anybody who’s got a complaint can go to that person and he’ll make sure that it’s fair whatever it might be.

Interviewer: Yes, I think that’s the ideal world.

R: It’s the ideal world but I think you can implement it a bit in these epidemic situations you know maybe you identify a person from the community who is well recognised and well respected and you actually fund or support that person to come to the hospital and to be there and be around to see that the practices that are going on are fair, not exploitative, if anybody wants to complain about the study they can go to that person and they’re independent

of the hospital, they're independent of the doctors, they're independent of that study. But you have some sort of oversight of practice" (Funder 1).

3.3.4 Integration with other health sectors in the overall response to epidemics

Similar to the idea of engaging national public health authorities in the research planning and conduct, there are solutions proposed by foreign investigators based at local research sites and other international experts in other countries with an emphasis on making research activities an integral part of public health response to the outbreaks of epidemics. The first solution is to combine research work and public health activities, and utilize existing public health resources, for example, human resources, clinical samples. Collaboratively working with the public health, duplication of work can be avoided in a way that research and public health activities can be planned and conducted at the same time to generate a quick response while relieving the workload of local medical staff. A good relationship between research and public health should, as a result, be built so that the two parties can understand the work of each other and thus to provide supports to each other. Illustrating the importance of collaboration between the public health and research, an investigator based in UK has said:

"Yeah that's a very good point and we've witnessed the necessity for that integration between research and public health recently in England in response to the novel coronavirus cluster. I think again ideally in advance of anything happening research has to build up a relationship with public health and vice versa. Now in some countries the research fraternity or group will be strong, in others it will not be, then another country's public health will be interested

in research and other countries less so. And so building up these relationships takes time and ideally it should be done outside of an outbreak. And then during an outbreak I think one has to make sure that neither one compromises each other's good work. But if at the end of the day if you had to prioritise one over the other I think the public health operational response will always take priority because they will be collecting samples too to monitor for example viral load, to investigate transmission between cases and so on. But I think if you've got good relations with public health then you should be able to even do a study with them or at least a study that they're aware of and they could facilitate you having access to the hospitals. I think it is important that each other knows what each other is doing because otherwise you'll cause duplication of work, which is a waste of time, you'll cause extra work for the clinicians when they don't have the time, you could have an indirect impact on patient care, so there's many good reasons why those two groups in a country have to actually work very closely together. Yeah" (Principal Investigator 7).

In very much the same vein, the second solution is to merge public health response and clinical research with a stress on mutual understanding. There is a need for collaboration between the two to collect evidence and assume an ethical responsibility to determine what best to do in the situation. Regarding this matter, an international expert based in Canada has shared the same view with an expatriate investigator based in Viet Nam:

"Interviewer: Yes, so how do you think the responsibility to do research on the part of the public health, I mean because most of the time public health

officials only care about you know to prevent and to treat the disease and try to apply the standard therapy for everybody and get the samples,

A: Right, right, no I think it's really critical, that's a critical issue. I think public health agencies need to be more involved in clinical research and the clinic then, equally clinical researchers and research ethics boards need to understand the public health perspective on this better so that there needs to be more of a merger between the two. Because yes you want to give standard therapy, but if you don't know what standard therapy is or whether standard therapy is helping your patients I think it is, it's wrong to say you should do this when you don't know with a high degree of certainty that that's actually the better, the better choice. And if that is the case then I think you've got ethical responsibility to determine what is going to be the best thing to do" (Principal Investigator 6).

3.3.5 Good preparation

A solution that was commonly shared by almost all groups was to have a plan for essential parts of research in advance. On a general level of international collaborative research initiatives during the outbreaks of REEs, this included having research networks and "collaborations to be established and tested" with a clear delegation of work, existing infrastructure, human resources and funding allocation set aside. An investigator based in China has explained:

"Yes so for getting involved in the international study it depends on the disease and also the complexity of the protocol. And also you know as I mentioned before whether there's funding to look at some specimens, and do

you have a central lab or a local lab, so all these need to be sorted out well in advance. Do we need to send the specimen to a central lab elsewhere, we don't know. For example I am also involved with a lot of COPD drug trials, and some of the central lab are actually in Singapore” (Principal Investigator 10).

Through the research networks and collaborations, it was suggested to build up an open access repository of protocols. These protocols should be reviewed and approved in principle prior to the outbreaks. While this model of rapid response has been applied in the public health in the event of SARS and shown its effectiveness in the prevention of the spread, a public health policy maker, in the interview, said that it would be important that research would take place in the same way and the establishment of ISARIC network could lead this:

“A: Well it's the same as with all emergency epidemics, there's money that's made available immediately during the time, but then that money disappears when the outbreak is over which is what happened with SARS. So there was some money available at the time of the outbreak and then it disappeared. So the answer to the issue is have the protocols ready before the outbreak begins, have funding sources in mind and have the ethical and other clearances you need well in advance. This is for any disease, that's why ISARIC is so important because they've followed that model and we set up during SARS of making sure that people are working together but they also have some protocols on the shelf.

Interviewer: Yes, so during that response, I mean for example like SARs do you have any ethical considerations?

A: Well during the response to SARs it was very important to know what clinical people were doing and whether or not what they were doing was successful. And so we set up a network around the world of clinicians who were dealing with this disease and they periodically reported to WHO and to others what they were doing so that we could see what was working and what wasn't working. What's needed though is a more standard way of approaching that so that the minute an outbreak begins there's a protocol which you can put in place so that everybody is collecting the same information in a standardised way" (Policy maker).

As indicated in the extract above, it is important that people are put together and jointly work in all research initiatives in a standard way of approach. And with protocols approved ahead of time, significant time can be saved when an epidemic occurs. This solution was also put forward in a commentary on research response in pandemic influenza research in 2009 by a group of international experts working in the field (Tran et al. 2009). A Vietnamese IRB member recommended that there should be a strategy to be developed towards this direction. When REEs share similar elements and characteristics, having preparedness plans or certain procedures are feasible and should be implemented in advance:

“That is the reason why I think if you have a strategy. For example, there are many situations until when they've already occurred, we just come up an idea to do research. But if at the moment, we have such a plan, for example, in the

future, there would be epidemics A, B, C or D predictably breaking out, we should prepare for them. If we have a plan to do research, we should prepare it immediately to avoid the situation when we only start to think about doing research when it's already broken out broadly in many places. It would be very rushing at the time to start writing a protocol. So I think there must be a strategy for this. All emergency epidemics share the same elements, similar characteristics. If we plan to do a research into such epidemics, we can prepare for the planning, or certain procedures in advance so that when it happens, we can set off immediately" (NHTD: IRB member 2).

However, the idea of having pre-approved protocols is still being argued by local IRBs and local researchers with more concerns for clinical trials of new investigational interventions. I will present this in further details in the chapter on IRB review. This reveals that although being acknowledged as a promising way to go forward, there are still uncertainties and uncomfortableness shared by local researchers and IRB members about this approach compared with a typical approach that has been long applied in research practice. There is not such record from the international expert group.

From the experience of British and other regional ethics reviews shared by a British investigator, it is interesting to note that some IRBs have shown positive attitude towards pre-approval of protocols and that building up good relationship with ethical committees, and engaging with them is important:

"Yeah and I've been pleasantly surprised by the reaction that I've received, at least by national ethics in England and regional ethics that they've responded

at least verbally very positively to the concept of a pre-approval protocol system which would allow us to be able to respond more quickly with clinical research during an outbreak. And if you'd asked me a year ago who do you think will be the biggest barrier to pre approvals I probably would have said ethical review committees. Now a year on I'm not actually so convinced that it will be ethics, I think maybe in some countries it still will be, but in another I think it may well be issues around for example logistical issues regarding delivery and operational aspects of a protocol, particularly if you have multiple hospitals being involved. You know how do you actually logistically make that protocol happen in multiple hospitals in a short period of time during the start of an outbreak. And all of that takes a lot of planning in advance and ideally already an infrastructure of a network of interested clinicians. And so yeah and so I've been, that's changed my mind, I think it would be interesting to see, to ask us again in ISARIC in a year's time you know looking back where have you found there to be the barriers, has it been ethics, if so what percentage of countries and if it's not ethics what has it been and what did you try and do to make sure it wasn't ethics. So one of the things that we're trying to do is actually build up good relationships with our ethical committees in advance of an outbreak and discuss protocols with them and engage with them and start off with an observational type study and then gradually build up to an interventional study and just build on previous experience and relationships. But actually I think for many countries there will be other barriers that will also have to address regulatory, administrative, operational, research and development" (Principal Investigator 7).

3.4 Discussion:

My analysis of the data indicates that the ethical issues arising in research in rapidly emerging epidemics can best be understood as arising at three ‘levels’: the micro level of relationships between researchers and patients; the meso level of research ethics review; and the macro level of collaborations at the national and international level. In this chapter I have presented data relating to this third, macro level. I have outlined the ethical issues arising in the context of research collaboration and have discussed some of the requirements for effective collaboration identified by my interviewees. In what follows, I bring these findings together and highlight some of the values that have emerged as particularly important for interviewees when thinking about the ethics of research on rapidly emerging epidemics.

At the macro institutional level where international collaborations in research and in other medical and public health related areas are established, there are several values that are considered important in determining the establishment and maintenance of all relationships involved. In the events of REEs, the duty to protect the public and the public good appear to be the key motivators for collaborative research. Well-established relationships and long-term collaborations involving values of mutual understanding, consensus, familiarity, trust, and openness are seen by interviewed stakeholders as crucial elements when deciding which partners to collaborate with and recognizing the need to preserve the collaborations.

3.4.1 The duty to protect affected public and the public good:

This principle is drawn upon from the account of local Vietnamese research partners including researchers and local IRBs and of international research partners and international experts working in related research networks about the importance of

doing research in collaboration. It is recorded as the primary motive for any research collaboration initiatives in the setting of REEs in which the protection of affected population and the general public is on top priority of the governments and international health organizations. Interviewees also shared experience about cases in which the duty to protect the national population and the duty to protect affected populations on a wider spectrum are weighed against each other. There are differences in the choice of collaborators and the nature of collaboration with different perceived benefits yielded from the collaboration, e.g. commercial interest versus benefits for the public.

This principle also serves as an ethical ground to override any collaboration which is considered to obstruct the progress in finding out treatment and prevention of REEs.

3.4.2 Mutual understanding and consensus:

Through discussions around how to facilitate a rapid response in the setting of REEs, it was propounded that there should be mutual understanding through which consensus could be reached by involved parties. These values are apparent through all relationships with stakeholders that respondents consider necessary to include in the collaboration. These include researchers, research participants/family members and community, IRBs, funders/sponsors and public health authorities. Consensus is furthermore seen as a strong base for the research to be conducted in case there might be conflicts regarding the risk or appropriateness of the research in a defined community by the weight it gains from the involvement of relevant stakeholders. Reaching consensus before implementing a research, as expressed by interviewees, would include opening up communications and discussions with relevant stakeholders on the research planning whereby responsibilities and roles are recognized, there are

opportunities for involved parties to raise their voices in the plan, and support is built up.

3.4.3 Familiarity and trust:

In this section, I focus on the relationship between local and international research partners. I will discuss about the concept of “trust” in the relationship between researchers and research participants/family members and community in the chapter on Consent as a continuum from the “trust” placed on medical staff to the “trust” on dual-role study staff, and the account of how the trust is established within the research setting with empirical data collected through their perspectives about research and research participation.

As described in the preceding sections, in the setting of international research collaboration, the value of familiarity appears as one of essential elements to consider in establishing the collaboration. Expressed by my interviewees, familiarity with a research organization has formed the sense of optimism and reliance on research partners’ capacity in doing some aspects of the work.

The concept of “trust” is mentioned in my interviews in two aspects. The first is related to the confidence that local research partners put on OUCRU as an international research organization drawing on their working experience. And the second aspect is the “faith” in the collaboration. The level of trust is varied in the collaboration depending on the experiences of involved parties have about each other. In the interviews, it demonstrates from one extreme in which there is no hesitation in actions that are expected to do to a state in which uncertainties exist due to the lack of experiences of each other.

By clearly laying out how the trust is perceived by respondents and the case in which the trust is at stake as above, it would help to shed light on factors which are often confused with trust, for example, familiarity through experiences gained about each other or confidence or optimism about some certain aspects that people can do. If trusting is generally required that we can, 1) be vulnerable to others (vulnerable to betrayal in particular); 2) think well of others, at least in certain domains; and 3) be optimistic that they are, or at least will be, competent in certain respects (Baier 1986), what serves as grounds for research collaboration does not necessarily fit this concept of “trust” built upon moral qualities of individual. Rather, the collaboration, especially in an emergency of REEs would be grounded in the reliability of the sources of information and practical experiences that a person or an organization has about the partners as an institution, e.g. long term collaboration, research networks, and the institutional context in which the collaboration takes place, e.g. research organization locating within local countries. And with legal mechanisms of agreements/contracts through which collaborations are established, there is not necessarily that vulnerability to betrayal. I will discuss more about this in the Discussion chapter to propound an argument that trust is a necessary factor in collaboration, but not all that research collaborators would count on to warrant the collaborations.

3.4.4 Openness:

During discussions about issues and solutions regarding establishing research collaborations in REEs, the concept of openness in collaboration is drawn from the need for information and resources to facilitate research activities in response to the epidemics. Openness is articulated in the way that research partners and other relevant stakeholders connect, support and learn from each other to generate an effective

response. Openness is premised on shared values and interest of involved partners. Being open in collaborations would bring more benefits by its outperformance in terms of connecting capacities of each partner together.

3.4.5 Transparency:

The value of transparency is deliberated through discussions about the issues of workload evaluation and benefit sharing as outline above. In the first instance, being transparent in work delegation, payment scheme and the implementation of research plans with all local study staff would help empower perceived disadvantaged groups, e.g. study nurses, low-paid study doctors, and elicit insights of local working culture and context. Being transparent in benefit sharing in the second instance is suggested to encourage research collaborations to be set up and maintained.

3.5 Conclusion

In this chapter, I have presented an overview of the international context of research collaborations in REEs, and examined issues arising in international collaborative research projects in this setting. The overview of the context of international collaboration and findings from the study shows that there is interconnectedness in the relationships of studied key stakeholders through their institutional collaboration. Research collaborations in the case of OUCRU of which both research units are based in Viet Nam and its research programme is an illustration of these institutional collaborations through their collaboration with local institutions and indirect collaboration with patients/family members and communities. Relationships can be divided in two levels: macro institutional level between institutions and communities under the management of administrative authority, and micro individual level

between individual patients/family members and study staff. I will present this micro individual collaboration level in Chapter 5 – Consent with concerns and challenges raised reflect clearly this relationship. Involved parties view each other's role as collaborators in this research relationship through their perceived roles of mutual support and beneficiaries.

Issues and challenges raised in international collaborative research projects on REEs happen in both macro and micro level of relationship. These problems are essentially grounded in 5 main causes:

- Difference in the perception of the role of each party based on their contribution to research,
- Difference in in the perception of categories of benefits and the expectation to gain these benefits,
- Local working organization and culture,
- Imbalance in the collaboration with other sectors such as public health and hospital-based medical staff,
- Out of alignment with the interest of national public health or global public health.

Discussions about the problems and solutions proposed by respondents are central to key values linked to mutual understanding and fairness, consensus, familiarity and trust, openness, transparency, the duty to protect affected public and the public good.

Chapter 4 Research ethics review/IRB review

My analysis of my interview data suggests that the ethical issues arising in research in the context of rapidly emerging epidemics can be understood as arising at three ‘levels’: research collaborations; research ethics review; and the researcher-participant relationship. In chapter 3, I presented data relating to the first of these levels. In this chapter, I will now go on to explore the meso collaborative level in the relationship between Institutional Review Boards (IRBs) or Research Ethics Committees (RECs)⁷ in general with each other, researchers, research institutions and patients/family members. Before going on to present the data, it is important to describe the system of research ethics review in Viet Nam.

4.1 Overview of IRB structure and operational mechanism in Viet Nam: from regulations to practice

Research ethics committees which are seen as a central tenet in governing clinical research and required by major research funders as a precondition for funding, are established in many institutions who engage in research involving human subjects. Institutional review board (IRB) is an English term commonly used in Viet Nam to refer to ethics committee whose function is to review and oversee research involving human subjects. As all Vietnamese relevant regulations and guidelines on IRB review use the term “biomedical research” to refer to all types of research involving human subjects, I shall hereinafter use this term to mean the same. Vietnamese IRBs are

⁷ In this thesis, the term IRB and REC are interchangeably.

divided into two main levels: Ministry of Health's and subordinate institutions'. All local research ethics committee and regulatory authorities in Vietnam work towards compliance with the International Conference on Harmonisation (ICH) guidance on Good Clinical Practice (ICH-GCP). Before 2012, the primary function of Vietnamese IRBs was to review both scientific and ethical aspects of submitted research projects. However, in February 2012, the Ministry of Health issued a new regulation for the organizing and operation of its IRB term 2012 – 2017 and accordingly renamed it as Research ethics assessment board (REAB). This change is aimed to increase the independence of the IRB separating it from the governmental administrative board with a new structure and operating method adaptable to ICH-GCP and practical situation. In the following section, I will present in more details about the two main parts of Vietnamese IRBs including 1) composition, procedures and function of the IRBs and 2) general ethical principles and particular ones applied in reviewing research projects.

4.1.1 Composition, procedures and function

a. Composition

The REAB of the Ministry of Health has a totally different organization compared to subordinate IRBs based in institutions. REAB includes one permanent office, one permanent subcommittee, three specialty subcommittees and a secretariat group. There is not a fixed number for the number of people of each session. However, the maximum number of people in each specialty subcommittee and secretariat group is nine. All members are required to be trained on Good Clinical Practice guidance issued by the Ministry of Health.

Local IRBs, following regulation issued by the Ministry of Health in January 2013, consist of at least five to eleven members. Although there are some minor differences in the criteria for the composition of members between REAB and local IRBs, both aim to ensure diversity in scientific and non-scientific backgrounds, professional specialties, sex, and include at least one member who represents research participants or is not affiliated with the research institutions (in the case of local IRBs). Besides institutional members, the IRBs can invite outside consultants if necessary to provide further insights on scientific and/or ethical aspects. This practice is in fact preferred by some IRBs since the IRB is supposed to gain more objective opinions from outsiders for any research project under review.

The composition of the three local IRBs who were in charge of reviewing this present study included mainly physicians based at the institutions. This type of membership can be explained by the nature of Vietnamese IRBs which combines both scientific and ethical review.

Besides establishing REAB, there was also a directive that in subordinate IRBs the leader of institution would not participate as chairman as was previously the case. This requirement is meant to ensure the objectiveness and independence of the IRBs. An IRB member has provided insight regarding independence, describing a set of principles that they uphold and act in accordance with:

“Independence, of course we have the independence. I agree that it is independent. We are not working in reliance on the Ministry of Health, are we? For example, we would follow whatever the Ministry asks us to do. We are not like that. We work in compliance with principles, and that is why we have our own independence. However, those requirements....since regulations

from the two IRBs would be different, it causes difficulty for investigators sometimes” (NHTD: IRB Member 1).

This view implies that there may be differences in “principles” involving different approaches taken in IRB review. Whilst these differences here may be derived from regulatory mandates which the IRB may choose to adhere to for its accreditation and institutional policies, there can also be differences in the way that the principles are interpreted by IRB members.

b. Procedures and functions

Requirements for IRB’s operations and procedures vary between institutions. Each institution will establish their own IRB depending on their policies, overall goal and available resources. Nevertheless, Vietnamese IRBs all share similar characteristics as follows:

- ***Combining scientific review and ethical review***

Evolving from its original function of scientific review, local IRBs accordingly still put great emphasis on scientific review. Historically explained by a local IRB member:

“H: [interrupt] It’s just the way they call it. At the beginning, it is named scientific review board, later added Ethics. That’s just a name and the review board’s nature is essentially the same...Actually in the past, people used to call it scientific review board. In this scientific review board, they review research projects, I don’t know how it happens in other countries, but here in Viet Nam, they review, firstly,

scientific aspect and secondly ethical aspect. That's why later they changed its name so that it reflects the true function of the IRB. In Viet Nam, we don't have separate boards" (HTD: IRB member 2).

This function is regulated in guidance on standard procedures for organization and operation of IRBs, issued by the Ministry of Health. Although with the REAB, the Ministry of Health has provided a clear definition that its function is to review ethical aspects of research projects, its duties which in part involve monitoring research and evaluating research outcomes may suggest that scientific review is attached to the overall research review conducted.

- ***Responsibilities***

Drawing on three fundamental ethical principles applied in research including respect for person, beneficence and justice, there are common responsibilities regulated for all the IRBs in Viet Nam (Ministry of Health 2012; Ministry of Health 2013). These essentially comprise:

- ✓ Protecting the safety of research participants and communities;
- ✓ Protecting rights of research participants and researchers;
- ✓ Ensuring justice for all parties involving in research;
- ✓ Ensuring scientific validity and feasibility of research projects

These responsibilities are further detailed and extended in regulations for subordinate IRBs. Not only to protect the safety, subordinate IRBs are regulated also to protect the health of research participants and relevant communities. Justice is referred to a fair sharing of risks and benefits among social groups, age ranges, sexes, economic status, cultures, ethnics and religions. It can be seen that these regulations are to some extent similar to

what generally perceived of and interpreted from the three basic ethical principles in the setting of research as mentioned above. The main points for subordinate IRBs are particular requirements for the IRBs' to review ethical aspects and the overall legal conformation of proposed research projects. It is stated that the IRBs have to ensure the objectiveness, democracy, honesty and timeliness in reviewing ethical aspects of research projects. While all of following regulations and guidance on the organization and operation of the IRBs are built upon these principles, e.g. voting for giving final decision, composition, etc., 'timeliness' is the element that is not clearly defined and expressed elsewhere. The guidance also shows that ethical review is not limited to potential risks and benefits to research participants but also includes issues regarding legal aspect and the whole institution itself. This is furthermore proven in the practice of local IRB review in which potential issues on politics, social matters, institutional administration and other legal requirements which might be seen as relevant to the case would be considered as part of their ethical review.

- *Level of review*

There are two levels of review that may apply: full review and expedited review. In full review, full members of IRB shall be convened to review submitted research projects. Full review is a default requirement for biomedical research unless the research fits criteria for expedited review. Expedited review is not uniformly regulated and varies according to site. There is not any special review issued to be applied for research ethics review in the setting of large communicable disease outbreaks like REEs.

In the next section, I will present my findings comprising of elements which emerged

from the interviews with stakeholders to affect the review of IRBs and concerns and challenges raised during this process.

4.1.2 Elements that affect IRB review: for normal research setting and REE setting

In addition to the description of general structure and working procedures of RECs/IRBs above, it is crucial that we learn about elements that may have some influence in their practical ethics review and decision. In this section, I am going to summarize a number of influential elements that are reported in my interviewees to be taken into account in the review of local IRBs and thus affect their determination over a research project. Of all elements shown in Figure 4.1, ones that are stated by IRB members to be taken into account in reviewing research projects in normal setting will include types of research and possible issues caused by the research, information about the disease, benefits and well-being of research participants and communities engaged in the research, collaboration with research institutions, research funding, credit and responsibilities of IRB members, regulations and instructions from corresponding governing bodies, professional/personal influence, and ethics training received by IRB members. In the setting of REEs, research projects on such diseases would involve a broader account of elements that are relevant to the setting. These include epidemic control and prevention policies with regulatory mandates of the MOH guidelines, information on the progression of the epidemic, public opinion which places demands on having research to learn more about epidemics and produce effective treatments.

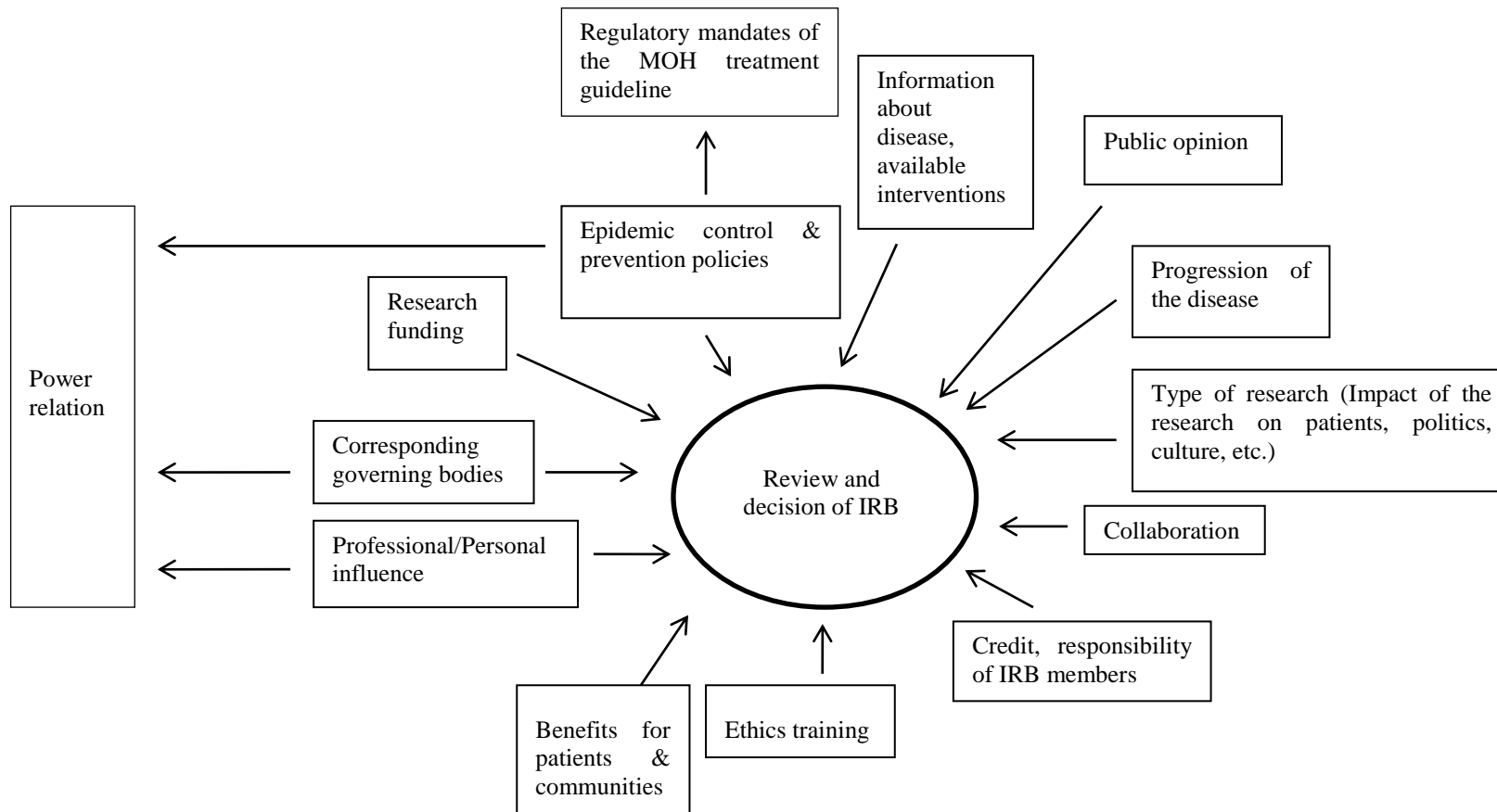


Figure 4.1: Elements that affect local IRB review of research projects in REE

Another element that is worth of further elaboration is a sense of duty to protect a wider population through implementing research for the benefits of the majority of people. As shown in the extract below, in this manner, benefits of wider afflicted population would be weighed more than that of individuals which is a typical focus of the IRBs in other disease settings:

“Actually...there is a general rule. What is that rule? Those difficulties will affect IRB’s decision. Sometimes the IRB is still reluctant to approve a study but finally it has to do so due to the pressure. IRB’s members feel uncomfortable and unsatisfactory but there are other reasons to consider. And so in this case, the IRB’s members will base its decision on, firstly, patients’ benefits and secondly the nature of the epidemic, be it dangerous or not. If the epidemic is lethal, sometimes we have to put patients’ benefit a bit lower for the majority of people. This is for the patients eventually. I wrote down 2 factors in the interview guide for you: 1) the patients’ benefit and 2) epidemic control and prevention work; the IRB bases on these 2 factors to make the decision. In the examples that I have mentioned, you can’t do it in normal situation, however, due to a special context like war, people may do research under the law of war, not the law in normal situation. For example, in war, 16 is the age for compulsory military service, isn’t it? In normal time, it is 18. Similarly, we have to base on the benefit of patients and epidemic control and prevention work to make the decision of approving a protocol or not. We are more relying on these because we lack of information about the epidemic and lack of everything in general. We have to base our decision on what is available. We have to put patients’ benefit on top and epidemic control and

prevention work in order to prevent the epidemic quickly. And to do this effectively, we sometimes have to do a research at the expense of everything” (HTD: IRB member 2).

This seems to suggest that in this approach, in the context of rapidly emerging epidemics, the duty to protect the population embedded in the public health work of epidemic control and prevention has, in no small part, driven the determination of IRB members, especially in some cases when there was not enough information needed as in usual situations. In this review approach, it is interesting also to note that there are ethical considerations at both individual and population levels, and how they are balanced though not in full details.

What emerged from the interviews is that some of the elements listed above have concomitantly created pressures on IRBs in reviewing and approving research projects on REEs, and that power relationship is shaped by and affects the IRBs as well. These types of pressures will be further presented in the following section on concerns and challenges.

4.2 Concerns and challenges:

In my interviews a number of challenges were identified with the current system of research ethics review in the context of research into rapidly emerging epidemics.

4.2.1 Combination of scientific and ethical review

Conducting scientific and ethical review in combination appears to cause ethical concern for researchers. Interestingly, this concern is only raised by foreign investigators who are working at local research sites while local investigators and

local IRB members do not see this combination as a problematic issue at all. Holding the view that IRB's primary focus should be on protecting research participants for their well-being, a foreign investigator expressed his concern for the fact that local IRB members instead went into detailed scientific examination of a proposed protocol:

“I think the ethical committees; their primary focus should be on the wellbeing of the patients and preventing harm. In the context of emerging diseases they will always feel under informed, that they don't feel they know enough to make an informed decision about whether something is going to work or not. So I think it's a problem with the scientific review part, you're asking non-experts to give a scientific evaluation of a project and that's not peer review. That's not genuine you know if it was a project grant going out I would expect people who know enough about you know the research area to make an informed decision but if you're sending an emerging disease protocol to an IRB that is full of people who work on cardiovascular disease or surgeons or anaesthetists or, they can't make an informed decision and will, perhaps would never make an informed decision because it would take too long. So elsewhere an ethical committee is focused on the wellbeing of the patient and preventing harm and judging risk benefit for the participant participating in the research. Is there benefit to the individual or to the community, does that outweigh the risk to the patient participating in the research and that's, that I think should be the focus” (Principal Investigator 8, Expatriate).

In the context of REEs whereby knowledge of diseases and treatment is still limited,

the need of IRB members to be fully informed of and to appreciate scientific background and methods proposed to gain confidence in making decision, in fact, adds more challenge to researchers and delay the whole review process. Talking about difficulties in scientific review of research protocols in newly emerging infectious diseases, a study sponsor has identified limited knowledge of the nature of diseases and uncertainty in the disease progress as the most challenging parts to make judgement on:

“...I mean ultimately in an epidemic, there are two types, so the one that we’re familiar with and there’s just a huge outbreak, so Dengue fever is an outbreak for some reason, so we’re very familiar with the disease and we’ve already got ideas of how to treat it. At the same time we don’t know why there’s a massive outbreak every time, and then the other is the diseases that we’re unfamiliar with, so SARS, H5N1, H1N1 at the time, we don’t know how to treat it so we’re reviewing and suddenly oh should we treat it with double dose Osetamivir or ventilate it, I forget all the flu drug names, anyway all the flu drugs, shall we treat with all these things. We don’t know how do we judge that science. You can go, you can do a literature review but there’s no, there’s no literature on that disease itself, we don’t understand it, everybody panicked with H1N, it was super severe, it wasn’t it all, we had no idea...” (Study Sponsor 1, Expatriate).

Being limited in expertise for scientific review, especially in the REE setting, may potentially delay the review process or lead to rejection of proposals on the basis of the lack of scientific information. In this situation the IRB’s duty is supposed to look

at ethical side of research to protect and to serve patients through the social value of the research.

Noted by another expatriate investigator based at local research site, as a result of their duty to review the scientific aspects of a proposal internally, local IRBs can bear different interpretations among the members regarding methodology, scientific evidence and what is supposed to be good for patients based on medical experiences of members as physicians. Discussions over scientific aspects thus consume time and eventually cause delay:

“What I always find difficult to do deal with the IRBs, the local IRBs is that with Oxtrec it’s easy, they’re an ethical board and they only look at the ethics of the study. All the IRBs here are also sort of a scientific board and they also look at the content of your study and I think a lot of Vietnamese scientists or clinicians have a whole different view of what is good for patients and what scientific evidence means and why you should do clinical research and that often leads to discussions and delay” (Principal Investigator 4, Expatriate).

Although there is not any particular example given to illustrate how different the review processes of OXTREC and local Vietnamese IRBs differed, narratives and my own experience gained from obtaining approval for this study show that local IRBs often inquire in-depth into scientific aspects to identifying potential design faults and proposing solutions. OXTREC also requires scientific review to ensure the scientific quality of the research project. Investigators can send their proposals to appropriate peer reviewers to get references as supporting documents to submit to OXTREC. In Vietnam the committee themselves have to do the job. That may be

where the confusion and miscomprehension of all the expatriates might come from. An expatriate investigator noted the opposite experience with local IRB's being mainly concerned with patient safety rather than in-depth analysis of science:

“Yes they have different priorities I think is what I see is that the Oxford Research Ethics Committee is often more concerned that the design of the study and the scientific questions are good enough and important enough to justify the activities and risks to the patients. So they're looking at the scientific kind of value of the project and that balances with the risk of the project whereas the Vietnamese review is often more concerned about the discomfort and the risk to the patient. But not in the context of the benefits of the research, it's just how much blood are you taking, how old is the person, because you take blood from children and what's the volume you know and they don't relate that to the scientific value of the project, it's just, it's almost like it's a separate issue, you know what's an acceptable amount of blood to give, how often and at what age” (Principal Investigator 4, Expatriate).

As noted at the beginning, it is interesting that local Vietnamese investigators do not raise this combined function nature of local IRBs as an issue. In contrast, most of local study staff and local IRB members share a view that it is normal as that is the function of the IRBs, and that there should be scientists and clinicians, and at best to include only these types of people to conveniently discuss on scientific topics. On the other hand, what emerges from the extract below is that the value of advancing scientific knowledge to improve healthcare for future patients is likely to be

unanimously given more favor by a group purely consisting of (Vietnamese) scientists and clinicians:

“It depends on the nature of each country. Honestly, when you do science, for whatever you may say, you have to base it on someone’s benefit, not only on researchers’ benefit. As a result, I think the combination is good. It is better than having a separate Ethics review board as if you don’t do science, you invite such people as representative from a labour union, representative of lay person but these people do not understand professional knowledge, it is very difficult. There are things that we who do science see doable but they may deem “touching ethics”, for example. Take another example of drug testing, if nobody dares do a drug test, that is testing the drug on animals than on human beings, be they volunteers or being paid, how can we know how effective that drug is. Of course there will be things to limit this testing procedure. On the ethical perspective, the fact that you don’t know this drug and you use it on human is unethical. But in this case, people only see it purely from the ethical perspective, not from scientific perspective. If there is nobody doing such thing as drug testing, people can’t do research, can they? So I think it is better if there’s science here, that means a scientists have to think about ethics and in ethics there must be science” (HTD: IRB member 2).

4.2.2 Review authority and review process

Another challenge confronted by foreign investigators in relation to the local IRB review particularly related to studies on REEs is who is the appropriate review authority as these situations are often considered specially sensitive, due to concerns

over widespread public panic and fear. While there is no specific guideline or regulation for research on REEs, as reported by a foreign investigator conducting influenza studies in local research sites, the investigator was uncertain about the review authority for submission, i.e. whether it should be reviewed by local institutions' or the MOH's IRB:

“Well yeah there’s just no clear dividing line, you know you hear various things, our work as a therapeutic trial has to be the ministry, if it’s a vaccine trial it has to be the ministry. But when it’s a sensitive issue like H5 sometimes the institution would be reluctant to give institutional approval because it may be politically sensitive so they want to go to the ministry and then certainly there is no clear process I’ve seen for rapid review in the ministry” (Principal Investigator 1, Expatriate).

Although it was not clearly specified if the MOH had applied the expedited review for these types of projects in practice, expedited review process as regulated and applied, as noted in the guidelines issued, may benefit from further clarification for its particular application in REEs.

4.2.3 Obligation of IRBs to comply with policies and accountability

As shared by members of local IRBs, the IRBs are bound by rules and demands from many other parties involved in the whole research system. As researchers themselves and having reviewed many research projects, members of local IRBs are well aware of research practice and its challenges. Balancing demands, policies and the research practice, as a result, may constrain IRBs. Illustrated by a member of local IRB:

“Actually in my experience, there are 3 factors that would affect ethical matter. Firstly, it is the patient rights. Regarding the patient rights, sometimes there are cases in which research participants said that they had to travel a long way to the hospital and if there is any support for their travel. That is a pressure because not all research projects can cover everything for research participant. Right? Then insurance has to be decided depending on each research project because it would be infeasible if we force all the studies to pay insurance for participants. That is the most difficult matter to consider and decide. The second one is pressure from the Ministry of Health. That means we have to comply with requests and regulations of the Vietnamese Ministry of Health and hosted institution. Don’t expose any weak spot or make any mistake. And the third thing is to meet demands from funders. We consider all three matters and have to combine them in harmony” (NHTD: IRB member 1).

In another interview, an IRB member discussed that compliance with the regulations means avoiding being charged ethical violation, and this might put IRB members in conflict between what happened as practical research practice and what is required by regulations:

“That is it. With respect to the job of an IRB in reviewing a project, we have to comply with its regulation. The matter of being able to do it or not requires effort. Investigators have to try to make patients understand and agree to sign on the consent form. While being in the position of an IRB member, and not an investigator, we are required to comply with regulations in order to avoid

unethical cases. We have to comply if we don't want to violate ethics" (CH2: IRB member 1).

This conflict is expressed through the case of information provided in obtaining consent from potential research participants/family members. Balancing obtaining consent in practice and requirements stipulated in relevant regulations and guidelines present challenges to local IRBs when reviewing ethical aspects in clinical research projects. Overall, this has placed local IRBs in a position of potential conflict with other research entities due to the embedded requirements and demands. More importantly, it shows us that local IRBs in such a position might not be free to make their own decision about the ethics of the research under review.

4.2.4 The “human nature” of IRB in relation to its independence

Following from further discussions in my interviews with stakeholders around factors that may affect review and decisions of IRBs, it appears that power relationships established through collaborations, collegueship, and authorities in managing systems places an impact on the IRBs. This feature is referred to the “human nature” of IRBs which actually compose of people bound by both personal and institutional relationships. In this perspective, a genuine independence which is commonly expected and required by research guidelines for IRBs or research ethics committees in general is less likely to happen. Noted on the structure of IRBs based in hospitals or research institutions, a local study doctor said:

“...there is a fact that the IRB that reviews and approves that protocol is also based at the institution that carries out the research, there is no

reason.....uhm...that they can't treat with some privilege flaws in the protocol so that the protocol can be implemented in their institution" (NHTD: Study doctor 2).

This was also confirmed by an expatriate investigator about potential effect of relationship to the IRBs at both individual members and the overall of its work:

"Probably you know I think the relationship, or the strength of the relationship, warmth for the relationship, even at individual level shapes perspectives on the IRB I think. I think what you hope is that IRB, the IRBs give you genuinely independent review. It's true anywhere in the world that if you've got a friend on the IRB, a collaborator on the IRB the reality is you're more likely to get a friendly review, I think that's human nature" (Principal Investigator 8, Expatriate).

In REEs where there was an urgent need for research and collaboration, there may be pressure from governing bodies and even public concerning reviewing research projects. Stated by a local IRB member:

"We had little time for protocol review, time pressure, and we also had to suffer pressure from public opinion. Governing bodies required us to give opinions and to have research projects, and community asked why we were late, why there was no research on HFM disease, etc., and responsibilities and credibility of IRB's members. They are those that create difficulties for the IRB, aren't they?" (HTD: IRB member 2).

In this case, IRB review was said to be mainly based on the benefit of population and guidelines on epidemic control and prevention:

“...Sometimes the IRB is still reluctant to approve a study but finally it has to do so due to the pressure. IRB’s members feel uncomfortable and unsatisfactory but there are other reasons to consider. And so in this case, the IRB’s members will base its decision on, firstly, patients’ benefits and secondly the nature of the epidemic, be it dangerous or not. If the epidemic is lethal, sometimes we have to put patients’ benefit a bit lower for the majority of people. This is for the patients eventually. I wrote down 2 factors in the interview guide for you: 1) the patients’ benefit and 2) epidemic control and prevention guidelines; the IRB bases on these 2 factors to make the decision” (HTD: IRB member 2).

4.2.5 Parochial independence

Having an independent IRB is said to make the institution convenient in its own review and oversight practice, individual IRBs however may hold their own set of principles which may bring about discrepancies between IRBs even within the same region, the same country:

“I think the most important ethical issue for patients is the IRB giving approval for that research project. That’s it...That’s the issue that I think is an impediment in clinical research because the research would be subjected to the IRB, specifically the capacity and knowledge of that IRB. Obviously, there

will be many cases in which a research will be approved by this IRB but rejected by another IRB. That discrepancy between IRBs shows that IRBs work in different principles that they put forward, even in the same country, the same region. That's the issue I think IRBs, if they can be well controlled by their own members to maintain their activities on being objective and scientific, there can be ensured to have good research" (NHTD: Study doctor 2).

Holding different principles as explained in the extract above has caused discrepancy between local IRBs. Another reason is given to account for this discrepancy is the parochiality of some local IRBs. This manifests through not accrediting capacity of other IRBs and standards commonly recognized elsewhere. As shown in an example of a local IRB in the North, which is accredited by the U.S, FERCAP (Forum for Ethical Review Committees in the Asian and Western Pacific Region), yet its approval decision for a project was rejected by other local IRBs as the decision is only at institutional level:

"We are qualified. The U.S has acknowledged, FERCAP acknowledged. But, in a response to us, I can't name them here, said: "This doesn't have meaning. This is only of institution. We also have to go to the Ministry of Health". There they go, we don't stop them. Why should you make hard for yourselves like that?! For example, if you have a research project on emergency disease setting, you can submit it to us for review. Our IRB has been accredited by the US and FERCAP. We have said to them that if you needed us, you could hire us to do the review; we were researchers and we understood your difficulties;

that was the reason we spent much time in establishing the IRB and invited experts for training in details so that we could resolve difficulties for all the research sites involved. If you send it to the Ministry of Health, as I said, I also had to spend from 3 to 6 months to obtain an approval. When I read that letter, I think they...they are just parochial...parochial. I see that those hospitals do not collaborate well with each other. They always think they are the best and reject other people, not acknowledge other. That's their weakness. How things can work....If you want to move forward, we have to take our hands to move together" (NHTD: IRB member 1).

The fact that local IRBs do not acknowledge the review and decisions of each other by requiring research projects have to be reviewed by their own committee has inflicted more burden on researchers regarding costs, time and efforts in resolving emerged discrepancies among IRBs. As noted by an expatriate investigator working at local research site:

"I think there's one approved ethical committee that's I think also the MOH regulation but still not, if we have a project within different hospitals, all hospitals want to do their own IRB which is driving us crazy, and everyone has different ideas and it costs a lot of money" (Principal Investigator 5, Expatriate).

When research on REEs takes the form of international collaborations in which there will be involvement of other IRBs based in other countries as required by their regulations, conflicts between local and international IRBs on ethics may result in

contrary requests for what should be done. To illustrate for this, a foreign investigator based at local research site gave his example of dealing with a dilemma in providing benefit for patients, namely incentives and inducement in research. In this case, local IRBs suggested the investigator provide research participants some incentives while in opinion of the ethics committee in Oxford University (OXTREC), this may affect the decision making of participants and is more likely to unintentionally coerce patients, as narrated:

“Another thing about it, the benefit for patients which sometimes leads to small conflicts of interest is that on the one hand often we need to get the Vietnamese institution on board say you need to give the patient something, especially with children you need to give them a present or something but Oxford Ethics says we cannot coerce patients into a study, you see the conflict?” (Principal Investigator 4, Expatriate).

Discrepancies among IRBs are seen as contributing to impede rapid response of clinical research to REEs and to put investigators in ethical dilemmas, for example how does it make sense for a thing both to be concluded ethical and unethical by IRBs even locating in the same country?; and if it is the case, then who is wrong and who is right?. As raised by an expatriate investigator when comparing how research ethics committees are organized in Netherlands with those in Viet Nam, if local IRBs always require to re-review a research project which has been already reviewed and approved by a local IRB with respect to its ethical acceptability, this working mechanism is wrong:

“I know and in the Netherlands if one hospital has approved it the others have to accept that decision and just do a, they just check can we actually do it in our hospital that’s all and do we want to do it, do we want to do it, can we do it, what resources do we need, which department should participate, is there any doctor there that wants to do it so they just check and then if that’s okay then they say okay we agree and then they participate. But not ethical because it’s already ethically cleared by a registered ethical committee so otherwise if you say it’s not ethical and the other one says it’s ethical who’s right? Does it make sense? It’s a good proper ethical committee, and they say okay it’s ethical why do you have to check that again unless there’s something wrong with the ethical committee. But then your system of creating ethical committees is wrong” (Principal Investigator 5, Expatriate).

Talking about the issue that one research project has to go through many ethical reviews required by different IRBs involved, based on his experience working with RECs in Canada, and other RECs based in other countries involving in international collaborative research projects, an international expert has portrayed the parochiality of RECs in general with its autonomy and representation:

“So that’s a very interesting insight because what it actually says is that all research ethics boards while they are quite autonomous, they are following standards that they feel represent what they do.

....

Well I think first number 1 that it’s absolutely central, number 2 that it is highly feasible, that there’s a tremendous willingness on the part of

researchers to collaborate internationally. I think there has not been an awareness or a sensitivity on the part of research ethics boards that they have to think internationally and collaboratively. And research ethics boards tend to be quite parochial, you know they say you know we have to do this and we have to decide, it doesn't matter if it's been approved by you know 20 other research ethics boards, we have our own standards and we have to review it” (Principal Investigator 6).

Through his experience, IRBs appear to uphold their own standpoints and standards upon which their evaluations would be reflected and made. More importantly, these standards seem to be deliberately chosen by their representation for what is being done in practice. In other words, standards are chosen to follow by the extent of how much they appear to be aligned with people's practice, instead of a mere look at their values and how they work in combination of other values attached in other principles. In this way, the judgement of one IRB cannot be served as a ground to rebut or override other ethical viewpoints expressed by other IRBs. Autonomy may grant the authority of an IRB to decide what should be done in regard to the institution and whoever they represent.

However, another study doctor has pointed out that a multi-review pattern would help as a filter to minimize shortcomings of a research protocol, or in other words, it would offer certain protections:

“Uh...if the quality of that IRB is not good enough, of course increasing the number of IRBs to review the protocol can serve as a way to minimize shortcomings of the protocol. However, the flip side of it is going through

many IRBs would sometimes cause unnecessary difficulties for clinical research to be carried out” (NHTD: Study doctor 2).

If the nature of “independence” of IRBs has led to the need for multiple review and disagreements among IRBs, which eventually slow down the review process of research, this is part of reasons for insufficient response to the context of REEs. In the next section, I will go on to look at this issue specifically in more detail.

4.2.6 Insufficient response to research in REEs

Besides concerns regarding the typical organization and function of local IRB system, there are other challenges especially arising out of REE situations that directly cause the late response of IRBs in reviewing research projects. These include:

4.2.6.1 The lack of information of the nature of REEs and pressures to put on IRBs in response to the situation:

The lack of information about the nature of disease and its progress is a particular challenge when reviewing research proposals concerning REE’s. The review process could be slowed down by IRB members needing time to acquire more information. As raised by a local IRB member:

“It happened long time ago. I forget about it so I can’t tell you my experience in reviewing the research. But for example, if the disease has already happened, and we have information about it, it would make the review easier. However, at that time, two of those epidemics, after H5N1 then H1N1 happened, we apply our experience drawn from H5N1, take it as a standard to

implement subsequent studies. Our experience is only accumulated gradually after the epidemics happen or after 4 months when people started to find out a conclusion about the epidemics. So if a novel one, for example a new disease suddenly appears in the future, and you require to carry out a study immediately when people still have little experience about it, this will slow down the review process” (HTD: IRB member 1).

This lack of information necessary for their review while also needing research to gain better understanding, has been stated as placing great pressure on IRB members:

“When a lethal epidemic occurs and widely spreads, which is a threat to community, public opinions from group meetings, forums, media, Internet, leaders, etc. urgently require to be given, within a short time, a clear explanation on the disease, pathogen, factors causing the disease, transmitted route, treatment and prevention measure, etc. So in order to have these kinds of information, we need to do research on the disease quickly, and these things: time, urgency, the danger of the disease, demand from leaders, put a big pressure to the IRB in reviewing research protocols” (HTD: IRB member 2).

IRB members also face other demands from public and national governing bodies to allow research that will provide evidence of effective management to prevent epidemics. Interestingly in the interviews local IRB members seem to see themselves as separate from the situation when reviewing a research protocol though they are

often also clinicians and/or researchers working in the field and directly interact with clinical cases of REEs occurring in their region. According to a local IRB member:

“...Sometimes the IRB is still reluctant to approve a study but finally it has to do so due to the pressure. IRB’s members feel uncomfortable and unsatisfactory but there are other reasons to consider...” (HTD: IRB member 2).

Challenges in reviewing interventional research in REEs are not only encountered by Vietnamese local IRB members. Through the interviews with other international experts based in China, similar experiences were reported:

“Interviewer: So again do you know any reason why the, you know what kept the IRB so long to give you an approval?

R: Well in fact I was expecting an earlier approval because at the time of the SARS everything was stopped so no surgery, no elected operations, everybody had nothing to do except for those from our healthcare workers, dealing with SARS. So those people who are in the committees should be quite free to make a quick decision. But maybe because they were concerned what the use of steroids for the severe viral illness it took them a long time to give the approval and that delayed my recruitment of patients. So we had more than 300 patients in total, had they been able to approve the study earlier I would have been able to recruit maybe 50 versus 50 in each arm and that might have come out in New England Journal because it was a proper randomised placebo controlled trial for a brand new illness” (Principal Investigator 10).

4.2.6.2 The lack of procedure to deal with REE situation:

Many of the issues in reviewing and obtaining ethical approval described above from both local and international IRBs appear to stem from the lack of a review procedure in place for the specific situation of REEs. As already discussed, routine systems intended for other disease settings often lead to delays and difficulties in the setting of REEs. While on the one hand, such procedures could be seen as intolerable by investigators, on the other, these attitudes and acts of investigators could be misunderstood and judged as unethical by IRBs and the public. As raised by a foreign investigator in his experience of obtaining ethical approval for a study on H1N1 pandemic influenza:

“Interviewer: Yeah H1N1 yeah it took you 6 months so what do you think is the problem with the procedures?...I mean if it’s only about getting samples then what’s the problem?”

A: Well that’s a very good question because I don’t know, I don’t know what the problem was. We were just giving the patients normal treatment for influenza which is Oseltamivir and then we were taking samples so why they needed six months for that I don’t know. I think there’s a lot of people in, in these procedural steps involved that are more concerned with following each and every single rule that there is, they cannot place themselves above the protocol and say well actually this is normal, skip it, there’s nothing special about this...” (Principal Investigator 4, Expatriate).

What is related in this theme is that because there is no special framework in existence for this unique situation, IRB members tend to embrace on individual rules or principles.

As noted by a study sponsor working at local research site giving her general assessment on obtaining ethical approval from relevant local and international IRBs:

“I think one thing we haven’t addressed is ethical review, we talked about the difficulty of having so many review boards and having to review it like that but for example the 032 protocol went through an expedited review through Oxtrec and then [interruption] so institutional review boards and their ability, I mean first of all the access to education on pandemic research is split in this country and lacking in others, even within Oxtrec, I mean just for lack of exposure to it really. But they don’t have procedures in place to deal with that research and how we dealt with the previous protocol it was reviewed overnight by the chairman and that did not follow an expedited review, it was reviewed by the Oxtrec but that didn’t follow the standard operating procedures of that board and the demands that we were placing on the boards here you know we were not forcing, we were trying to encourage them to meet now to get this done” (Study Sponsor 1, Expatriate).

4.2.7 Perceived responsibilities of local IRBs: to protect the rights of patients from undue pressure

An issue recognized by expatriate investigators is that patients or family members in REE situations may experience undue pressure from the media, or researchers and medical providers. In situations where a power imbalance exists in relationships

between researchers/ community leaders and participants, potential coercion might be felt by patients or healthy people in response to requests by researchers and community leaders. This type of implicit coercion has been widely recorded in literature discussed around ethical issues in consent practice taking place elsewhere.

“I think one of the main things is, that’s not well addressed is stigmatisation of the patients because you know patients with SARS and H5 particularly were over exposed to the media, over exposed to academics, over exposed to the local officials, over exposed to you know the healthcare sector so they got very, you know there comes a point I think where they’ve had enough, they just want to get on with their life without being, you know somebody knocking on their door a few days asking to do, fill in this questionnaire, asking about exposure, wanting to take blood samples, you know swab their household, all these things, their comes a point where I think it’s too burdensome on the individual. And of course they can, they should be able to say no but often they might be reluctant to say no because you know if a person in an institutional hierarchy comes to them and say can you do this, can you do that. It seems that there’s no sort of one agency that can have overall oversight. Okay this is the tenth study when H5 cases and they’re sick of it, it’s too much you know leave them alone” (Principal Investigator 1, Expatriate).

Literature around ethical issues in research on acute epidemics has reported that when community support is secured for research projects to be carried out within that community, this may result in explicit or implicit coercion for individuals within that

community to participate (Ezeome and Simon 2010). Community support might include support from national governing bodies, medical providers or other identifiable community groups. On one hand, these representative groups can help to better inform research to the community, on the other hand, these advocates can simultaneously appear to coerce inflicted individuals.

In REEs, due to the urgency of the situation, communities with existing research infrastructure are almost most likely to be selected (Ezeome and Simon 2010) thus further increasing the likelihood of intense sampling within the community:

“...Okay it’s a natural emergency, maybe it’s a global emergency, it’s a disease and everyone is scared about it, you’ve got to find out everything about it and then the, the rights of the patient come lower down the list of priorities and so there maybe you know over intense sampling, over intense recruit to studies because of that. And also overdue pressure on patients, I think you know ethics review is you know yeah more important you know in a rapidly emerging context because there can be a lot of pressures to take short cuts” (Principal Investigator 1, Expatriate).

4.3 Suggested solutions by stakeholders:

In the preceding sections I have outlined the main challenges in relation to research ethics committee review identified by my interviewees. The interviewees also suggested a number of ‘solutions’ to the challenges they identified. In the following section I describe the variety of proposed solutions which can be categorized into four following principal themes.

4.3.1 Investigators have the duty to facilitate the review of IRBs

Raising a need to have rapid research initiatives in the setting of REEs, a local IRB member has suggested that investigators should communicate with IRB members to inform and raise the urgency of the situation and the importance of the proposed research projects. Proposed research projects should be quickly written and particular attention paid to giving as much background information as possible on both scientific and ethical aspects:

“Salient...ah...uhm...is its nature of urgency. Those research projects have to be quickly approved. I think if you want to do research in that setting, you have to quickly draft your idea, then write the protocol, however, we should also pay attention to and prepare questions or matters that may be asked by the IRB. For example, they may ask about scientific background of the disease. So if we know any sort of related information, we should put everything into the protocol so that the IRB doesn't need to spend more time on further investigation. And in the protocol, we also need to consider ethical, religious, cultural issues, etc. That means when we write the protocol, we have to plan ahead those issues. If not, once the protocol is submitted to the IRB, your protocol is an example, the IRB will not approve and suggest you re-write the protocol. And in this case, if the next IRB meeting will be hold at least in the next one month, how can you implement your research? As a result, we have to facilitate the IRB by understanding what they need, for example, they will review issues on ethics: if the research procedure violate patients' right and benefits or not, benefit of the research, its feasibility and scientific background of the disease” (HTD: IRB member 2).

This solution may be challenging to implement due to constraints posed by the rapidly evolving nature of epidemics, e.g. constraints of time and resources, uncertainties in the nature of diseases and the lack of evidences of proposed treatments. Another idea is to prepare in advance as much as possible as suggested by a local IRB member:

“That is the reason why I think if you have a strategy. For example, there are many situations until when they’ve already occurred, we just come up an idea to do research. But if at the moment, we have such a plan, for example, in the future, there would be epidemics A, B, C or D predictably breaking out, we should prepare for them. If we have a plan to do research, we should prepare it immediately to avoid the situation when we only start to think about doing research when it’s already broken out broadly in many places. It would be very rushing at the time to start writing a protocol. So I think there must be a strategy for this. All emergency epidemics share the same elements, similar characteristics. If we plan to do a research into such epidemics, we can prepare for the planning, or certain procedures in advance so that when it happens, we can set off immediately”(NHTD: IRB member 2).

In a more detailed level proposed by local and foreign investigators, and international experts working in epidemic setting, there should be an open access repository of protocols to share within the networks and other researchers. Ideally, these strategic protocols should be reviewed and approved in principle by relevant research ethics committees prior to epidemic outbreaks. However, when being prompted to think about to what extent the idea of pre-approval protocols may be feasible in the current

system of local IRBs at the time of interview, local investigators and some IRB members said it would very much depend on the types of the proposed research project. Specifically, research projects with novel interventions would be reviewed with more prudence because of the lack of necessary information on the safety and efficacy of investigational interventions. When there is a ‘standard of care’ recommended by the Ministry of Health during an epidemic period, a new different therapeutic intervention which might be never applied before would be far more complicated to go through such a pre-approved process. As anticipated by a local study doctor:

“That thing can be done. I mean we can make a plan ahead for such emergency epidemics and we will present these framework protocols to the IRBs. When we need to implement it, we only need to submit important points for the IRBs to approve. So that is it...and we can implement this plan now. But of course as I have said, it still depends on the types of that research. If that is just a simple clinical research like identifying etiology in which interventions on patients would be minimal, we can easily implement it. But if the research is for testing a new intervention, the review procedure would become much more complicated. And sometimes even if we can prepare such a interventional protocol in advance, it is not sure that the protocol can meet all the requirements put forward by the IRBs” (NHTD: Study doctor 2).

It is further affirmed by a local IRB member that caution should be taken with a possibility of approval for a pilot study with a small number of cases:

“So when you do observational or epidemiological study, it doesn’t touch anything. They only put forward hypotheses. The value of observational study is to give some hypotheses, proportion, for example, I think the hypothesis like this, then we will have further studies like analytic ones to apply certain interventions for improvements. However, if we apply some interventions immediately on diseases which are never known before, sometimes, we have to do pilot study. That means we will carry out with a small number of cases. That is also the reason that partly slows down the research response. It is the nature of interventional studies on epidemics that partly hinders the research implementation. We don’t have much information about it and thus we have to do on a number of cases to convince the IRB” (HTD: IRB member 2).

4.3.2 Researchers to engage IRBs in the design of research

Another common solution proposed through all the interviews is to engage with IRBs. This is a part of the overall plan of engaging relevant stakeholders in research initiatives in response to REEs as mentioned in the solution section of Collaboration chapter. What can be drawn from discussions around this solution is that this engagement specifically requires openness and transparency from all relevant parties. Investigators would thus involve RECs/IRBs in research planning and implementation so that all parties can be prepared for the situation under discussion grounded on mutually agreed principles. As highlighted by an international expert:

“You have broad discussions that are as inclusive as possible amongst researchers, amongst ethicists, amongst public health agencies about what are the general principles for ethics. And then you meet with research ethics

boards, not necessarily individually, ideally at, you know there are organisations of research ethics boards and that you ask them to engage in this. And in part it's the notion that if you're going to have full engagement, collegiality, transparency, open stuff amongst investigators, research ethics boards have to in some way be at the table as well with us and that they have to be prepared to engage under those same, under those ample principles” (Principal Investigator 6).

This need to engage IRBs in research in the setting of REEs is also suggested by local IRB members and investigators as a way of getting local IRBs to quickly proceed with their review and approval. The key point is that investigators should raise the urgency and importance of proposed research projects in response to the epidemic setting. As pointed out by a local IRB member:

“Particularly, if you want your research proposal to be quickly approved, you have to take advantage of public opinion if there is any to push it on. That is one way to get IRB's approval soon. If you don't have any reason, they don't review and give you approval soon as you wish, you see, they don't care if your research proposal is approved or not because it doesn't affect the IRB” (HTD: IRB member 2).

By being aware of the urgent nature of epidemic situations, in his experience, a local investigator said that local IRBs and the Ministry of Health would accordingly see the need to act immediately:

“If that really is an epidemic, the Ministry of Health itself would also recognize a need to do act on it immediately. They will do it immediately. The problem here is that you have to raise the urgency of your research subject. If you can raise this so that the Ministry of Health can see it, they will take it on board. In that case, sometimes it can take them one day to review and approve. For example, say there is the hand, foot, mouth disease at the moment, or the meningitis meningococcus happens recently, that’s also an epidemic, and if there is anyone doing research on this immediately, I think the Ministry of Health...[end of the sentence]” (Local Principal Investigator 13).

4.3.3 Working towards greater consistency between IRBs through the development of shared principles/ethical frameworks

In response to concerns over the parochialism of IRBs in which different boards may place different emphasis on different principles, a local IRB member suggested that local IRBs acknowledge common standards. That would also involve respecting opinions of people and values that people uphold:

“That is the way for things to be worked out. If you just reject opinions of this person, of that person.... For example, when I came there to work, I knew that.... I can work in anywhere I go to, but when I came there, I knew that they didn’t discuss with each other. Though they are very kind, they didn’t discuss with each other. But our hospital here, people from the Hospital for Tropical Disease, when they come here, they can work with us. I respect opinions of people, respect value of people” (NHTD: IRB member 1).

Along the same line, foreign investigators based in local research sites expressed that there should be one centralized international ethics committee to review ethical aspects of proposed international research projects. Decision of this ethics committee should be respected by all institutions participating in the research. This solution implies that there should be some sort of concurrence in ethical view on the same one research project at least within a country. Stated by an expatriate investigator:

“Interviewer: So regarding getting the ethical permission in Vietnam and also from international ethics committee that we need to get for a project, do you have any ethical consideration when you seek for ethical approval from all of the partners?”

A: Well I think the, if there is an official ethical committee, Vietnam should learn that that a committee has approved it, the other ones don't need to approval any more, they just need to have a scientific committee saying okay just the feasibility, can we actually do it, that's all. But they also go through the whole ethical process which I think is incorrect. So if you have an approved ethical committee, they approve it, all the other hospitals should respect that decision and say ethically it's okay the project, we just have to look, how can we implement the project in our hospital and do we agree with the terms and the funds and the budget and do we actually have the patient for instance and actually do what is expected?” (Principal Investigator 5, Expatriate).

At a broader spectrum, having common ground on ethical principles is crucial in international research collaboration. The need for good research to be done can

override the autonomy and personal views of individual ethics committees. As highlighted by an international expert:

“They are following standards that they feel represent what they do. So what you really need to do is to get the people who are establishing the standards to talk to each other and define some common ground amongst them so that you know in Canada we have what’s called the Tri Council Policy on Research Involving Human Subjects and it sets out ethical principles that research ethics boards like to adhere to...I mean that’s the notion why this has to be global and international, people have to be prepared to talk, to give a bit and to you know recognise that the larger issue of enabling research is much more important than your own autonomy and your personal views on that”
(Principal Investigator 6).

4.4 Discussions:

In the previous sections, I have explored the challenges identified by my interviewees arising in the approval and conduct of research on rapidly emerging epidemics. I have also outlined the solutions they propose to such challenges. During discussions about concerns, challenges encountered by stakeholders and solutions put forward, two key values began to become apparent across accounts provided by the stakeholders. These values were ‘openness towards shared principles/ethical frameworks’ and ‘duty to protect’:

4.4.1 Openness towards shared principles/ethical frameworks

The concept of openness is implied throughout narratives of issues around procedures

applied to the IRB review, IRB's deliberations and relationship between IRBs working with each other in reviewing the same research projects. In the first instance, openness, manifesting itself through open communicating between IRBs and other relevant stakeholders in IRB review procedures or approaches taken, is supposed to be key to gaining mutual understanding through engagement and a possibility enables a common ground to be found among parties. Openness is also reflected through IRBs acknowledging each other. In this manner, openness is seen as a sign of mutual respect. IRBs by mutually respecting each other's opinions and values would be able to more open to communication and cooperation with each other. While the independence of each IRB in adhering their institutional norms and principles is important, openness can help IRBs to learn from each other in attempts to improve their organization, review and sufficient response to epidemic settings. Shared by a local IRB member as an example of how IRBs should be open to learn from each other is the story of how their IRB has actively suggested other IRBs based in collaborative hospitals share knowledge of research ethics review trained by international organizations and offer supports if required:

“Just as what you said these were emergency research....This hospital is a big centre for emergency epidemics so we must review research projects quickly. That is why we need to establish and we are willing to support other hospitals. If they have any opinions, just send to us and we will help them out. For example like Bach Mai Hospital, if they need us, we are very happy to do help them” (NHTD: IRB member 1).

4.4.2 Duty to protect

The duty to protect research participants and afflicted population is described as the main focus of IRBs. In the setting of REE's where there is a great urgency to initiate projects, IRBs may place more weight on the value of research in order to trigger a timely response. IRBs furthermore could look at other possible effective measures to protect research participants, for example, establishing an oversight mechanism to protect participants from any overdue pressure caused by research, and ensuring the safety of research participants when the full understanding of research information is infeasible in some circumstances like in the case of REEs⁸. In public health emergencies where protecting the afflicted population is crucial to the whole society and global population, there is an added dimension to IRB review as they need to consider duty or protection towards this broader population rather than just the study population, balancing duties at both.

4.5 Conclusions:

This chapter describes the general structure of the Vietnamese IRB system, its operation and empirical findings related to elements that may affect IRB review and determination, exploring the concerns and challenges encountered by stakeholders in the local IRB review together with corresponding solutions in the setting of REEs. As the intention of this chapter is to provide a rich account of ethical considerations arising in the IRB review experienced by key stakeholders, description of the local IRB environment is only limited to characteristics that are in common of all the IRBs

⁸ Refer to section 5.2.1 for further reference of the consent practice in research in REEs

and would offer a better understanding of ethical considerations articulated through the interviews. What can be drawn from the understanding of the local IRB system and related empirical findings so far include:

- Although working on the same set of ethical principles, the IRBs are also bound by other regulatory and institutional policies. This in part leads to variations in approaches taken to their review and added responsibilities perceived by the IRBs in working in compliance with all such requirements.
- IRB deliberations are not only taking into account reasoning about ethical principles but also other elements within a research environment. When the IRBs are established by institutions and governed by those institutions, power relation and collaborations that are attached to the institutions are inextricably linked to the work of IRBs. These elements in some cases have created pressures on the IRB review process.
- IRB review in the REE setting is also involved in consideration of the benefits of the overall population, rather only of individuals. Although it is not clear to what extent there is some degree of flexibility of IRB review and potentially the possibility overriding other ethical principles pertaining to individual rights.
- Themes of openness, particularly with respect to communication, and responsibilities generated from the duty to protect also emerged during discussions. These themes were raised not only in the context of Vietnamese local IRBs but also other research ethics committees in other countries as requirements for an appropriate response of IRBs to the REE's.

Whilst many of the challenges my interviewees describe are produced by the special features of the context in Viet Nam, some of them are features of other places too. Insufficient response to the research context of REE is a typical example.

Chapter 5 Obtaining consent in clinical research on rapidly evolving epidemics (REEs)

So far I have been presenting my findings on two levels of research relationship, i.e. the macro level of international research collaboration and the meso level of Institutional Review Boards/Research Ethics Review in their relation to other groups of research stakeholders, for example, investigators, sponsors/funders, health authorities. In this chapter, I will focus on consent which explores the research-patient relationship – the micro level.

5.1 Experiences of key stakeholders about consent process in REE clinical research: research practice and the nature of consent

In this section, I report on opinions and experiences about obtaining consent from patients and/or family members for research on REEs from all of the interview groups, mostly shared by study doctors, study nurses, investigators and IRB members, all of whom have been directly involved in the consent process.

5.1.1 Obtaining consent in hospital based setting

In all the clinical studies on REEs that my interviewees were involved in, it was only the study doctors who were responsible for obtaining consent from patients and/or family members. This pattern reflects practice in normal clinical practice and research in other disease settings in Viet Nam. Study nurses regularly see patients and family members, but only take part in the consent process by helping contact patient and family members and sometimes explaining to them about the research. All local study

doctors, investigators and study nurses are medical staff based in hospital departments participating in the research.

As would be expected from the role of study doctors and from the findings of my pilot interviews, the process of obtaining consent in research into REEs presented important practical challenges and these were mentioned and discussed by all study doctors. Discussion of these topics took up a large part of all my interviews with them.

Narrated by study doctors and study nurses working in hospitals, obtaining consent is started commonly by grasping the general health status of potential participants and other basic information, e.g. occupation, working place, age, then approaching the patients or family members, and talking with them about the illness and the proposed research, summarizing the main points of the research in a way that is understandable to the targeted patients/family members. They are then left a while with a research information leaflet so that they can read and think more about the research and are able to ask further questions. A copy of the research information leaflet would be left with the patient or family member for further reference. This informing process has been shown to be not simply an exchange of research information process. It is also characterized by “more communication”, “establishing the trust”, “persuading” and “assuring them to make them less worried”:

“When I get consent, usually I will firstly by establishing some sort of trust, for example by asking family members around, and that the parents when looking at me would less hate me, then I will move on to introduce about the research” (CH2:Study doctor 2).

Part of the process of obtaining consent inevitably involves reassuring patients about what is involved. There is a fine line between ‘informing’, ‘encouraging’ and ‘insisting’ as the following quotes illustrate:

“ Well, I said to the family members “Ah, we are going to do these types of tests today...”. I also encourage them to keep up with the research, there are only a few days to complete... We have to persuade them because many family members feel sorry for their child, even me, I also feel sorry for them, not the family members alone”. (CH2: Study nurse 1)

In studies on influenza which can be easily transmitted through the airborne route, communication between study staff and patients usually has to happen with staff wearing protective equipment such as masks or hoods, and the patients themselves may be isolated from family members. Although none of my interviewees experienced this as presenting particular problems with communication, they did suggest that the protective clothing can sometimes make people scared. As shared by an international expert:

“Well some of them are quite nervous but then you know I think they were more scared sometimes when they saw me walk in, and I’d always say look I’m going to put this crazy mask on now before I come in, but don’t worry about it, it’s just to protect me because I see so many flu patients” (Principal Investigator 2).

In practice in Vietnam consent is not only a matter for the individual patient but also for family members. In order to obtain the consent from patients, study staff also talk with family members to explain the research and enable them to support the patients. Sometimes in this case family members raised questions about the patient's ability to give a valid decision when patients were sick. As a result, study doctors sometimes felt that also talking with family members would support the process of obtaining consent from patients:

“I think we should talk to their family members. It is the best way. If we talk to the patients only, and then if something happens, the family members will blame on us that because the patient was not completely conscious at that time, s/he could not make a right decision” (HTD: Study doctor 3).

5.1.2 Obtaining consent in the community

Interviews with researchers involved in community studies on influenza revealed a broader approach for obtaining consent. In this setting it is necessary to obtain the agreement of the community's leaders.

“I wanted to do swabbing and bleeding of children in schools and Binh Thuan province and when we wanted to do that I went first to the Department of Preventive Medicine and then to the People's committee to talk about it and they would take care of talking to the whole community so they went to sub-departments of the people's committee and talked to the community at the People's Committee level. So they would talk to their, what they call their community leaders, yeah so they would talk to them and they would go to the

schools and we wrote patient information sheets for, for all the teachers in the schools, for all the children in the schools and their parents, even before we went to do the study so that everybody knew about it already” (Principal Investigator 4).

This mechanism is explained as part of the collective mode of decision making in Vietnamese communities and the administrative systems, and is suggested to be different from Western settings where the importance is mainly placed on the individual.

“Yes the first thing you have to convince the people’s committee or the women’s union or something you know that it’s worthwhile engaging on an issue. Until you’ve done that you can’t really go into community. I mean that’s different for hospital patients obviously it’s more of an individual thing but when we do community studies then that’s important...and you know I think in Vietnam often people participate in studies because they feel some sort of community, not obligation but some kind of community coherence that you know if the leaders think it’s a good idea and we think as a community think it’s a good idea then as an individual if you say no then maybe that’s not a good thing to do. That’s another perspective that’s kind of missing from a western perception, isn’t it?” (Principal Investigator 1, Expatriate).

5.1.3 Surrogate consent and family decision-making

In this thesis, I am using the term ‘surrogate consent’ to refer to consent sought from the research subject’s legally authorized representative. In what follows, I report on

experiences shared about two cases of taking surrogate consent: for adult patients and for minors under 18. Emerged from these cases is the importance of family decision-making in Vietnamese research context.

5.1.3.1 Surrogate consent and family involvement for adult patients:

My interviewees reported that surrogate consent for adult patients who participated in REE search was sought in cases in which those patients were in coma or unconscious or their decisional capacity was judged impaired at the time of obtaining consent. In such cases, consent was obtained from the patient's father or mother or spouse. Family members I interviewed who had given their surrogate consent for their adult children to be enrolled in research on H1N1 influenza and acute post-infectious measles encephalitis said that decisions were made independently by a parent or spouse based on their understanding of the research, their rationales about benefits and risks of their relatives' research participation, and all these reasons were expressed as their own thinking, not as a result of consultation with other family member(s).

In 2 out of 3 cases it was the mothers who gave consent. The adult patients were, however, looked after by both of parents or the spouse, and sometimes with the help from other family members. This co-caring of both parents with other family member(s) may suggest an implied concurrence within family members for the patient's research participation. Adult patients were made known of the research by the family members, and they agreed to participate.

“Interviewer: So when your son knew about the research on measles caused encephalitis, did he have any opinion on the participation?”

A: No, he didn't have any opinion. He joined it enthusiastically" (NHTD: Family member 1).

5.1.3.2 Surrogate consent and family involvement for minors under 18:

Surrogate consent for minors under 18 years of age was mostly sought from either mother or father. Decisions were primarily made in discussion between husband and wife and other family members. Accounting for a reason why surrogate consent for this group of age was preferably obtained from parent, a study doctor said:

"Caring is mainly done by parents. When they're too tired, grandparents or other family members would come to help. However, when obtaining consent, I only meet family members that are parents of the child. It would be easier than talking with people who don't have the right to make the decision on behalf of the child, especially it may be related to other following legal matters, and that's complicated" (CH2: Study doctor 1).

In some cases, care provider(s) and person(s) designated by law are not the same. In this case, the person designated by law is chosen over the person actually looking after the child.

Findings from interviews with study doctors doing research at pediatric departments or hospitals suggest an involvement of many members of a family in making the decision for a minor, to participate in the research.

"To children, as I said before, there are maternal and paternal grandparents, uncle, aunt, such a whole family is also an effect". (CH2: Study doctor 2)

And that achieving consensus of both parents for their child to participate in research would ensure the child to remain in the research:

“So, usually when explaining, there should be the presence of both father and mother. It would be more effective. For example, if they both agree, and see that it is necessary for their child to do that, they would both go throughout the research” (CH2: Study doctor 3)

The statements above signify engagement in decision making which can be explained to some degree by Vietnamese culture. Vietnamese people are highly family oriented (Vuong et al. 1998; Galanti 2000) with a traditional patriarchal family structure (Centers for Disease Control and Prevention 2008). In the family, respect is placed in order, with the oldest person acting as a family spokesperson. Nowadays, there is a shift, as a result of acculturation and migration from extended families to nuclear families whereby decision-making can, in some cases, be kept within the spousal couple as they no longer feel bound by a responsibility to seek advice and consent from other family members (Galanti 2000). Whilst these two models are coexisting in the society, connectedness and consensus between family members is still deemed crucial and thus those I interviewed believed that the specific wishes of the family should be appreciated and followed.

In sum, interviews with family members and study staff about obtaining consent in REE research setting in Viet Nam suggest an involvement of not only parents but other family members in the decision making, and that involved authorities over

surrogate consent, though have been made explicit in law and relevant regulations, sometimes cannot be clearly defined in cultural practice.

5.1.4 Dual role, dual relationship

In Viet Nam, the relationship between study doctors or investigators and potential research participants is usually built on pre-existing relationship between medical staff and patients. Relationships between study staff and research participants/family members are built on the perceived duty of protection as physicians towards their patient. They also involve viewing patients as research participants. I will detail these two forms of relationships in what follows.

a) The perceived duty of protection

Interviews with patient and family member groups have revealed some of their impressions as follows:

“At that time, I was suffocated that I couldn’t bear. My body was stiff already, and had to be taken to the hospital immediately. I was awake only until 8 or 9 o’clock in the morning on the following day.... When I was taken to the hospital, the doctor took care of me so dedicatedly” (HTD: Patient 2).

“...I only remember doctors who directly did the work are Dr. T and Dr. Th. I have a very good impression with Dr. T....I like the way Dr. Th works the best....He gave very careful instructions like urinary catheter shouldn’t be left in for too long so that it can affect patient’s condition. That is very useful because, honestly, there are not many doctors and nurses telling us about this” (NHTD: Family member 1).

“I only believe in this hospital so I brought my child here” (CH2: Family member 2).

This describes the trust experienced by patients and family members about the caring and treatment given by staff in their role as medical staff and how it makes patients and family members decide to take part in the research.

My interviews with patients participating in REE research, furthermore, suggest that research participants might place their trust in ‘the doctor’ who would not harm them because ‘the doctors’ had treated them when they were in emergency situation, and because they were sick at that time:

“So when the doctor told me to think about the research, and that taking part or not is not important, I said to him “Yes, I take part”. When I was taken to the hospital, the doctor took care of me so dedicatedly” (HTD: Patient 2).

A father explained how he decided for his child to participate in the research:

“I heard the doctor talked like that so I supposed he knew about my child’s disease, he was also the person who took care of my child so I made my decision at random” (CH2: Family member 3).

In the role of a medical doctor, the investigator may have self- awareness of his inherent power, especially in emergency cases in REE research:

“When patients are brought to the emergency ward, doctors are considered to have supreme power” (CH2: Study doctor 2)

As well as their strengths when communicating with patients and family members:

“As the medical knowledge of our people is low, they usually trust the doctors and follow what is advised by the doctors” (CH2: IRB member 1)

And then responsibilities of medical staff become part of that of a study staff; that is to protect the ‘patients’ who are research participants.

“They are your patients. If you see any risk that may happen to them in research, but you still want to do that research, you’ll not be allowed to do it. That’s for sure” (HTD: Study doctor 1)

b) Relationship between study staff and research participants/family members as a ‘collaboration’ with perceived rights and responsibilities: collaboration at micro level

Collaboration from patients and family members is considered to be one of the important factors in obtaining consent and in doing research as a whole:

“If we want to obtain consent quickly, firstly that doctor has to have experience in obtaining consent. Secondly, there must be cooperation of patients. Those are the two important factors. Of course, we also need time” (Local Principal Investigator 13).

Similarly, research participants and family members see research participation as a choice which they can make on the basis of what benefits they perceive to gain from research and their willingness to help researchers to do research, and thus there are certain rights and responsibilities perceived as collaborators in this relationship:

“Yes. I think, to ourselves, when we agree to participate, everytime they need us, we have to do our duty, that is to collaborate with them so that their programme can’t be discontinued because this will cause them impediment. In general, when they need us, we have to collaborate” (HTD: Patient 1)

“Interviewer: Do they provide you with any report of the research’s result after its completion?”

FM1: I haven’t got report from the hospital since then.

Interviewer: In your opinion, do you want to be reported back the research’s result?

FM1: Of course yes. It’s great if there’s a report.

Interviewer: But what if there’s not?

FM1: Well...I think once you invite people in the research, you should send them a report” (HTD: Family member 1).

“A good research is first to inform patients before being done, and second, to inform some result to family members after the research being completed. So that is a good research” (HTD: Family member 4).

As expressed in the extracts above, some participants believe there are certain rights and responsibilities in research, for example, the right to be informed of the research

before participating, the right to know the research's result, and accordingly, the general responsibility to collaborate with scientists in doing research.

In sum, what expressed in the interviews reflecting the dual relationship shows that these study staff are seen as medical staff doing research with expectations that research participants and family members place on them are both in the role of medical staff and scientists altogether. Demands placed upon study staff are accordingly various and conflated. They can be a requirement of a research report which is of one of the duties of researchers, or simply a commitment of duty to treat of a doctor, or even a greater number of responsibilities based on the assumption that research has to do good for patients.

“A: So for example, I have to say the fact that when doctors take part in a research, their role is not as usual. They become study doctors instead and their goal is the research.

B: Then they have more responsibilities....more responsibilities.

A: Do you think if they are study doctors, they will put the research goal higher than the benefits of patients?

B: No...I must say that it is for patients' benefits because, for example, I myself treat the patient, and if I want to enroll that patient into the research, I can't do it alone, but have to rely on the whole committee. The committee can't overlook wrong things” (HTD, Family member 4).

“In terms of ethics, it is...generally...I see them taking blood, testing...generally I think all those things they did eventually help me and help other people. After they finish the research, they should give patients a report. It's not necessary to give details of the whole research process because

patients may not understand, but it should report results, final result of that research, be it good or failure, something like that” (HTD: Patient 2).

Thus far, I have described how the relationship between study staff and patients/family members is an important factor that can influence the whole consent process, especially in the setting of research on REE when patients and family members often totally rely on ‘medical staff’ for the treatment and hold some expectations for research on REEs. Consent, in my research, appears to be based on multiple relationships established throughout the research. During this process, information is exchanged and discussed, with interaction between involved parties taking place, the dynamics of which would not only influence the consent process, but also affect other duties and commitments that may go beyond what is written down on the consent form. The following descriptive accounts of how patients and family members make decisions shed light on other factors that might play a role in shaping how the interaction between study staff and research participants/family members occur particularly in REE research.

5.1.5 How are decisions about research participation made?

From what I have presented above about the consent practice deliberated by interviewees working in the context of REEs in Viet Nam and other countries, it is apparent that deciding to take part in research is based on a variety of factors. Information provided by study staff about research and the relationship between study staff and research participants/family members are central yet not the only factors involved..

5.1.5.1 Making decision in connection with people:

The literature and regulations around consent tend to suggest that the decision of whether or not to participate in clinical research will be made upon information provided by investigators through discussions with investigators, potential research participants and family members if required or necessary. Drawing on the sections above describing how consent for research in REEs is obtained in practice, we can see that in Vietnam there is an involvement of many figures in the consent process and in making the decision. This involvement happens as a consequence of the medical-research environment, relevant legal requirements and cultural norm. In this section, I will present a wider account of people who can be approached by the decision-maker for information about research participation and outline the reasons given for such a consultation to demonstrate a general pattern in making decision in the studied research context.

It appears that to those making a decision over research participation, consultation with study doctors and family members plays the most part in the consent process. To patients and family members, this comes out as a need for their understanding and assurance about components of the research:

“P1: Well...actually when I don't understand clearly about the research, I do have some concerns that if doing so can bear any effect on my health. But I think because they only told me to take such a little blood volume so....my mother also works in medicine, she told me that it should be fine so I think that was okay” (HTD: Patient 1).

“A: So you made the decision by yourself or did you think more about that and discuss with your family?”

B: Yes, I did ask my sisters, and they discussed with me.

A: Did they tell you something?

B: They said they didn't know too. Well...uhm...we didn't know what they would do. The doctor told me that there would not be any problem, they just simply took blood for testing and observed patients.

....

A: So when you decided for her to take part in the research, did you ask her opinions?

B: I did. My daughter said that she didn't know too, and what if they took much blood [laugh]. Well...she didn't know too" (HTD: Family member 3).

This type of consultation is not limited to immediate family. Instead, other groups of people are also sometimes involved. These include 'in-group' people who were in the same situation, specifically, people participating in the research or people staying in the hospital, and people whose knowledge of the topic and opinions are judged to be reliable by the person seeking advice.

"Interviewer: So the person who lied next to your daughter also participated in the research?

B: Yes. They did the same thing.

Interviewer: So did you talk or discuss about this research with them?

B: Yes, I did" (CH2: Family member 3).

"A: When he [the study doctor] asked me if I wanted to participate in the research, I called a friend of mine working in medicine, and my friend said that it was okay to participate". (NHTD: Patient 3)

Talking about the communication that might affect the decision of whether to participate in research or not, a study doctor raised a special situation particular to REE's that when her hospital had experienced multiple epidemics such as H5N1, H1N1 influenza, acute measles, and was loaded with a lot of patients admitted:

“...Or in the case of having multiple epidemics, lots of patients going to hospital, they can ask people around like “How is the research, how is the doctor when participating in that research?”. So that means they learn information from in-patients who participate in research. Then they will become much more trusting, and decide to participate” (NHTD: Study doctor 1).

and when patients were kept in the same insolation room:

“Firstly, isolation was a policy of Vietnam Government at that time, therefore, everyone must be kept in a hospital environment to be taken care, observed and was not allowed to communicate directly to family members or anyone outside. From that, there were something like... ah... our community was isolated, but the disease was not severe, so it turned out to be... funny [laugh]. When it was time to collect blood sample or doing throat swabs, we played a joke on each other” (HTD: Patient 3).

It appears that having a high number of cases in hospital during REEs may favor communication among people more than in other ‘normal’ disease settings. Through these communications familiarity and trust are formed, resulting in increased numbers

of patients and family members deciding to take part in the research. In the interview – illustrated in the extract below, a patient who participated in an H1N1 influenza study shared that she encouraged others to participate the research. This may help to explain somehow why people could build up more trust and decide to sign up for the research through communicating with other research participants as suggested above by the study doctor.

“Some students were reluctant deciding to take part in the research, but I told them that they should take part in the research so that doctors have a base to do research and diagnose. Then they all decided to take part in the research” (NHTD: Patient 2).

Another interview with an IRB member regarding the decision making of patients and family members in consultancy with others suggests that reading the research information leaflet carefully and discussing with other people before making the decision happens more with people in the North than those in the South:

“Well...the consenting here is like this...patients in the South would not have any question. They trust the doctors. But it's different here in the North in which people interpret each of the word in the information leaflet, and they even bring the leaflet back home, they ask other doctors, and this makes the matter to be misinterpreted and difficult to get their consent” (NHTD: IRB member 1)

It is unclear that by reading the information provided carefully and asking for more advice from medical experts means that Northern people are less trusting of the study staff there, but this generally suggests a need for other sources of information beyond what is provided by study doctors.

5.1.5.2 Media:

Media such as television, newspapers and Internet are also mentioned as one of popular information channels that patients and family members lean on to make their decisions. Study staff acknowledged that patients and family members, especially in times of REE used media information to understand more about the disease and treatment used in the disease, whether experimental or routine.

“Nowadays, there are newspapers, Internet, media, and people will know when they read it. They may not fully understand about the disease, but when they read its treatment, they will know that this drug must be used” (HTD: Study doctor 1).

“Interviewer: Did other participants know it was a mild disease?”

P2: Yes. They also had information. Some information they knew via media. News about H1N1 was popular, so it was updated every day. Most of the patients stayed in the room, in the isolated area, and they were taken nose swab in the morning. Patients who did not join also had to do the same things” (HTD: Patient 3).

“I know the drug used in the research is also the one used in routine treatment, I’ve heard of it so I agree to participate in the research” (NHTD: Patient 4).

The impact of information provided by the media about REEs could be both positive and negative in aiding the decision making of patients and family members. People could be aware that it was a global health problem and thus they would want to do something to improve global health:

“My expectation is to find out better treatment so that the epidemic can be stopped, and if someone gets infected, they can get a better treatment... That is to help, not only ourselves but relatives and society. We do whatever we can to contribute to society” (HTD: Family member 1).

But people might get a false impression of the situation, added by an international expert in UK:

“...The issue with a pandemic is quite emotive so you could argue they're vulnerable because they think you know it's a greater importance than say if it was an asthma study because it's a global problem, it's in the newspapers, it must be very bad. You know if it's in the newspapers everyday therefore I should help which is great for recruitment numbers but again ethically you kind of think well are they, do they have a false impression of actually how bad the situation is and they're only taking part because they think it's actually worse than it is...” (Principal Investigator 2).

5.2 Concerns and challenges in obtaining consent

In the preceding section, I presented findings relating to the consent process in Viet Nam in general and in the setting of research on REE in particular. In this section, I

present stakeholders' perspectives and experiences with the current practice of consent with respect to their concerns and challenges raised in the field. On reflecting generally upon obtaining consent in Vietnamese research setting, one local principal investigator has commented:

“...I think most of the time, consent is not obtained in compliance with the spirit proposed for obtaining a consent. It means patients don't read it, it's not 100%, but at least 80% of patients don't read the research information leaflet. The first reason is, one objective reason is that they don't have time to read it. The second reason is that they are being confused at that time and thus they don't want to read it. And the third one is that some study doctors didn't want to give the leaflet for patients to read, they even didn't want to provide it, they said what if after the patients read it, they didn't want to participate in the research anymore. It did happen” (Local Principal Investigator 13)

This comment captures a general situation of consent process taking place in clinical research when it comes down to practice, to specific research settings, and to different cultures. In what follows, I will illustrate this entire picture of reality of consent as well as critiques to current principles which have been applied to consent.

5.2.1 Understanding and cultural perception of research

Level of understanding

Although population having fairly high rate of literacy level (93.4% as shown in Figure 2.3, Chapter 2), helping research subjects, family members or other relevant

people understand about research is seen as the most challenging task in clinical research. According to interviews with study doctors, most of patients and family members do not fully understand what is provided in the information leaflet. These types of information are even difficult to understand to people working in the medical field.

“I think, to Vietnamese people, they do not understand even when they read it. Even to us who are working in clinical field, sometimes we do not understand it fully. Even to us who are working in clinical field, sometimes we do not understand it fully. I think explaining verbally will be better, and then we ask them to sign. Otherwise, if you give them the sheet to read, some of them may not have time to read, others will become frightened after reading” (HTD: Study doctor 3).

An IRB member and a local study doctor shared that the process obtaining ‘informed consent’ is not familiar with Vietnamese people, and that there are concepts in research which are alien to Vietnamese people:

“Firstly, consent form, because we....generally speaking, our Vietnamese people are not familiar with obtaining consent in that way. Only until when foreigners come, the movement of consent becomes popular” (CH2: Study doctor 2).

“I think with current conditions, especially in countries similar like us, when the matter of awareness or education level of our country.....I won't say it

isn't high, but it can't be the same to that of developed countries. Because they....because...to many people, the word "research" is something far away, then putting forward the idea of voluntariness and involuntariness. To them, that is something that they can't fully understand. So I think that is difficult...very... very difficult" (NHTD: IRB member 2).

The unfamiliarity of study staff, patients and family members with 'research' and 'informed consent may become an impediment to the consent process in such a setting. Adding to the paternalism of Vietnamese medical culture, the lack of medical knowledge of people is stated to contribute to difficulties in obtaining consent:

"The medical knowledge of our people is low, so they usually trust doctors and follow whatever doctors say to them" (CH2: Study doctor 4).

Talking about ways how to explain to research participants and family members, interviewees have raised challenges in discussing the research as follows:

"Actually, talking with persons who are already known a little bit is easier, but to farmers, they don't know anything, they think whatever we do would harm them. To intellectual people who understand about research, we would explain about how the research would be conducted, and they easily agree to take part. Normally, with farmers, it would take up more time talking with them carefully, and we have to...have to...give them time so that they can understand and share their opinions" (NHTD: Study doctor 1).

The quote above is from a doctor who shared her experience in obtaining consent from clinical studies, where 80% of participants were farmers. Explaining terminologies and concepts in research is a challenge to study staff, for example what are ‘randomized’, ‘open or blind research’, and other medical procedures involved. When these concepts are imported from a different country with a different culture and backgrounds, this job is even more difficult and requires integration with local culture and explanation appropriate to the educational level of research population. Difficulties in translating foreign research concepts into local language are given more attention in research on H1N1 influenza studies when the majority of infected patients were farmers living in rural areas, who were judged as “don’t know or don’t know much about their disease, and their social knowledge is not good enough”. Translation of the information leaflet is generally judged by local IRB members as wordy and confusing including words that are not inappropriate to the culture. Said a local IRB member:

“Consent form as regulated in developed countries is written in detail, but sometimes it is not appropriate to the local culture of a country. Say, for example, in SEA001 [an influenza study], in the consent, they say “2 tablespoons of blood”....”we need two tablespoons of blood” or something. In Viet Nam, when people imagine of the tablespoon, they got panic-stricken. If you convert it into ml, Vietnamese people can understand” (NHTD: IRB member 1).

I wouldn’t use the phrase ‘low education’ here to label this group, and instead, I use an extract from an interview with a study doctor above in which she describes this

group as such: “don’t know or don’t know much about their disease, and their social knowledge is not good enough”. Another reason for this is that it appears from the data that there is not a clear classification between low education and high education groups of people. The group which is said to be ‘knowledgeable people’ is described as knowing about medicine or certain parts of research, ‘being knowledgeable’ or ‘intellectual’. This suggests a group of people who have certain knowledge of medicine, research and of other social areas. As a result, if ‘education level’ which is usually used as a typical scale of schooling, and those who may have high education on that rank but not know anything about a particular disease or research may not be out of the list of ‘knowledgeable’ as described. Talking about differences among these groups of people, a study doctor has given out a classification of ‘grassroots’, ‘seem to be knowledgeable’ and ‘know things deeper’ as follows, and these are not based on a typical educational levelling scale:

“When there are things which make people worried, to the grassroots especially, they will become so worried and frightened. They do whatever we tell them to, and it is easier. They will participate in research. No matter in what way the doctor may say, they will participate. But for some people who show to be intellectual, it would be quite difficult. However, that sort of people is the one that may give consent to research. To those, who also show to be intellectual, but don’t really have knowledge, they won’t participate in research. They seem to be knowledgeable, but they don’t participate because they do know things but do not know them thoroughly. Or maybe the doctor doesn’t explain clearly enough or explain but their understanding level is just that so they can only think that we are taking their children to do research.

They have knowledge, they do know certain parts, however in terms of research, they do not know the good side of research; that is to help this thing or that thing, and there must be research to improve the treatment. It is so difficult to deal with those people. To those who know things deeper, they agree to participate in research” (HTD: Study doctor 1).

This raises an important implication: in order to understand a research, specific knowledge about the research seems to be not enough. Instead it also requires a link with general knowledge about research, e.g. its good in overall to advances in medicine. I will discuss this in more details in the discussion section with regard to current guidelines around consent and how it matters in the setting of research on REEs in which information about the disease, available treatment and research activities is limited.

Another element that is reported to possibly constrain the understanding of patients and family members about research is their disease and emotional state. Infected patients were or thought they were in severe, life threatening condition, and family members might be emotionally fragile knowing their children get infected. In such conditions, some investigators argued that making patients or family members fully understand all information about research and therefore to make an informed decision on research participation is unrealistic:

“And when you’re asking the wife of a farmer from Sa Dec....her husband is in the intensive care unit on a ventilator and you’re asking her about blood sample schedules, we might test some genetics of your husband, we’ll study the virus, we’re going to study his immune response and that you know we

might ship some samples overseas and if it's a clinical study we might also you know collect lots of clinical data and might even randomize him to different treatment. Now the idea that you can convey that information in 3 hours or even 3 days is silly, I don't believe you can, you really genuinely get fully informed consent for complex protocols for a disease, for people who are in some of the most stressful situations of their life, it's not real" (Principal Investigator 8, Expatriate).

Recruitment in research on REEs was therefore easier than in a normal disease setting because most of patients and family members would adhere to doctors' advice:

"Interviewer: Yes. How about in emerging pandemic? For example: H1, H5 and SARS, etc. Is it easier to get consent than in normal disease?"

B: Very easy. Very easy. Why? Because it is severe and life-threatening. At that time, their life is very important to them. They do not care much about how we do it" (HTD: Study doctor 3).

"Interviewer: So when you decided to take part in the research, did you think of anything?"

B: I was so sick at that time so just go with the flow. I wouldn't know.

Interviewer: Were you afraid that they would do anything else besides....?[B interrupted]

B: Regarding that, I didn't think about anything at that time because I could be awake at the time. If I died, I had died. I had fainted away.

Interviewer: Uhm...so you thought that just leave everything to doctors' decision?"

B: Uhm, it's up to them. They do whatever they want" (HTD: Patient 2).

Patients and family members who are in this situation are seen as "vulnerable" when participating in research is supposed to be their only hope for treatment. In that situation, risks and benefits involved in the research might not be fully assessed in their consideration:

"B: Actually there are things, for example, we say that patients have to sign consent for their research participation which we didn't pay attention previously. The second thing is that after going through that training, we begin to pay more attention to a group called vulnerable, for instance, low literacy people. In the past, we equated them, we explained the same to everyone. Later, we pay more attention to that group.

Interviewer: So in your opinion, patients or family members participating in research on REEs, are they vulnerable?

B: They are vulnerable. They can't have any choice because those are emergency epidemics, and for some of which there is not any cure. So that is their only hope, and they easily agree to take part in the research. Usually they can't anticipate all of the risks and benefits in participating in the research" (NHTD: Study doctor 1).

In assessing of the capacity to give consent of patients and family members under the situation of pandemic influenza, an international investigator in UK has shared the same opinions about their state of being emotively "vulnerable":

“Yeah definitely you know they’re, so the patients may just feel terrible, and you know perhaps are more willing to sign something because they’re feeling sick or equally they may not want to do anything because they’re feeling dreadful, it can work both ways. The issue with a pandemic is quite emotive so you could argue they’re vulnerable because they think you know it’s a greater importance than say if it was an asthma study because it’s a global problem, it’s in the newspapers, it must be very bad. You know if it’s in the newspapers everyday therefore I should help which is great for recruitment numbers but again ethically you kind of think well are they, do they have a false impression of actually how bad the situation is and they’re only taking part because they think it’s actually worse than it is” (Principal Investigator 2).

Negative pre-conceived notions about ‘research’:

In addition to practical issues around understanding and the quality of the information provided, a distinctive problem in the Vietnamese setting is the perception of the word ‘research’. Coupled with difficulties in understanding the content of research, negative pre-conceived notions to research is stated to block and mislead the understanding about the research in discussion. First of all, there is a feeling of being treated as a ‘Guinea Pig’ for research:

“They are so scared of the word ‘research’. Actually, in most of those cases, we didn’t give any therapeutic intervention, but when we said “You have symptoms ABC, and they match such a clinical research and that we are carrying out...”, so when they heard the word ‘research’, they have a feeling that they would be put into an experiment or something similar. So there is

almost none of the patients 100% agree to give their consent at the first time”
(NHTD: Study doctor 1).

“There are many people, family members’ psychology when they hear ‘research’, they are just so afraid of it. It’s just like making their children a Guinea Pig” (CH2: Study nurse 1).

Secondly, as has been seen above, taking part in a research is equated with taking a large volume of blood and having side effects from testing drug. And by having too much blood drawn, people might feel getting weakened due to the loss of nutritious source:

“...But generally, patients are always afraid of being taken blood. I don’t know if it’s different in Europe, but to our Asian perception, blood is considered as a nutritious source, a source for living, and thus taking blood will make them weaken. The more blood is taken, the scarier the patients are. So this is the matter of psychology in society, not of ethics or science”(Local Principal Investigator 11).

Perceiving that research does not bring any good them, even may cause some harm, in a new and quickly progressed epidemic like REEs, patients and family members were reported to tend to refuse to take part in a research on an REE:

“Study doctor 2: It is a novel disease, and it's an emergency epidemic. Firstly, it's novel, lethal, and many cases were of bad prognosis so patients were scared. And when they were scared of the disease, they were stuffed with the

word "research", do you think they were frightened?! So it is kind of psychological matter. It is that they're scared of severe disease, novel epidemic. That's it" (HTD: Study doctor 2).

Talking about an issue in which negative notions about research have passed to other patients in an isolation ward, a sponsor based at OUCRU admitted that it created more challenges to obtaining consent from potential participants and how it would badly affect the understanding of patients and research participants about research:

“R: Who was contained with H1N1 at HTD and was invited to participate in the study and said no and then told everybody else to say no, patients who were on the study started thinking oh my God what do they mean, what are they doing here, what are they doing with that and started to create these problems in the hospital so that containment situation also created a lot of challenges with the ethics because we had patients who were vocally opposing the research in ways that were totally uninformed” (Study Sponsor 1, Expatriate).

Deciding to be in research also begets a complex of being seen in poverty in Vietnamese Northern culture:

“In terms of culture, I don't know how about in the South, but in the North, people always think, I learn this when I do lots of research and act as a consultant, that is when we say the word 'research' to patients, they always have a feeling of complex that...that...they are not hungry to have to bring...I

mean having to accept to be enrolled in a research to earn a small sum of money....People think that only the poor need to accept to take part in the research to earn some money” (NHTD: IRB member 1).

The complex of poverty was, however, not raised in any interview conducted with people in the South of Viet Nam.

5.2.2 Volume of information:

In this section, I would present practical issues raised by study staff in informing potential research participants and family members of a clinical research and how these issues correspond with findings from the patients and family member groups.

5.2.2.1 Avoiding the word ‘research’

Negative notions about clinical research preconceived by potential research subjects and family members as mentioned above have influenced ways in which study staff choose how to communicate. The first common way reported by study staff based in hospitals in the South of Viet Nam is that they use the word ‘research’⁹ – translated as “nghiên cứu” in Vietnamese, less frequently when introducing research information to prospective research participants and family members:

⁹ There is no single translation for the word 'research' in Vietnamese. The word “nghiên cứu” is usually used, but is equivalent to both 'research' and 'experiment' in English.

“Usually when we explain, we seldom use the word ‘nghiên cứu’. We only say that there is a survey programme to examine the child’s blood, and that’s it. We seldom say ‘research’ because our Vietnamese psychology, when they hear of ‘research’, they think of being a cobaye and get frightened. The word ‘research’ makes things sound so important that they don’t dare let their child to participate in the research. So I avoid the word ‘research’ but still explain by whom the research is conducted, what kind of supports are available in the research, and how we would do it. It is compulsory that we have to explain, however, there are some words in which it is just the way how we use them and it is not so important. Actually, we just respond to the psychology. They hear the word ‘research’ and get scared of it, so I avoid using it. But when I read the information for them, they read the information leaflet again and they also see the word ‘research’ in it. It is not that they don’t see the word, so it is not....[she left the sentence unfinished]” (CH2: Study doctor 1).

“The second way is....we can say it a noncommittal way; that is we don’t say it a “research”, we say “your child participate in this programme, that programme” instead. And so this...ah...this...may lead to different treatment, to do more tests and to be monitored more closely, and we will not tell about things after that”(HTD: Study doctor 1).

Although this is not in compliance with what is stated in Good Clinical Practice, some study staff however did not find it unethical. As in the extract above and common shared by most of study staff across the two sites in the South, using a different word for ‘research’ is seen to be appropriate in conversation. The word ‘research’ is still in

the information leaflet. The research is still explained fully to research participants and family members, and thus people can see the word and have a proper understanding about the research. Another account is that if a clinical research is good for patients to participate, and if we want to conduct the research, we must get patients into research:

“It is unacceptable according to research principle....Those are the common ways to get consent and recruit patients into research. Those are the violation of ethics. But if we want to do research, we must have patients. Actually, in general, it’s good for patients, not bad for them. Doctors just do like that to have patients for the research. Outsiders looking at this will judge that this is a violation of ethics during the process of prospective research participants approach” (HTD: Study doctor 1).

And doctors see themselves as having better understanding about the disease and treatments and able to make judgements about what research is or is not in a patient’s interest:

“D1: I work for free for some studies in the hospital. But I think if it can help patients, I should do it. Doing research will help patients in the future. Some studies are good and beneficial to patients, some are not, and I don’t join in the latter.

Interviewer: When you say the studies are good, in what aspect are they good?

D1: It is beneficial in terms of treatment. Secondly, it's beneficial to our knowledge and that we can help patients better. This is not an immediate benefit.

Interviewer: How about benefit in treatment, is it immediate or prospective?

D1: Both immediate and prospective. If it is a disease that we know clearly about, understand clearly about, we will be able to treat it easier in the future than at the moment when we are blind, we have to grope and provide treatment incorrectly. When we are clear about something, it is easier for us in providing treatments for patients. That's also a benefit for patients. Doctors are good then patients get benefits. If doctors are not good, how can patients get benefits? Is that right?" (HTD: Study doctor 1).

The necessity of conducting good research in the setting of REEs is seen to be significant with regard to the urgent needs of understanding about the nature of epidemics, diagnostics, medical treatment and direct benefits for research participants, which otherwise would not be available in the normal medical setting, especially in low resource countries like Viet Nam. Thinking about the need of a large sample size for an international research on epidemics, an IRB member has shared that if Viet Nam is invited to join such a large scale research group, but cannot get any sample of the disease for the sample pool, it would be a miss in having a chance to improve the treatment for Vietnamese afflicted population. This leads to tension between how to get patients into research for the sake of epidemic control and treatment and respecting the rights of research participants:

“First of all, ethics in epidemics is that finding out the best method to control and treat the disease would be on top of priority. The second principle, to other research, this principle is the first principle, but in epidemics, this second principle is put in parallel with the first principle as I’ve just talked; that is to protect the rights of research participants. In REEs, the rights of research participants can be affected, and this is a difficulty for the IRB to consider. How to affect them without violating ethics is not guided in anywhere. There is also not any guideline to allow us to induce or coerce people to collect enough sample size” (CH2: IRB member 2).

Another IRB member has also stressed the need to put the benefit of the majority of people higher than individual patients in case of an epidemic which is able to induce high mortality rate although there are uncertainties about what risks that may happen. The good for the majority of people, at the end, serves for individual patients as well:

“Actually...there is a general rule. What is that rule? Those difficulties will affect IRB’s decision. Sometimes the IRB is still reluctant to approve a study but finally it has to do so due to the pressure. IRB’s members feel uncomfortable and unsatisfactory but there are other reasons to consider. And so in this case, the IRB’s members will base its decision on, firstly, patients’ benefits and secondly the nature of the epidemic, be it dangerous or not. If the epidemic is lethal, sometimes we have to put patients’ benefit a bit lower for the majority of people. This is for the patients eventually. I wrote down 2 factors in the interview guide for you: 1) the patients’ benefit and 2) epidemic

control and prevention work; the IRB bases on these 2 factors to make the decision” (HTD: IRB member 2).

5.2.2.2 More information, more anxiety

Study staff and local IRB members reported that subjects and family members tended to be frightened when they were informed about clinical research. In some cases infected with REE, patients or family members are likely to refuse to participate in the research due to the severity of the disease, and that they wanted to get cured:

“Interviewer: So you think in those emergency epidemics, do they in any way affect psychology of parents of children when they make the decision to let their child be enrolled in research?”

A: Yes of course. For example, in epidemic which has high mortality rate, say H5N1. Patients are in emergency room, you ask them to take part in a research, they don’t agree, and they say: “My child comes within an inch of his/her life”. It does affect, very much. It is a determinant factor. If their child’s illness is very severe, there is very likely that they don’t agree” (Local Principal Investigator 13).

An investigator in China also mentioned the disinterest of patients in participating in research when being in critical condition:

“So you have to talk to the relatives but some of the relatives they maybe a bit better educated you know so when you explain about the double dose versus single dose they will still accept randomisation or a trial. But many of them

would not be interested in being research patients in sort of critical illness. So they would just ask you why what's the best for the patient. So sometimes we encounter these problems" (Principal Investigator 10).

This decision may be linked to the fact that patients and family members held some negative notions about research and that research was of no value to them.

In other cases which are more general to other disease settings, knowing information about risks involved in the research makes patients and family members anxious.

Explained by a local study doctor:

"In my opinion, we should write but if we write too much, it looks quite scary. Even me, I feel scared when reading because there are too many risk factors: risks in throat swab collecting, risks in taking blood, risks in lumbar puncture, etc., so when family members read these, they get panic. Plus, they themselves are not medical staff. They get panic when reading so many of them withdraw from the research" (CH2: Study doctor 1).

"The more you explain, the more the patients become frightened. And they don't dare participate in the study. That is because we take too much blood for the study, and only this makes them scared already. That is not to mention other information. We, of course, give them the drug under investigation, so they're worried if there is any terrible side effect or not, and they're scared" (HTD: Study doctor 3).

Due to this reason, study staff reported that they have tried to strike a balance in the amount of research information provided so that people were not getting afraid, yet giving enough information to protect them from being exposed to a lawsuit though in fact lawsuit in medicine in Viet Nam is rare:

“We assure to summarize information to explain to patients shortly but still enough, without going into details. People don't have professional background so they get scared when listening to many details. Secondly, we have to tell them enough information, otherwise they will sue us if there's any problem in the future” (HTD: Study doctor 2).

5.2.2.3 Tension between providing information about research and the need to have patients for research

Difficulties about giving participants information become even more pronounced in the setting of the outbreaks of REEs due to pressures of time and resources and at the same time the duty to provide research participants and family members all necessary information.

“If I were in the position of being convinced by study staff, of course, before making the decision to participate in a research, I have to know its advantages and disadvantages so that I can make my decision. Because deciding to participate or not is my voluntariness, and if anything bad happens to me, I would be the one to suffer, so I have to know all necessary information” (CH2: Study doctor 3).

The duty to fully inform research participants, in this case, rests on the idea that the decision maker is the one responsible for and thus bear any consequence of his/her decision.

Study staff also acknowledge that by not explaining in full or using other words to replace, it may make it more difficult for research participants and family members to understand about the research:

“Uhm, if we use other words to replace which is different from this version, it can't be 100% accurate, the meaning would be diverged. But because we want to gain an ultimate purpose is that they accept to give consent, we have to change into words that are easy to listen to, easy to understand, and elusive. Strictly speaking, if we say so, they can't fully understand what we explain” (CH2: Study doctor 4).

And this means of explanation should not have been done as it is unfair for research participants and family members:

“Yes, there is a research being done out there. People...like....threaten...not really threaten, it is also a way of threatening, and inducing, all sorts of things. Of course, that is just a way that people use to talk, but in overall, on considering something which is....To be fair, that it shouldn't happen” (CH2: Study doctor 2).

In discussions with IRB members about the types of information that are considered necessary to be included in a research information leaflet, it is interesting to learn that

they find the types of information required in international research guidelines and practical conditions to be challenging. As an IRB member noted:

“Interviewer: From your view, as a study doctor and an IRB member, IRBs always want to put as much information as possible...

B: That’s right.

Interviewer: As much information as possible, but on the contrary....

B: I was in the same that contrary situation. When I act as an investigator, I am also hesitant with the current informed consent

Interviewer: I wonder that...because you have done research, you took consent, so now when you work in an IRB and review research protocol, do you find any conflict between many types of information regulated to be put in a research information leaflet for research participants, while, on the contrary, in practice, it is difficult to explain to patients so that they can understand all. That’s the first thing. The second thing is there is not much time as our doctors are already overloaded...

B: That is it. With respect to the job of an IRB in reviewing a project, we have to comply with its regulation. The matter of being able to do it or not is to make effort. Investigators have to try to make patients understand and agree to sign on the consent form. While being in the position of an IRB member, and not an investigator, we are required to comply with regulations in order to avoid unethical cases. It is compulsory if we don’t want to violate ethics” (CH2: IRB member 1).

“Interviewer: Ah, I understand. So for example, information in a consent form, in your opinion, do you find it too much for the understanding of a patient,

especially in a REE in which patients are confusing about information and treatment. With an information leaflet like this, do you think it is too much? Is it really useful?

H: I agree. If we apply exactly everything in an international consent form into Vietnamese context, I find it sometimes too much and lengthy. And sometimes it is because of those too many details, it makes people misunderstand” (NHTD: IRB member 1).

Interviews with IRB members have shown that they have recognized difficulties in explaining all types of information to research participants and family members. Even IRB members find it challenging to apply international and local guidelines to practical research practice. Study staff wish to avoid the misconception that research is sort of experiment from which participants would definitely experience bad consequences. The need to do good research on a REE in an international collaboration to find out more about the disease leads to pressure on study staff to get the research done and recruit patients. The fact that no guideline is available for practice in the setting has resulted in investigators and IRBs finding different ways to handle the issues basing on what they have known about the situation and what they think is right for it.

5.2.3 Persuasion

The role of persuasion has been widely argued in informed consent. It is accepted by many commentators that apart from the duty of providing information, health care provider should also persuade patients to accept medical care considered for their best interest (Aveyard 2004). This is based on the view that the health care provider is able

to give better assessment on different care options than the patient himself. Viewed it as a moral requirement for health care provider, Faden and Beauchamp argue:

“Frequently in clinical situations, professionals would be morally blameworthy if they did not attempt to persuade their patients to consent to interventions that are medically necessitated. Reasoned argument in defence of an option is itself information and as such is no less important in ensuring understanding than provision of acts” (Faden and Beauchamp 1986,pg.347)¹⁰

As generally described by my interviewees about consenting procedure in which persuading¹¹ becomes a crucial part. In explaining why study staff, besides providing information about research, had to persuade people to take part in the research, the main reason given was that people were confused or scared when hearing about research, therefore, persuading would help to make them understand that the research is good and not causing any harm to them. Persuasion is reported in my interviews to involve giving types of information that can contribute as a guarantee for research to be safely conducted such as approval from ethics committees and any immediate emergency aid when needed:

¹⁰ I shall not mention Faden and Beauchamp’s definition of persuasion here because my intention in this thesis is to explore what interviewees think about “persuasion” and practise it in the studied context.

¹¹ “Persuade” is used in this context as the overall meaning reflected from my respondents connotes changing a person's mind by what we say, or cause somebody to believe by what we say, not by what we show/facts/factual data as connoted in “convince”. “Convince” will be used in places where there is a clear indication of a need of factual data. (References: Merriam-Webster Dictionary of English Usage, “Convince or persuade: is there really a difference?” – Martin Shovel at CreativityWorks.net)

“B: We can say that, for example, this drug is being investigated. However, when a drug is approved to do research, it is usually okay in terms of medical ethics. It’s not that it can be used to do research easily. There is ethical committee, they approve, accept. That’s the first thing. We have to say this first.

Interviewer: OK.

B: Secondly, if there is something happens, we will solve it out right away.

Interviewer: OK.

B: For example, doctors will give emergency aid to get the patients out of critical condition, or the doctors change the drugs or stop prescribing the drugs. We will solve it right away; we won’t leave it lasts for a long time. We have to explain so that they can understand” (HTD: Study doctor 3).

Persuasion also involves correcting information that was misinterpreted by research participants or family members during their research participation so that they can remain in the research. As I have mentioned in section 5.2.2 about cases when negative notions about research is passed around isolation room, persuading and convincing by providing more information as needed is shown to stop the misinterpretation and make patients get better informed:

“R: Who was contained with H1N1 at HTD and was invited to participate in the study and said no and then told everybody else to say no, patients who were on the study started thinking oh my God what do they mean, what are they doing here, what are they doing with that and started to create these

problems in the hospital so that containment situation also created a lot of challenges with the ethics because we had patients who were vocally opposing the research in ways that were totally uninformed.

Interviewer: So in that situation did you have any solution, I mean you stopped recruitment and then did you explain anything more to patients?

R: We spoke to the patients who were already on the study and tried to balance the information that they had so that they were well informed. I think one or two of them did withdraw and others stayed on. We spoke to the patient but they weren't interested and they stopped recruitment" (Study Sponsor 1, Expatriate).

However, there are cases in which persuasion became problematic. First, there was the manipulation of information in which risks involved in research are withheld. As shared by a local study doctor:

"That means...there are some ways to make them accept. We can choose not to fully mention all aspects of the research. It takes so long to tell all about the research, a whole page, 1 page or even 2 pages. You give them to read but they don't read. In principle, you have to give them to read, then we have to explain in up to an hour. How we can have enough time for asking and explaining. That's it. That's not an easy job. Giving patients enough information is not easy. Secondly, we can choose to hide things that may be harmful. And the third way is to threaten people. Yes, that's the truth. It is unacceptable according to research principle, but sometimes we have to

threaten people because people always follow doctors' instructions when their life is in such situations" (HTD: Study Doctor 1).

In another case, a study doctor has shared that in research on REEs, it is the lack of information, particularly about nature of the diseases, medical therapies and outcome that makes gaining consent for research especially difficult. In these situations, the study doctor expressed that he has a feeling that he was coercing his patients/family members:

"The primary difficulty I think when doing research on REES in particular is that...that...most of them are new diseases, and thus their treatment is still controversial. As a result, giving patients a research consent form and asking them for their participation is sometimes like coercion towards them, rather than being voluntarily participate. Because, essentially, they, they don't know....we don't have information to provide them, information about previous studies and what we have known about the disease. It is simply that we ask them to participate in a research which even we themselves don't know which outcome the research can gain or which information can be yielded from it. So sometimes, I can't answer them all about risk factors or benefits from taking part in the research, especially research on newly emerged and emergency" (NHTD: Study doctor 2).

5.2.4 Lack of information

Not only making study doctors felt that they were bordering on coercion in persuading patients and family members to take part in the research, the lack of

scientific information on the nature and specific treatment also presents other challenges to researchers in providing research information, and patients and family members when deciding to participate in the research. Comparing REEs with rare diseases and diseases with no known cure, a study doctor said:

“Ah...if it is a drug testing trial, I think we always must ask patients about it because actually, such REEs are not much different from situations of rare diseases and diseases having no drug for treatment. That means they don't have any other choice, and if we stop at that, the story has no much difference. What would be different here, comparing with disease having no known cure, is that: first of all, that disease is the one that has imposes an immediate big impact to the psychology of patients, secondly, investigators who deploy such research don't have enough time to prepare a protocol or they don't have specific knowledge to assess risks that may occur to research participants. So sometimes, we may miss or create loopholes that can affect patients. In other diseases that have no known cure, patients may be asked to choose taking drug or not, but they've already had time to know more about the diseases, and they are able to assess risks or mortality rate related. But to diseases that are completely new, sometimes even investigators, they are not aware of all effects or consequences of the drugs on patients, or they have no notion about the pathology, the nature of the diseases” (NHTD: Study doctor 2).

As indicated in the quote above, psychological factors imposed by the disease and the lack of information about anticipated risks that might be involved are characterized as fundamental to research on REEs. Along the same lines, an international researcher

based in Canada has shared his view about a basic difference between research on REEs and research on critically ill patients:

“I think there are two basic differences in pandemic research versus other research in critically ill patients. Issue number 1 is you don’t actually know the natural history of the disease, so when you’re entering them into a trial you don’t know if their mortality risk is 5% or 95% and so that’s, you can’t really fill them in on a lot of what you would anticipate how the course of the disease might change because you don’t actually know the course of the disease yet”
(Principal Investigator 6).

On the basis of uncertainties about risks to research participants, the nature and progression of the disease, and available treatments, asking patients and family members for their consent to be in such a research is emphasized by local study doctors as a significant important step, especially in drug testing trials which may bear higher risks, and as such, obtaining consent before enrolling them into the trials is supposed not to be overridden.

5.2.5 (Lack of) Availability of time

Securing a fair amount of time for obtaining consent, specifically to explain about the research, answer questions and leave them time to consider, is found challenging by study staff. In low resource countries like Viet Nam, this is an added burden to an already constrained medical setting. Predominant in medical services in Viet Nam are public hospitals ranging from commune health stations to district hospitals, provincial hospitals and central hospitals. Although having such well-organized healthcare

delivery, there exists a great imbalance between central level and provincial/district, commune levels. It was reported in September 2013 that there was an overload crisis in City's hospitals and that, until 2013, on average there were only 42 beds available for every 10,000 people (Hoang 2013). Specialized central hospitals with well-equipped healthcare facilities and better treatment provision were usually hit the hardest. Research work, consequently, oppresses routine intensified medical work. A local investigator has stated:

“Interviewer: So did the influenza pandemic make your work be more difficult or challenging?”

R8: Of course. First of all, there have been a lot of patients. Secondly, having many patients results in the increase of enrolled patients while the number of our study staff is fixed. There was time that number of patients in Ward D went up to 80 which doubled the usual number. They were all infected with influenza. Doctors and nurses have been put under the pressure of patients, pandemic, and being infected” (Local Principal Investigator 11)

Being overloaded with excessive cases of patients in an epidemic such as influenza pandemic as mentioned above has constrained the time available for obtaining consent. When study staff have to face both the lack of time and different attitudes of the person giving consent, a common response to the situation was to think about how to get patients' consent in a shorter time

“So you can see, that's the fact. Actually, they have to think of a way to get consent from patients within a comparatively shorter time. So you see, I think your research should, I mean should get the real data about how consent is

actually obtained in Viet Nam. Speaking frankly with you, there is 90%, well, it is quite too much, about 80% of cases in which doctors would interpret the research information for patients, patients agree and sign, and about 80% of patients don't read the information leaflet because even when we gave them to read, they said they were confused, their child was sick, they didn't read" (Local Principal Investigator 13).

In other extreme cases in which patients were difficult to deal with to get consent from, those cases would be skipped:

"That is what I mean, regarding obtaining consent, that is how it is. If patients are difficult, they skip. I don't know if it would affect the quality of research or not. But that is it. I think that's the common situation. Everyone would do the same thing. If patients are difficult, in the end, they wouldn't agree to participate anyway, so the doctors just skip them" (Local Principal Investigator 13).

The matter of time for patient recruitment is perhaps a unique feature of research in REEs when the progression of the epidemic is unpredictable or may actually be of very short duration. There is a need to enroll patients rapidly before the epidemic disappears in order to answer research questions and prepare for any future epidemics. Compared with other chronic diseases, in REEs, delay in patient recruitment may result in research being inconclusive and thus to waste all efforts and resources that have been made:

“In general, it's difficult because the epidemic doesn't last long, its duration is very quick, and it's gone in a twinkling. That's why when doing research, research implementers have to be very quick, people at research sites also have to become positive with our studies. That means when there is patient, we have to enrol immediately, we shouldn't drag out the work. For example, if we say "okay, I have enrolled 2 cases today. That's enough for today. If there are 5-10 more cases, though they are eligible to research, I wouldn't enrol them in", but actually, tomorrow, the epidemic might go, then nothing left for research. People at site also have to do research on epidemic positively in order to achieve good outcome. It's not like other normal diseases that we can drag the work out, like if we don't do it today, we can do it tomorrow, like dengue, it lasts all year round. If in H5, H1, SARS, we don't enroll patients immediately, how we can have enough patients to do research, right?!” (HTD: Study nurse 1).

5.2.6 Therapeutic misconception

The issue of therapeutic misconception is manifested in my interviews in several ways. First, it is the misconceptions from patients and family members that what was available in research might be better treatment and consenting to research was necessary for treatment provision. In REEs where diagnostic tests and intensive treatment are in huge demand, and may even exceed available supply, more intensive monitoring and post-discharge follow-up visits, for example, were raised by family members as benefits from participating in research, compared with routine treatment:

“It is good, that isolation was good and so was the follow up. Of course, that means they monitored his health status during the time since he was transferred to here until being discharged. They always monitored. The food regime is served according to patients’ need, and patients were isolated from outsiders, for example, visiting was made through phone call, of course they were totally isolated because that’s infectious diseases” (HTD: Family member 4).

“I was worried. There were only options at that time: live or die...so I was so worried. But I still decided for my son to participate. I would decide to participate anyway for, firstly, experiment, secondly, to see my son’s health status, and after one year, he can have follow-up tests. I want my son to participate to know more about the disease, for his health to get better” (NHTD: Family member2)

In responding to this misconception, some study staff suggested that such ‘benefits’ from research should be emphasized when disclosing information to patients and family members:

“Uhm...In my case, I also explain everything about the research for them, which means I emphasize more about what they can gain, what we can do for their child because they care about what we can do for their child and if it leaves any impact on their child or not. So we emphasize those things. Secondly, regarding disadvantages of the research, I aslo have to mention briefly those for them. So with the same way talking, I mean during our

conversation, if we emphasize more about what they can benefit, in terms of psychology, when they can see benefits outweighing, harms are there too, but not much, usually, they would be prone to giving their consent” (CH2: Study doctor 3)

In an interview with an investigator based in China, a similar concern was also raised. In his case, patients misperceived that one drug would be superior over the other, and consequently, chose to participate in a research on influenza:

“R: Well if the patient agreed to take part then we would certainly recruit the patient. So for example we also have the study comparing Peramivir versus Oseltamivir, so we were involved in an industry sponsored study a few years ago. So eventually we recruited a few patients, but that was relatively easy because they assumed the intravenous would be superior. So some people would try and agree to be randomised yeah. So sometimes it really depends on your point of view, when there is a lot of unknown, people tend not to take part. But when they have some maybe misconception that something would be better then they would try” (Principal Investigator 10).

Participating in research was mainly expected to have a good treatment and better outcome, as shared by a patient:

“I only want the doctor to do correctly to his commitment; that is to treat well. Treating well, adhering to the treatment schedule...Uhm...that I can be recovered. I don't need anything else. Everything has been written down very

clearly on that paper [He meant the Patient Information sheet of the research]”
(NHTD: Patient 1).

Research was also misperceived as being good and safe because it was done by the hospital and the government:

“Interviewer: For example, if the doctor said there would be a research in which they were going to test a new drug for HFMD against one that was used in routine treatment according to the Ministry of Health, would you agree for your child to take part in this type of research?

B: I think, whichever that the government and the hospital think it’s good, just do it. We are normal farmers, so whatever good and safe for my child’s health, the government and the hospital just do. And I would let my child to take part in” (CH2: Family member 2)

5.2.7 Conflict of duty

In the overlapping of the two roles as I have described above in section 5.1.4 on dual role, physician-researchers reported that this dual role could cause the conflict of duty and thus compromise the research. It was particularly raised with respect to the necessity of being impartial and the amount of time study doctors can spare for this process:

“If doctors based in the hospital do research, there will be some points like this. Firstly, doctors would receive salary and certain benefits from organization who hosts the research, and thus, they will have a tendency to

enroll their patients into the research as many as possible. Secondly, the second disadvantage is that the time they can give to patients and to research would be divided. So they might tell you that the work wouldn't be affected, but it would be in some ways that we don't know about. Thirdly, in my opinion, another bad thing about a medical doctor doing research at the same time is that they would tend to...ah...ah...what to call it? They wouldn't tend to...of course they have a tendency to make that research to have better information, however, due to some reasons, they would lose the objectiveness in carrying out that research" (NHTD: Study doctor 2).

"Uh...Actually I haven't seen it too difficult! But as I said, explaining to patients requires being objective. A doctor cum investigator, their explanation would be more or less affected by the research they are doing. As a result, it is best conducted by a third person, independent of the research"(NHTD: Study doctor 2).

In research on REEs, these concerns apparently become more pressing due to the need to do research quickly.

The duties of a physician-researcher are generally described by my interviewees as the combination of responsibilities. They include recruiting participants for targeted research sample size, protecting their patients and being accountable for those who have consented to participate in the research:

"This is very hard, sometimes it's very hard. If everything goes smoothly okay, everything is fine they are not, they do not argue with you. So without

issue, without arguing, what you do is fine. And if something goes wrong, it'd be a big issue so the researchers, they don't have to be responsible for that, they just...if they get the blood, it's done, they're just happy to do the stuff they want, they don't worry about family members or arguing with them, suing them" (Principal Investigator 12).

5.2.8 Media role

As I have outlined in the general description of the role of media in section 5.1.5 that it can serve as a useful additional source of information for prospective research participants and family members to help make their decision. However media was also raised as a concern because it may cause misunderstandings about research on a large scale and thus make research informing more difficult. As shared by a local study doctor:

"A: Media, oh God, it affects very much. Media is the most terrible thing in this life. Media carries a horrible power, something like killing people. If the media has a right direction...ones, who have a good mind doing the media, they would head for something good for community. Well, our scientists do lots of work, but each area has its own characteristics. We do the work behind, and the media show the face. Ones, who do the media, have a heart...the capability to change people's perception or the capability to provide information and the capability which...change a lot. The media is something like an appearance outside, and people always like the appearance. If they can do it well, it would be very good, if not, it's like killing people. It very much

affects to our research. For example, now, if they write an article talking nonsense about us, we can't even lift up our head.

Interviewer: For example, they might say that our research is doing wrong or something?

A: Uhm. For example, they write about nonsense, say, we are doing a clinical trial, they may write something like there are companies testing drugs in developing countries, something like that, that research would thus be stopped”(CH2: Study doctor 2).

Talking more about the effect of media upon patients, the study doctor went on citing an example in hand, foot, mouth disease epidemic that patients required what was posted in the newspapers although it did not pertain to their condition:

“Generally speaking, if newspapers post something, it would create something like a heatwave, and patients talk with us about the same thing and require exactly that one. For example, there was an article mentioning about successful blood purification, and so when there were very mild cases, but family members wanted to do the blood purification, and I got frustrated over it. How they can write in such a one-sided way like that!” (CH2: Study doctor 2).

5.3 Solutions suggested by stakeholders

In the previous section, I have explored issues and challenges associated with obtaining consent in the context of research in rapidly emerging epidemics. These have fallen into 8 categories related to understanding, volume of information, persuasion, lack of information, lack of time devoting to consent process, therapeutic

misconception, conflict of duty and media role. In this section, I will report on some of the practical solutions to these issues/challenges that were suggested by my interviewees.

Being asked to put forward solutions to resolve issues or make obtaining consent less challenging, study staff, IRB members and international experts with direct experience of the process have proposed 5 solutions:

5.3.1 Procedures:

5.3.1.1 Replacing the word ‘nghiên cứu’:

This solution has been proposed as a way to adapt to the cultural perception of Vietnamese patients and family members about ‘research’ when, as reported by most study staff and IRB members, people still hold negative pre-conceived notions if the word “nghiên cứu” is used and the concept of research itself is unfamiliar. Another reason given is that while the educational level of Vietnamese research participants is still low, using more familiar terms can allow people to become familiar with research activities and understand them in a good way; the aim of research is to create new knowledge for the improvement of healthcare and treatment, not to cause harm or exploit poor people. In the setting of REEs when there is no standard treatment, or no proven effective and safe treatment, there is a pressing need for research aimed at providing the evidence base to inform clinical decisions in a timely manner, and this requires participation of patients and/or healthy people in studies. In support of this solution it is suggested that study staff should understand the research, know its potential benefits and risks, and using simple terms to explain the research should encourage the participation of patients and family members (assuming that the research is believed to be ethically acceptable).

“As I said, we still keep exactly the word ‘nghiên cứu’, don’t we? Because it is a research. However, in practice, it should be implicitly understood because each country, each nationality, it can be used by... Vietnamese words are rich. We can use other words but still convey the same purpose of what we do. We find a way to approach patients and sometimes we have to use terminology to steer to another way so that patients...but what’s the important morality in the research? We have to understand that whichever way we talk, we shouldn’t affect patients. That’s the nature of researchers. You use this way or that way to encourage patients to take part in research which you think it’s good for patients is ethically acceptable with respect to our profession” (NHTD: Study nurse 2).

Some study doctors interviewed in the Northern site, contrarily, suggest that the word ‘nghiên cứu’ should be kept because research participants have the right to know that kind of information. Following from that, they chose to talk straightforwardly to research participants and family members about what would be done in the research even though it might take more time for research subjects and family members to understand, and this could slow down the progress of recruitment:

“Actually I find no problem with it because in the end, patients have the rights to know that information. So in any situation, even you can’t keep pace with recruitment rate, and if patients don’t agree to participate in the study, it is best that we don’t...we can’t implement that study. From my perspective, I think there is not any trouble with it. For the fact that they’re afraid of the word

‘research’, I myself think it is good for them because they understand....maybe they understand too well about research, and they can realize benefits from being in the research, and sometimes they risk their life. As a result, the fact that they understand, they understand too well or they don’t understand about research, from my viewpoint, it is not as important as providing them enough information and they decide. If they understand, they agree to participate, if they don’t they have a right to refuse, and all that is up to the amount of information which investigators provide to them” (NHTD: Study doctor 2).

“No, here I would, I use the word ‘research’. And it’s fine. I just say....in general, at the beginning we just talk with them straightforwardly about what we do, like “we have a research like this, you will have such benefits, risks, etc. We would explain all aspects of benefits and risks, then let them decide. Maybe there would be some inquiries from them afterwards, and we would explain more, consult more, we might say that this is a research, but it....you would be receive the same treatment as other normal patients, and other matters such as taking blood, if you don’t participate in the research, you will also have to do these tests, and generally, it’s not much different from their routine treatment. So almost everybody agrees, and most of them found no problem with it” (NHTD: Study doctor 3).

In their view, the fact that people are afraid of the word ‘research’ is sensible because it suggests that they understand that there exists research in which its risks may

threaten their life, and it is the duty of study staff to provide them enough information about the research for them to decide.

5.3.1.2 Greater flexibility with type of information presented

Based on factors including the availability of time, workload, the ability of understanding of listeners, it has been suggested that research information should be adjusted to the context and requirements of regulations. Summarizing key points relevant to each situation was thought to be sufficient for patients and family members and was suggested by study staff and several IRB members. In fact, this is already used in research practice, not only in Viet Nam, but other countries such as China and UK. A summary version which is written or verbally explained based on the main version is proposed by a local IRB member as follows:

“In practice, when we obtain consent, we can say “Excuse me, we have this long informed consent form (ICF), you please read it, we will have one version...”, or an investigator can explain to patients the ICF or basing on the summarized version, so “these are main parts that you need to read, supplemental parts also need to be read, but you can have them as reference” (CH2: IRB member 1).

Or we can exclude section describing about research method as suggested by an IRB member. In fact, he has suggested this to research partners in other countries.

“Actually, in the consent form, I myself wonder that, in some countries, they mention some parts such as method, research method I mean, but in other

countries including Viet Nam, this is not compulsory. For example, I am working on a research project, that partner said we had to put the information of research method in, I argued and said no. I said to them that it was not necessary because in my opinion, consent form only needs to be like this: explaining work that we would do, benefits and disadvantages, and information of method is not compulsory. But they still force to put that information in. So I see there's difference in perception. That's an example. Of course, each country, each region has slightly different perception from each other" (NHTD: IRB member 1).

The consenting process in which participants would be informed about the main points of the research, then depending on the situation, further information would be provided, is confirmed to be a pragmatic approach by an international expert in UK:

"Yes to me I think if you're an ethical researcher if you follow good ethics and I, my approach to obtaining consent is that concise summary in a few minutes, a chat basically the opportunity for them to ask you questions based on what you've told them and then the additional opportunity for me to go away and then come back if they want more time to read the consent form in full. In my experience the majority of people will say no I don't need to read the patient information leaflet in full. I would then go through with the consent form and read out every single line on the consent form because I think that's very important. And if there was anything in the patient information leaflet that I thought was really important and had to be highlighted I would circle it on the patient information leaflet and say, and show it them in writing. So I think

you just have to have that, you know it's a very pragmatic approach to obtaining consent" (Principal Investigator 2).

What is shared in the consent practices in Viet Nam and UK or possibly elsewhere in this case is that there is always a judgement of study doctors in how much research information should be imparted to potential research participants and family members in particular circumstances. Fully informing participants about all aspects of the research appears to be not a common approach chosen by the study doctors interviewed.

5.3.1.3 Not providing patients and family members a copy of research information leaflet

Proposed as a way in order to avoid misinterpretations caused by patients or family members not understanding the information provided in a research information leaflet, study staff said it might be better if patients and family members were not given a copy of the research information leaflet. Taking an example of a state funded research which she was working on, a similar way is suggested to be applied whereby there was research information leaflet for family members to read and consent form to sign, but a copy of these would not be given to them:

"I think there are some studies that I have worked on, studies on HFMD at state level. There is consent form too, but after it is signed by family members, we don't give them a copy to keep. There is only one form, and we will of course give them to read, not that we won't give them for their further reading. After they sign to consent, we will get their signature, and family members

will hand that signed form back to us so that we can file it in study files as a proof' (CH2: Study doctor 1).

This idea might be explained from the routine medical procedure in Viet Nam. There is a standard consent form issued by the Ministry of Health for medical interventions (refer to Appendix 3). The main content of this consent form is an indication of an agreement of patients or family members for doctors to conduct necessary interventions for treatment, and that the risks have been verbally explained by the doctors. Following from this form, other types of information about the intervention such as risks, benefits, complications, etc. which are not listed on the form are verbally explained to the patients or family members. Patients or family members are not given a copy of the form. Another example of this application into research is the consent form designed for an influenza study as shown in Appendix 2. This form had been used by the hospital before an official version including a research information leaflet and consent form approved by international and local IRBs for the use of all research sites involved. Its information is quite simple and similar to that of medical practice. So this proposal seems to be understandable if we look at the general culture of obtaining consent in the medical setting in Viet Nam.

This solution however is not agreed by all study staff, and there is a view based on the duty to protect that research participants and family members should have an objective source of information for their reference and proper understanding about a research. Verbally informing is seen as subjective, and the information might be distorted:

“It is not to protect us, but to protect our patients because even having the same persuasive method, it may turn out to be different. For example, I can say that there is this programme [she meant the research] and that we may support the fact that there shouldn’t be this kind of information in the leaflet...It means we try to avoid sensitive words or over...something, but it can’t mean we can be crooked to cheat them. Saying we would verbally inform patients and don’t let them keep a copy of the information leaflet sounds to be a kind of cheating to me because when you say things, you have many different ways to communicate, like, for something which is really good, don’t you? But in fact, it is not like that in its nature. What put on a paper is something which is fairly objective than words from your mouth. For example, I am kind of a charismatic person so I can persuade anybody to do what I say, they say OK to everything I say, but when they come home, reading the information, they may find out what has been told is not exactly to what is written on the paper or they may find out the risks involved are more than what we told them, they would come back, return the paper and refuse to participate. So we have to accept that. Talking and convincing is a capability of each person, and if you give a person who is good at convincing to talk with people, it is like a kind of cheating, a kind of that”(CH2: Study doctor 2).

5.3.2 Researchers who are delegated to obtain consent:

5.3.2.1 Researchers competent for obtaining consent:

A mutual understanding and trust between study staff and patients or family members is judged to be significant in obtaining consent. Because of the complexity of research information and variations in the level of understanding and experience of persons

who give consent, study doctors are supposed to understand the people they approach and establish trust with them.

“Research participants and researchers have to have the trust or mutual understanding. Secondly, researchers have to understand the level of understanding of participants to explain to them, otherwise a normal person alone would find the research information leaflet panic-stricken” (CH2: IRB member 1).

In this manner, researchers are supposed to possess specific attributes including having a thorough grasp of their subject, knowledge of psychology and sociology, and sensitivity to cultural aspects.

“So there is only one solution that I think feasible is that there must be an investigator team very good at professional knowledge, psychological and social knowledge” (NHTD: IRB member 2).

“A: So we have to draw experience by doing this way: the consultant [he meant study doctor who obtains consent] must be enthusiastic, open, knowledgeable, having communication skills, consulting skills, yes we send people to learn consulting skills too.

Interviewer: So knowledge you mean here is knowledge of medicine, of research, etc.?

A: Medicine and society. Must include social aspect. Both knowledge of medicine and society” (NHTD: IRB member 1).

5.3.2.2 An independent party to obtain consent

As mentioned in the section on conflict of duty, partiality in obtaining consent is a matter of concern for study doctors. To have a person working independently of the research responsible for obtaining consent has been suggested as a solution for this problem:

“Uh...Actually I haven't seen it too difficult! But as I said, explaining to patients requires being objective. A doctor cum investigator, their explanation would be more or less affected by the research they are doing. As a result, it is best conducted by a third person, independent of the research”(NHTD: Study doctor 2).

Having a person who is independent of the physician-patient relationship to obtain consent is similarly recommended in the Declaration of Helsinki 2013 in situations when there is a dependent relationship between research participants and physician-researcher and consent might be accordingly given under duress (Section 27, DoH 2013).

However, in another discussion with a study doctor about the feasibility of this solution, she expressed a concern that this would be difficult as people might not trust a person not involved in their treatment:

“It is difficult! Because honestly, we are doctors and so they trust us. Now suddenly, there is a Mr. A coming in. Firstly, they don't know where he is coming from. That means it's the background of that independent party that makes people feel not believing. Even when we have an independent staff

here, there must be a doctor working in this hospital to introduce him/her to the patients, something like “Okay, this is Mr. A or Mr. B, etc.”. But in fact, we’ve never had such an independent person like this in our studies”(NHTD: Study doctor 1).

5.3.3 Review and overseeing mechanism:

5.3.3.1 IRBs to focus on protecting research participants

In view of the difficulties in making patients or family members fully understand about research in the setting of REE, an expatriate investigator working in Viet Nam in the interview has stated his view on the role of IRBs is particularly to ensure the wellbeing of patients:

“I think the ethical committees; their primary focus should be on the wellbeing of the patients and preventing harm. In the context of emerging diseases they will always feel under informed, that they don’t feel they know enough to make an informed decision about whether something is going to work or not. And I guess that’s the role of the IRB, important role of the IRB to protect the participant, you know people can say yes without understanding and that’s true anywhere globally you know people will participate in trials without truly understanding of what the trial is and that’s the important, the primary objective of the IRB is to protect the participant” (Principal Investigator 8, Expatriate).

5.3.3.2 An oversight team to remain a balance

Pointing out that strict compliance with the Good Clinical Practice guidelines is very challenging, particularly in the context of REE's, local study staff as well as IRB members raised a proposal for establishing an oversight mechanism for the consenting process. This should be operated in the principle of flexibility:

“But we should do in a way that, what matters is we should have an oversight so that they can't go too far to two extremes. For example, one extreme of carelessness: they don't say a word when family members come in like “This is how your child is, we should take his/her blood, that's it, you read this and sign on this for me”, then the person signs. So that's just too careless. The second extreme would be on the opposite: they give a mechanical response like “So this is your child's condition, but I have to say this first that this is a research, do you want to take part or not? If not, then it's fine. If yes, just sign on this”. Many study staff are like that, you know, and as a result, many people oppose and do not want to take part in the research. They just say “So your child, he/she is eligible for that research, would you want to let your child participate in the research? Research, I have to tell you about this first, that it's going to involve taking blood, each tube for each person”. Then, nobody would dare participate in the research” (Local Principal Investigator 13).

So there are two extremes that are suggested to avoid in consent process: 1) ill-informing to patients and family members, and 2) almost excessive information that only makes people scared, rather than understand about the research and feel a duty to help by their contribution.

5.3.4 Special regulation for patient recruitment in emergency epidemics

Doing research for the benefit of patients and public health is crucial and in the setting of REEs with high rates of mortality and morbidity, it is one of the top priorities. Because of the benefits it can bring to society, research on REEs sometimes requires flexibility:

“In the examples that I have mentioned, you can’t do it in normal situation, however, due to a special context like war, people may do research under the law of war, not the law in normal situation. For example, in war, 16 is the age for compulsory military service, isn’t it? In normal time, it is 18. Similarly, we have to base on the benefit of patients and epidemic control and prevention work to make the decision of approving a protocol or not. We are more relying on these because we lack of information about the epidemic and lack of everything in general. We have to base our decision on what is available. We have to put patients’ benefit on top and epidemic control and prevention work in order to prevent the epidemic quickly. And to do this effectively, we sometimes have to do a research at any expense” (HTD: IRB member 2).

In the same vein, another local IRB member based in a different hospital suggested there should be a specific regulation for research on REEs which is aimed at improving treatment. When there is an urgent need to have such research to be carried out and patients or family members are not willing to take part in the research the possibility of automatic enrollment was raised:

“But I still see it necessary. That’s why I said patients taking part in research on dangerous epidemics like H1N1 and SARS which caused mass of deaths, so to those situations, the Ministry of Health must have a clear regulation that patients who can’t be cured, after explaining to their family members, we can find some studies to enroll them to help improve treatment. For example, autopsy, when I know there is a regulation for autopsy, I can do it without any worry. It would be the same with research, if you do research in order to help other people, what sort of things are you allowed to do? Is there any regulation related to that? I have been learning many courses and haven’t heard anyone talk about such a rule. All I am taught is that if people don’t want to participate, you absolutely can’t force them. But in emergency case, can this force be applied? And when? I have no idea about this” (CH2: IRB member 2).

5.3.5 Public education

Along with those solutions listed above, educating the public about the nature of research and its necessity for the improvement and advance of science in medicine is proposed as a long term project to make people understand more about research and to encourage their participation. Specific aims that have been emphasized in this plan are 1) to change their negative attitude towards research, e.g. being a Guinea Pig; and 2) to let people have a better understanding of research, scientific methods in treatment and healthcare, and the role of research in support of medicine.

“Secondly, in a long term, we should enhance the propaganda, besides professional knowledge and healthcare. We should propagate through mass media about research aspects so that people know more about scientific

matters that support treatment course. Things are difficult until when they know that there would be no new technique, no new therapy without doing research, etc. And I don't think this can be done quickly" (NHTD: IRB member 2).

"Regarding to the public health education, we need to educate patients that they are not guinea pigs, and research is very necessary to find out new drugs as well as evidence to prove the effectiveness of a drug. If we don't do research, we can't never know about that drugs or new therapy. We need to let patients know about this as well as taking blood. This can only make treatment better. We have to try to persuade patients" (Local Principal Investigator 11).

5.4 Discussion

So far I have described the issues and challenges identified by my interviewees arising in the consent process of the REE research setting. I have also outlined possible solutions they propose to address the issues/challenges. In the following discussion of this chapter, I will present my own account of ethical issues derived from my evaluation between what has been learnt from the interviews and my overall view of actual situation¹².

¹² This is part of the critical examination of the respondents' ethical claims and arguments that I have outlined in the schematic analysis in Chapter 2 – Methodology, Section 2.3.2.

5.4.1 Issues upon reflection

Out of the issues and concerns raised by all the key stakeholders, there are three main issues that I found crucial for further deliberation on the practice of consent in this research context.

5.4.1.1 Vulnerability of research participants in research on REEs:

Circumstantial factors that might undermine the decision-making of research participants/family members in the context of research on REEs have been raised and discussed in several papers writing exclusively about this research context. As described in my literature review and this chapter, emotional distress, preoccupation about survival, power asymmetry between researchers and participants (Calain et al. 2009; Macklin and Cowan 2009; Ezeome and Simon 2010; Edwards 2013) are circumstantial factors that make research participants in REEs become vulnerable in a way that their deliberation and judgment might be impaired for consenting. These factors are consistent with my interviews. My research also shows that due to the incomplete understanding of research information, and the relationship between physician and patient which is long ground on the principle of beneficence and trust, research participants/family members in most cases rely on their physician-researchers' competence and good will to make their choice. In this manner, research participants and family members, to some extent, have relinquished their full autonomy to experts and as a result self-reliant and a fully informed decision is less likely to happen (Tauber 2003). While this type of vulnerability exist in normal research settings, it can become more complicated in the case of REEs with the combination of other factors that might influence the decision making of research participants. In his taxonomy of vulnerability, Kipnis has also pointed out deferential

patterns of behavior of patients towards their physicians, political and economic context of research setting as sources of vulnerability (Kipnis 2006). These sources appear in my interviews through the dual role of researchers based in hospitals or communities, the lack of access to good medical care, partial coverage of healthcare insurance and poverty of certain part of provincial population. Definitions of vulnerability provided in international guidelines in research ethics still contains ambiguities and confusion by their labelling approach; that is identifying individual or groups as vulnerable (Luna 2009). This has neglected people “who are vulnerable in ways not identified by current accounts” (Rogers 2006). Although not appearing in my research setting, such vulnerable circumstances as having unattended needs, limited access to effective treatment (Bayer and Fairchild 2004; Aultman 2013) should be considered in resource poor areas during REEs. In REEs, research participants and family members exposed to such sources of vulnerability seem not to be considered for addition protection while pregnant women and children who are necessary in research to establish the benefits of treatment for these groups are usually excluded just because they are listed as default as vulnerable groups, without full consideration.

5.4.1.2 Labelling issues as ‘cultural perceptions’ and being responsive to the perception of research participants and family members

A general pattern emerges that there is a responsiveness of researchers to misconceptions of research participants and family members about research benefits and their negative notions about research. This responsiveness is justified by my interviewees on the basis of several reasons. They include to meet the needs of research participants and family members motivated by their self-interest or the trend

of benefit and cost weighing in considering giving an aid (Dovidio et al. 1991), to adjust to difference in ‘cultural perception’, difficulties in understanding scientific concepts (Dawson and Kass 2005; Moodley et al. 2005; Marshall 2008; Appelbaum 2010), or low level of education. These result in suggestions and the actual replacement of the word ‘research’ reported in this research and other previous studies done in other low-income countries (Molyneux et al. 2004), using different explanations instead, and emphasizing the benefits provided in the research. However, these solutions would, in my view, become problematic in the long run because they may misguide people in their perception of research. Research may be perceived to bring direct benefits of health and even of others unrelated to health needs, for example, financial aid in exchange for their participation, or general health services which might be unavailable in the region. While considering participants’ perspectives, especially their costs and benefits once taking part in the research is encouraged (Patel et al. 2003), only focusing on personal needs and not correcting negative preconceived notions towards research can make people to become individualized and loosen their sense of duty to help. In the context of research, medical research is defined as “activity aimed at collecting knowledge in order to develop new methods of treatment, therefore, no promises about the superiority of an experimental therapy can be made to an individual participant” (Lötjönen 2002). If we are to agree on this definition, any benchmark calling for delineating potential for direct ‘benefits’ to research participants and communities from the conduct and result of research (Emanuel et al. 2000; Emanuel et al. 2004) should provide a clearly defined account of what should be included in the form of these benefits. The solution of public education about research should also be considered in addressing these issues.

5.4.1.3 Paternalistic approach based on the duty to protect and the trust to research

Responses in the interviews imply a paternalistic approach in the way that study staff and IRB members advocate flexibility in provision of research information to participants and family members. They, on the basis of their knowledge of how a research might be good for research participants and population and presumption that participants or family members with the lack of medical knowledge would hardly handle ambiguity and assess risks involved, show a disinclination to a full disclosure of all aspects of research. Incomplete understanding of given research information is common (Eyal 2011; Malik 2011; Naanyu et al. 2014) supporting the presumption that full disclosure would complicate the consent process. It might even make patients or family members ‘extremely distressed’ or ‘overload with too much information’ at the time of emergency life-threatening situation (Tobias and Souhami 1993). Nevertheless research participants and family members should be able to understand as much information as possible so that they can make an informed decision. Interviews with research participants, family members and researchers in my research show that in cases in which participants and family members understood that they participated in research, they clearly expressed their expectation to help future patients and the overall epidemic prevention from their research participation and showed their commitment to the research. This commitment involves a trust in study staff in carrying out research procedures for the benefits of patients and future afflicted population, and thus overcoming fears of risks that might occur. Applying the paternalistic approach therefore should be carefully considered in its application to bring out a desired outcome to both researchers and research participants and family members.

5.4.2 Emerging values

As in previous empirical chapters on International collaboration and Research ethics review, I have presented emerging values that are either implicitly or explicitly expressed by the interviewees. In this section, I am going to do something similar. That is to outline key values that are acknowledged and shared within specific groups or across all relevant interview groups over consent. The values shaped from their experiences of research involvement include:

5.4.2.1 “Good research” and the duty of protection:

The concept of “good research” is viewed by study staff and IRB members as including being able to bring some direct benefits for individual research participants such as free testing for diagnosis, financial aids in treatment and regular health check-ups. These benefits were said to be integral to the clinical studies on REEs that they worked on. These studies are in fact designed to improve diagnosis, treatment and epidemic control. At a population level, research on REEs should contribute to the knowledge of epidemic control and prevention which is of pressing need of all afflicted countries. The concept of what counts as “good research” here is perceived by stakeholders in its relation to patients and society at large. It is constituted by what perceived benefits research could bring to both individual patients and society. In this relationship between these two levels of beneficiaries, the sense of responsibility of protection perceived by study staff and IRB members appears as a key to limit any extreme in the two ends, which means leaving the rest at risk for the benefit of one end. The duty of protection in this studied setting is linked to clinical duty and research duty borne by the dual role of study staff. This duty is also confirmed in interviewees about the role of RECs/IRBs as one of important emerging values.

5.4.2.2 Trust

Trust is seen as central to the relationship between study staff and research participants/family members. “Trust”, as articulated by study staff, is established through the role of medical providers and by familiarity through communication. While possibly having negative preconceived notions or incomplete understanding about research, the trust research subjects and family members places on study staff guides their decision to participate. Participants and family members trust study staff and IRB members not to subject research subjects to harm, and only to allow research that would benefit participants. This important role of trust has been proven from interviews with research participants and family members. Not being subjected to harm in research is the most pressing concern of research participants and family members when deciding to take part in research. To them, the account of trust is, however, in most cases, extended to the trust of being received good medical advices and effective treatment.

5.4.2.3 Honesty in information provided and transparency

Being honest about information provided to research participants and family members is seen by study staffs as most important issue in informing participants about research. This is regarded not only a good quality of medical staff but an ethical and legal obligation. According to study staff and IRB members, honesty in information provision would maintain the trust and relationship between study staff and research participants/family members. Being honest in this context is suggested to be manifested through the accurate word we use to describe about research, e.g. the word “research” should be kept and exactly convey in verbal communication, through

discussing about what would be basically done in research including risks and benefits involved. This honesty here, however, does not equate with transparency. Transparency in obtaining consent, mentioned by study staff and research participants and family members indicates the idea of being frank and telling all about aspects of research, even uncertainties in therapeutic options available. While most study staff are in favour of being honest in their information provision, patients and family members express their preference for transparency from study staff, i.e. telling them clearly about all the choices available and what would be carried out as part of research with its risks and benefits so that they can have a careful consideration based on the information given.

5.4.2.4 Fairness in the interaction

Fairness in interaction between study doctors and research subjects/family members in obtaining consent is implied by study doctors as being free from influence related to the power of a physician over patients. In emergency situations or when there are many uncertainties in a particular research project, research subjects or family members might feel unequal in the relationship with their doctor, and consequently under pressure to make a particular choice. An equal partnership between study staff and research subjects/family members whereby both are out of influences of a usual relationship of physician/patients, and patients/family members can make their choice on the ground of a fair amount of information, is desired as a good consent practice.

On the whole, how the values are perceived plays an important role in forming relationships in relation to involved parties. Here in this context of consent practice it is the main relationship between study staff and research participants/family members

that these values continue to influence ways people view about their relationship, constitute their responses to things under consideration with their position of defence and bear upon each other's responsibilities. This process, then, serves as a reflection upon which the values are consolidated and new values are built.

5.5 Conclusion

In this chapter, I have presented a general description of consent practice with its focus on Vietnamese research setting and particularly in REEs and stakeholders' perspectives of concerns and challenges they have confronted during their research practice. Obtaining consent emerges a major challenge in the research practice of study doctors and one of the main concerns of IRB members who have direct or indirect experiences of consent practice. What stands out most from my interviews about consent include:

- Vietnamese people are reported to have negative attitude towards research. Interviews with local study staff including study doctors, study nurses and principal investigators and local IRB members show that research is perceived to bring harms or risks to patients, or at least patients would have to sacrifice something. Data from interviews with patients and family members, however, point to a different viewpoint in which most of them understand the value of research of achieving new knowledge and bringing certain benefits for the treatment of diseases, and they support the conduct or research. This contrast might result from the patients/family members I selected for interview, who were limited to people who have participated and mostly completed research, and were willing to come back to the hospital for the interview. This group seems to include people who have some commitment with the research and the

hospital where they received treatment. As a result, their positive attitude about research would be predominant in the interviews. Research on REEs whereby patients could gain perceived direct benefits such as specific diagnosis, better healthcare and free specific drugs for treatment, which otherwise hardly to access in normal overloaded medical setting in REEs.

- Providing full information about research is judged as not necessary to help patients and family members have a proper understanding about research. Contrarily, it is supposed to complicate the process especially when people are in critical conditions and/or stressful situations. There are challenges with how and how much information of a specific research project should be provided and explained to research participants and family members. Data from international experts also confirm these challenges in their consent practices.
- The influence of the researcher's status as a medical doctor in influencing the decision of to participate has been mentioned in previous empirical studies (Nelson and Merz 2002). Data from this study have illustrated how this dual role can define the relationship between research participants and researchers and influence in the way both parties perceive their positions and responsibilities related. These as a whole shape the interaction between the two and produce an influence on the decision making of people to participate in a research. There is a transition of paternalistic style in Vietnamese medical setting to research setting in which study staff presumed that participants or family members would be unable to fully appreciate risks involved. Providing as much detailed information about research as regulated in international and local guidelines are consequently considered to be unnecessary. "Trust" holds a decisive role in the consent practice of this way.

- Study staff, in providing research information, tend to respond to misperceived research benefits of participants and family members to persuade people to take part in research.
- Key values emerging in consent practice include: good research, honesty in information provided, transparency (on the side of research participants and family members), protection of patients, fairness in the interaction. These values are expressed as a combination of both local cultural embedment and acculturation, a result of an international collaboration in research. The values are variously balanced in the relationship between relevant stakeholders involved, and this is reflected through their perceptions about research, consent practice, and the dual relationship between a physician-study doctor and a patient-research participant or family member.

Chapter 6 DISCUSSION CHAPTER

6.1 Introduction

The research question with which I began this thesis was what is considered as ethical research conduct in the setting of REEs. In order to answer this question I conducted interviews with researchers, health professionals, ethics committee members, family members and patients with personal experience of research participation in the context of REEs in Viet Nam. I also interviewed international experts with experience of research in epidemics and collaboration with Vietnamese institutions. In chapters 3, 4 and 5 I have presented the findings of my empirical research under three headings: research collaborations (macro level); research ethics review (meso level) and researcher-patient relations/consent (micro level). In each chapter I have outlined the key important ethical challenges, the solutions to these challenges proposed by my interviewees, and I have also highlighted some of the emerging values in the analysis of the data. In this final chapter, I will present a general conclusion on the construction of ethical problems and several conclusions drawn from a summary of the main findings of this thesis. Based upon these conclusions, I will discuss further, appealing to relevant normative debates and ethical principles/moral values and propose an account of solutions to address the ethical problems identified. Finally, I will highlight possible limitations to the thesis, key contributions of this thesis to our understanding of the ethics of research in rapidly emerging epidemics and areas of future research.

So far, my empirical data suggest two main conclusions. The first is that in relation to the construction of ethical problems of stakeholders, the issues and types of considerations and their relative importance were raised and valued differently between key stakeholder groups due to their role and experience in research

participation. Overall, these issues were similar to those in other health related research; however some aspects were unique to the setting of REEs. The second conclusion includes three key general conclusions specific to the three main themes emerged as important areas for key stakeholders participating in research on REEs: consent, research ethics review and international research collaboration.

I subsequently developed ethically relevant potential solutions for the problems identified. These solutions are structured around three broad tasks:

- 1) Establishing and strengthening research collaboration on the basis of familiarity, trust, reliance and open involvement for the good of global health
- 2) Enhancing the research review process and research oversight of research ethics committees
- 3) Improving the consent process in research in rapidly emerging epidemics based on the duty to protect research participants and develop prosocial behavior.

Before going into details I want to first of all will give a general reflection upon the whole research process that I have implemented in my research and describe elements that might influence the data collection and my interpretation of the data.

6.2 Reflexivity

Reflexivity, as defined by Finlay is a process of thoughtful, conscious, self-awareness, in the form of ‘disciplined self-reflection’(Finlay 2002), and is an important aspect in qualitative research. Manifesting itself through a process of self-critical interrogation of the researcher’s role in her research process and an acknowledgement of how it impacts on the research and knowledge claims drawn from the data, reflexivity in this way increases the credibility in qualitative research (Finlay and Gough 2003;

Horsburgh 2003; Cohen and Crabtree 2008). In an empirical ethics research project, being reflexive to ethical components embedded is also crucial. Reflexivity in bioethics has been called for and largely discussed in what so called reflexivity in 'philosophical bioethics'(Ives and Dunn 2010) and 'critical bioethics' (Hedgecoe 2004). Drawing on the need to produce more defensible moral arguments and the acknowledgement of unavoidable *social embeddedness* of moral philosophy in which morality and moral argument is believed to be embedded and embodied in the *person* (Rachels 1997; Nietzsche 1998; Ives and Dunn 2010), being reflexive in bioethics is required to manage the inevitable subjectivity of the process of ethical analysis and to reveal potential bias and conflicts of interests in public and political engagement (Ives and Dunn 2010). In other words, what makes reflexivity in bioethics distinct from that of a pure qualitative research is that in addition to reflecting carefully on her position and the assumptions she brings to her interviews and analysis in the sense relevant to qualitative research more generally, the researcher also has to manage her intuitions, make explicit how her experiences and theoretical knowledge shape the analysis interwoven moral elements such as values, arguments, and how her moral arguments are constructed. Within the scope of this present research which combines both qualitative methods and ethical analysis, I have drawn on the common elements of reflexivity proposed for both qualitative research and bioethics.

I have presented in Chapter 2 - Methodology the need for acknowledgement and reflection on preconceptions that may influence or bias the study, and expressed how my experience and my knowledge of literature has shaped the research question and

influenced the research with respect to the adoption of research strategy and interpretation of data¹³. In the empirical chapters, I have explicitly woven my narratives of experience of research sites and relevant knowledge drawn from the literature of relevance in the interpretation of the data. In this section, I will focus on outlining and reflecting upon a number of reflexive concerns over the entire research process.

My background as an academic lawyer and a clinical coordinator at OUCRU has given me an understanding of the setting where my study was conducted. While trying to keep research questions open to catch diverse perspectives of respondents, it is impossible to subscribe to absolute neutrality during the whole research process. There are conferred advantages for the data collection and analysis from pre-existing relationships - notably the fellowship I felt in inviting and doing the interviews with the majority of respondents who I used to work with or knew them through my work or just simply because they are also Vietnamese. It allows me to ask questions, prompt to further topics, especially sensitive ones and discuss them in deeper level including challenging their reasons for the richness of data and well-thought arguments. Similarly, data analysis is facilitated by my shared culture, understanding and experience of the context and problems in discussion. However, on the other hand, there are reflexive concerns upon the research process. First of all, it is important to reflect on my position. In the interviews, there were times when

¹³This is expressed through sharing my own experiences of the research context where appropriate in relation to the interpretation of data including providing explanation for the studied context and describing respondents' view over ethical considerations in their research practice in three empirical chapters.

respondents addressed me as “your Unit” or “your OUCRU” – indicating that I was classified as the other side of collaborator, and other times, “our Vietnamese people” by Vietnamese respondents when talking about Vietnamese culture, or “we” by foreign interviewees when talking about research practice and working culture which I, as an employee of OUCRU, share with them. With respect to the group of patients and family members, there were some cases in which I appeared to be a representative of the ‘foreign study sponsor’ or the hospital where the research that they participated took place. This shift of “identification” conferred by respondents in some circumstances automatically resulted in some sort of barriers in the way that respondents seemed to decide which topics they would share and would not if it was classified as their internal private things or sensitive topics that I, seen as an ‘outsider’, should not be shared with. Some degree of reluctance was sometimes shown when I posed questions on their opinions about international collaboration with foreign partners including OUCRU, or when they talked about their actual research practice which was seen as deviating from standards of research practice assigned by OUCRU in collaborative research projects. To encourage interviewees to open up and share comfortably about their perspectives, I stated clearly and repeated when necessary the aim of my research, which is to identify ethical problems and challenges in the research practice in attempts to address such problems, and that all information disclosed would be kept confidential. Showing support and recognition towards responses is also applied during the interviews where the interviewees seemed to be struggling with a question and types of information that they provided (Patton 2002). Respondents have shown to be open and confident in narrating their experiences and discussing about problems raised and possible solutions.

In examining my perspectives on the data collected, I felt surprised and challenged by the limited views expressed in several of the initial interviews, mainly related to procedural or typical problems such as obtaining consent, deviations from the protocol and standard procedures and legal concerns. It was difficult to elicit their views about other topics or to prompt them to reflect more generally about the problems and how to deal them. This might be explained by the precise roles of the staff I interviewed where each group of study staff specialized in specific tasks, and hence, their views were bound by the scope of their work. With a certain amount of pre-existing knowledge of ethical problems drawn from literature review, I sometimes considered using hypothetical vignettes as a way to prompt respondents to think about the issues and relate them to their practice for a deeper level of reflection and reasoning. However, in discussing with my supervisors about this challenge, I was advised on techniques to prompt them to think about moral aspects in their practice in a more neutral and open way and to continue with this strategy to see how the interviews would go because the ultimate research aim and the most important point is to identify what and how key stakeholders understood and experienced the research they were directly involved in, not to confirm of what I had read from the literature or my pre-existing knowledge of the field. This decision was justified when with subsequent interviews I was able to collect a wide range of problems or challenges from each of the stakeholder groups with rich description of the research practice involved. I was also able to explore novel issues which were not discussed in-depth in the literature review. Another concern was that when carrying out the initial analysis, with anxiety searching for ethical problems, I tried to relate issues to those I had read and thus my first draft of summary of issues was limited to and imbued with themes similar to previous literature. On discussing this with my supervisors and following

interim analyses I realized how I had been influenced by my pre-conceived knowledge and that I needed to be open-minded and neutral in obtaining and listening all the information shared by respondents. I then revised my analysis by keeping closer to the data and leaving them open in a form of mess of as many provisional themes as I could see from the interviews. These provisional themes were gradually refined in support of further data. As the data collection and analysis move on, the knowledge of theoretical literature becomes valuable in the way that it becomes something like a reference for possible general explanations to what I see from the data and a big picture of what is happening drawing on my observations and data collected.

Reflecting on these experiences I became interested in understanding more about the perceptual construction of ethics in the setting of healthcare practice and their proposed approaches to address ethical problems. It appears from the research that in doing this kind of exploratory empirical ethics research which aims to be part of a continuum process of identifying and putting forward an account of normative judgement or solution, the researcher needs to consider sociological aspects of ethical perception of people in practice, for example, what factors may influence their ethical perception, and what types of knowledge might enable them to come up with solutions. Overall, on comparing theoretical understandings of ethical problems discussed in the literature, we need to consider the status of this empirical data in contributing to the development of solutions based on the understandings of the place of ethics in society and theoretical proposals of relevance.

In sum, I have presented my reflexive concerns during the course of the research in two main aspects: the impact of my role towards the research setting and research participants and the interaction between me and the whole process of data collection

and analysis. I hope this part of reflexivity on the overall research process and other parts spread through the chapter on Methodology and empirical chapters would help to make the research transparent in how it has been conducted and how my reflexivity has been used in informing me of developing strategies in data collection and analysis. In the next section, I will present some of the implications for the ethical perception of all the groups of key stakeholders at a general level. Following from that will be summary of the findings of the three empirical data, my own account of ethical problems with recommendations and finally the limitations of the research with suggestions for further research.

6.3 Construction of ethical problems

Before going to discuss key themes derived from empirical chapters, I shall now first present a general account of my findings on ethical perception and factors that might influence this perception based on my analysis of the data and my experience of conducting all the interviews in the research.

6.3.1 Indication of problem area: the role of contextual features in the construction of ethical problems

As described as an interview approach employed in this research whereby general research phases and main tasks were used as a prompt for respondents to reflect on possible ethical problems by relating to their research practice, this method however is in almost all of the cases needed further prompts indicating certain areas in which there might be problems occurring such as “obtaining consent”, “healthcare provided in the research” or “reporting research result” with some suggestions of characteristics of REEs, i.e. the contextual features of REE setting. In some interviews respondents

needed to know a specific area that I wanted to talk about to recall what they had done in their practice and infer from their overall experiences involving features of the specified situation and context. The more specific the situation and context I mentioned to prompt the interviewees, the more detailed accounts of ethical problems they provided. This is particularly shown in the level of specification of narratives and the length of discussions in the interviews with principal investigators and IRB members. This can be explained by their exposure to a broad range of research work and professional knowledge enabling them to have a level of generalization bearing on specific situations in the research context of REEs and other clinical research. Documented in my field notes for my reflection upon the whole interview process, some respondents prior to officially starting the interview¹⁴ asked about which specific area that I wanted to talk about although they had been explained of the aim of my research; that is to identify ethical problems in research practice of REE setting. Upon this request, I suggested some examples of specific areas that, based on their description of their role and work involved, I could expect their work would cover the most part of it and that they could be familiar with the practice and concepts. This approach continued to be used during the interview process to prompt respondents to other areas or topics which might be neglected or forgotten by the respondents and also I wanted to further explore their perspectives about. Following is an illustrative example of how an IRB member responded to my broad question about ethical problems that he might encounter in reviewing research projects on REE. While the

¹⁴Before signing the consent form to accept for the interview to be started and tape-recorded.

rest of the interview he discussed many problems of the IRB review process, particularly issues regarding obtaining consent and research collaborations when I prompted him to such areas, his response to my initial question which was devoid of a specified area and attached contextual features was that he stated the standard of review procedure that the IRB was applying and identified no problem by or in its application:

“Interviewer: So can you please let me know that when our IRB review such research projects on REEs, is there any ethical problem that the IRB would especially consider?”

A: Actually in Viet Nam, we are trained in accordance to FERCAP. It means all our 9 members are trained according to FERCAP’s strategy and standards. That is why all research projects reviewed here is applied in a proper way...expedited review...that means reviewing in a way that...uhm...There are levels of review. Then....full review, expedited review, and review for reapplied protocols. So there are 3 types of review and we apply exactly the same. Everything is implemented in compliance with FERCAP and in reality there is not any problem” (NHTD: IRB member 1).

In the interviews with the groups of patients and family members, the ‘problem area’ that I used to prompt them to reflect upon was the area that I, following from their narratives of the process that they had gone through, thought might be unrecognized or neglected. By discussing the context and practice involved, respondents gradually raised what they then perceived as problems. As shown in the extract below derived from an interview with a patient:

“Interviewer: Do you see any difficulties, or any problems between you and doctors, or with the research or any advantages when you participated in research?”

P: I see no difficulties. When the hospital needs me to come in, they just call and I will come to the hospital to help them so that they can carry out enough tests they need. This also affected my studying time but in general, it was just not worth considering. I could arrange.

Interviewer: So in terms of ethics, during your time being in research, do you see any ethical issues?

P: In terms of ethics, it is...generally...I see them taking blood, testing...generally I think all those things they did eventually help me and help other people. That's good if they can find out something and from that they can somehow prevent the disease. So I see not any problem.

Interviewer: Do you think they should have some duties to you?

P: Well, I think if they want to do test on a patient like that, they should have some actions like following patients closely, talking more with patients about their health.

Interviewer: So do you mean at that time they didn't do that to you?

P: No, they didn't.

Interviewer: What do you mean by following patients closely? How did you want them to do that?

P: It can be like doctors go to patient room everyday to ask patients how they feel, their health status, or if they need to eat or drink anything or have any

different symptom. Everyday like that. You know, because I see doctors rarely came to the patients and asked”(HTD: Patient 1).

Influence of contextual features in a situation over the construction of ethical problems is claimed by Holm (1997, pg. 112) as well in his study on healthcare professionals including doctors and nurses. In his study, Holm pointed out that this construction is formed by inference from a range of features embedded in a situation and that the respondents felt that they had to complete the context in various ways before reaching any decision. While the former is affirmed in my research as shown above, the latter is manifest in the way that respondents provided their own description of context and particular situations in support of their narratives about what ethical problems might arise in these situations. These descriptions are partly derived from their recall or supposition based on their account of contextual features constructed at the time of the interview. The need for support of contextual features became obvious through the range of ethical problems raised and the depth of discussions on them when respondents could recall the situation as much as they could and based on illustrative examples of ethical problems provided by me throughout the interviews.

6.3.2 Situations in which interviewees identified no ethical problems

In this section, I will present 5 specific situations when respondents reported that there was no ethical problem that they had recognized in their research practice. These situations may have, to some extent, limited respondents to report and reflect on ethical problems that might happen in their research practice on REEs in my interviews with them. It is important to recognize these situations throughout an

empirical research study on identifying ethical problems such as this research as it helps the investigator to realize limitations of the applied research methods and methodology as a whole, and ways in which we will be able to elicit experiences of respondents on ethical problems¹⁵ and other ethical perspectives on other matters.

1) Respondents were not able to recall immediately all of relevant contextual features to provide a clear account of what were the ethical problems that they have encountered. In these cases, further indication and suggestions of some areas to reflect upon within the context could give a hand in their reconstruction of what they perceived as ethical problems or in their construction of new problems that they have neglected.

2) Problems could have been resolved and there was no longer a problem in the mind of respondents.

3) Respondents lacked the knowledge for example, ethical problems in obtaining consent were mostly provided by study doctors who are the group mainly in charge of the process while they are rarely articulated in other groups of respondents like study sponsor or investigators who have not participated directly in the process. This leads to situations when being asked about other processes of a research, respondents could not provide any issue or difficulty. An example of this is as follows:

“Interviewer: So if there is risk occurring to patients, do we have any measure like providing insurance for research participants?”

¹⁵This is reflected in the Methodology chapter on how I have approached research participants and revised my methods as the interviews were progressing.

D: Ah...in research in Viet Nam, common research, there is not. But in interventional study, there must be. That is according to...ah...what you have learned....ah....ah....

Interviewer: GCP?

D: Yes, GCP. It is compulsory. You learned it.

Interviewer: When taking part in research, do you know who will pay insurance for patients, or do you arrange any party to provide insurance for patients?

D: That's of administration. That belongs to other groups. I only care about clinical aspect. There is a separate unit to do that. I only know that that thing will be arranged. It is compulsory. It is required for interventional study. For common research, risks still happen with or without research. And those risks are acceptable. Those are the risks occurring in doing things that we have to do. For example, in antibiotic injection, this disease requires injection, the risk is shock. But what if you don't inject? Risk may be higher. If you do, risk still occurs but lower. Those are the risks under control and written in the study protocol. It is written in the protocol all potential risks of a new unknown drug. It is compulsory. This matter of risk was rarely asked in Viet Nam in the past. Do you see the case of a vaccine trial on dengue in Tien Giang? That's the case" (HTD: Study doctor 1).

What appears in this case is that although the study doctor is aware that insurance for them is compulsory, all details of an insurance arrangement are however left to administrative group who are specifically assigned to this task.

4) Respondents rely on a mechanism for all ethical aspects of the research to be checked and ensured. Once this is done, the respondents feel certain about all the work they are going to implement. For example, some study doctors and nurses expressed their feeling of security once the research project was approved by the IRB. In other words, the ethics of the research project is believed to have been addressed at this stage and as a result, no ethical problem seemed to exist in their mind to be attended to. As shown in an interview with a study doctor:

“Interviewer: So if in case of a study comparing a high dose or a new drug which you don't know its effectiveness with a standard dose which you, or doctors in general like you, already used to it and prescribe for patients, would you have any dilemma in doing this kind of study?”

B: Of course to the disease which there is treatment regime already, following the regime is...correct and ethical. Going against the treatment regime means we do it unethically, but in that case, we have to wait for the IRB's consideration. When the IRB approves, we just do it because once they give approval, they must have considered the study in many aspects for example international guidelines and the severity of the disease as well. Once they approve, we are assured to carry out the study” (HTD: Study doctor 2).

5) Respondents accept an issue as a common phenomenon or a regulated procedure and normalize it. Problems as a result are pushed to the back of the mind and not raised anymore. An illustrative example for this is when I discussed about the local IRB review process with study doctors:

“Interviewer: And then we will have to submit it to the IRB of the Ministry of Health?”

D: Uhm, we have to. We will wait for the hospital’s approval, then we’ll submit it to the Ministry of Health. An approval board something... they call it IRB something. That’s the procedure.

Interviewer: Okay. That means we will have to wait for 45 days more since its submission to the Ministry of Health.

D: Uhm. That’s the regulation. But this happens everywhere. It’s a big deal. It involves in patients’ health. Just normal paperwork is time consuming. That’s a bureaucratic matter! You live in Viet Nam, you know it” (HTD: Study doctor 1).

In this case, the whole review process mentioned is already a type of regulation that everybody has to follow. Thus it appears to be familiar and this seems to make the respondents feel it unnecessary to raise it as a problem.

Whilst it was clear that some of my interviewees struggled with the notion of an ethical problem and found it difficult to talk about this, it is nonetheless true that many of my interviewees were able to articulate and explore practical ethical issues arising in their work during the conducting of research in the context of REEs. As the discussion in my previous chapters shows, these interviews and my analysis of them has made visible a complex moral world in which those involved in such research – whether as health professionals, researchers or patients and families – experience and engage with a number of important ethical problems.

In the next section, I will go on presenting how respondents in the different groups of stakeholders I interviewed have given different perspectives on ethical problems, and how these differences might affect their solutions to the problems perceived.

6.3.3 Differences in ethical perception between interview groups

a. Differences based on experience of research practice:

The analysis of the interviews of each group of stakeholders has confirmed my speculation at the beginning that each stakeholder group provided quite different accounts of what they perceived as ethical problems in their research practice. This first of all can be explained by their exposure to each procedure involved in the whole research process in terms of type of work and the accumulated amount of information they have learnt from processes involved in research.

Differences in the types of ethical problems raised also depended on accumulated experiences that respondents gain through their research involvement. While there is almost no correlation between ages of respondents and the types and amount of ethical problems raised or the depth of discussions on ethical matters, and the same seems to apply with their specific working position at the time of interview, working place and ethnicity, differences are however clearly shown in their experiences drawn from the types of work they have been involved in and the amount of time they have spent working in their research field. In some interviews with principal investigators or IRB members, for example, if people had actually engaged in many types of work, they showed a broader understanding about illustrative examples given or provided detailed description of processes involved in a research, and was able to discuss about ranges of topics in the interview, for example, setting up collaborations, discussing with colleagues and research partners in composing research protocols and

procedures, submitting the protocol to all required IRBs, dealing with research participants and family members and working with different research collaborators in a research network.

Differences between local Vietnamese scientists and foreign scientists:

Important differences were revealed between local Vietnamese and foreign group of interviewees. A wider variety of ethical problems and ethical perspectives were discussed at a deeper level with foreign scientists working at Vietnamese research sites and other countries. In particular, problems raised and discussed by Vietnamese researchers were mainly limited to legal and procedural compliance, for example, conflicts between requirements of GCP, international guidance, national law and the research practice in reality in cases of obtaining consent, IRB review and financial support. These problems when being discussed with foreign scientists, were backed up with a deeper layered account of moral values, principles and ethical reasoning of, for example, what kind of moral value or principle the respondents think was involved and at stake in the issue. The foreign scientists, moreover, mentioned a wider account of issues such as engaging community, sensible research procedure, or research activity in relation to other healthcare sectors during the time of a REE. This difference may be explained, by the broad experience that foreign scientists have had which might enable them to have a clearer overview and more insights into research activities and ethical problems that might arise out of the activities. It could also be that research ethics is a relatively new concept to local Vietnamese researchers and IRB members. This does not mean to give any judgement on the ethical attention of local scientists. However, it may suggest a connection between training on ethics or familiarity with concepts and principles of ethics broadly speaking somehow equips

people in their moral sensitivity, moral perception and reasoning. This link has been pointed out by Iris Murdoch (Murdoch 1985) and Holm (Holm 1997) that much of our ethical perception requires training and knowledge to function and that most health care personnel have probably experienced situations where they themselves have overlooked important ethical features, or where they have felt that colleagues have acted in this way.

b. Differences in the perception:

Differences are also demonstrated in the way people perceive a situation. In other words, one situation could be viewed as different problems across groups of stakeholders who directly experienced that aspect of the research. An example of this could be different views expressed about the volume of blood that had to be drawn in research projects on REEs. One investigator labelled this as a psychological matter, not anything of ethical:

“Taking blood is a matter of psychology, not of science. For example, in a blood donation, the blood volume that you can give within 15 or 30 mins is possibly up to 250ml. Even I myself have donated 350ml. But generally, patients are always afraid of being taken blood. I don’t know if it’s different in Europe, but to our Asian perception, blood is considered as a nutritious source, a source for living, and thus taking blood will make them weaken. The more blood is taken, the scarier the patients are. So this is the matter of psychology in society, not of ethics or science” (Local Principal Investigator 11).

Others viewed this as an ethical issue due to 1) the volume of blood drawn in such research projects were much larger than that of routine care, and that they felt sorry for research subjects who were subject to the research procedure, 2) research subjects who were in critical conditions had to be exposed to many times of blood drawn, or 3) research subjects were usually afraid of being taken too much blood, and this could make them not want to participate or withdraw from the research. These differences might have their root in differences in understanding or professional stance. For example, an investigator cum physician may hold a different view from a pure scientist about the attitude that researchers in general should have towards their research participants:

“Yes for more assays, for more research, the more people to do, the scientists sometimes they, I think sometimes we should teach the scientists to be nice to the patients, sometimes I feel that” (Principal Investigator 12).

These differences in perception may accordingly lead to different sets of moral values and principles. In the case above, for example, the investigator appears to sense a duty to protect his patients. Whether this sense of duty comes from his stance as a medical doctor or a fellow countryman or maybe both towards the patients, it is that his stance shapes his view over the same fact which might be viewed differently by others.

So far, I have presented my findings on ethical perception and factors that are influential in perceiving ethical problems in my research population. In a research project which involves exploring ethical problems through perspectives of stakeholders like this project, these findings are important in the way that they inform us of how ethical aspects are constructed and how they might be different across

groups of research participants. In general, the findings indicate factors that might affect our research methods and data collected, and how qualitative research methods prove to be useful in exploring ethical perception of people.

6.4 Summary of key findings in the empirical research

In what follows, following the key overarching themes identified in my analysis, I break my discussion down under the headings of ‘collaboration’, ‘ethics review’ and ‘consent’. In the end I return to the question of how these themes relate to one another.

6.4.1 Collaboration

Through the narratives of key stakeholders about ethical concerns and challenges arising in research collaborations in REEs as well as their solutions, I have laid out factors and moral values that are generally taken into consideration in such research collaborations. These challenges arise in the interactions of these actors at both macro institutional level - between institutions and communities under the management of administrative authority - and micro individual level between study staff.

Challenges/Ethical problems	Solutions	Reasons (For/Against)	Principles/Values
Local researchers perceive themselves as research executor in the collaboration	Enhance local research capacity	Against to this perception: local researchers' contribution is important, and the relationships involved is perceived as equal	Self-capacitated Value of local contribution
Hierarchical structure of local health system might cause unnecessary delay in planning out research in an outbreak setting	No solution has been put forward		Timely response at the urgent request of the disease setting
Differences in the perception of benefits and benefit sharing	To be listened and gain mutual understanding; being transparent; having an oversight mechanism like an "ombudsman"	For: to meet practical needs of local people; to encourage people to participate in research	Mutual understanding To be respected Transparency Fairness
Tension between doing research and focusing on providing medical care	Sensitizing and consensus building on research plan; engaging relevant stakeholders	For: Increase the recognition of local people about the situation of epidemics, thus necessary resources can be utilized and made available; avoid duplication of work; relieve the tension of medical work of local medical staff	Mutual understanding Consensus
The disconnection between clinical research and public health activities	Integrating with other health sectors in the overall response to REEs		
"Each country has each own ethics": too many standards to follow	Sensitizing and consensus building on the research plan; engaging relevant stakeholders; preparation plan to put in place	For: Create a quick response to REEs	Timely response Consensus
Competition in research agenda and the good of global health	Open collaboration; having commitment	For: To protect the common interest towards to the global health	Duty to protect affected public and the public good

6.4.2 IRB review

My research findings on the ethical challenges associated with the processes of IRB review have highlighted the general review practice of local IRBs applied in research projects on REEs and ethical problems arising in the practice with proposed solutions from relevant stakeholders involved. Challenges/ethical problems with proposed solutions and values attached to the review practice of RECs/IRBs can be summarized in the table below:

Challenges/Ethical problems	Solutions	Reasons (For/Against)	Principles/Values
Misunderstandings about the function and process of local IRBs (the combination of scientific review and ethical review, and review authority and process)	Open communication and transparency	For: achieving mutual understanding and mutually agreed principles	Timely response Saving resources Openness towards shared principles/ethical frameworks
Obligation of IRBs to comply with policies and accountability	This is raised as a nature of IRBs. No solution to be put forward		
The “human nature” of IRB affects its independence in reviewing	This is raised as a nature of IRBs. No solution to be put forward		
Parochial independence	Acknowledge and respect each other’s capacity and values		
Late response to REEs: Lack of information about the disease or effective interventions Lack of procedures in place	Investigators have the duty to facilitate the IRB review Engage with involved IRBs/RECs Achieve a common ground for all involved IRBs	For: to create a quick response to the emergence of REEs	Duty to protect research participants and afflicted population
Protection of the safety and the right of patients from overdue pressure	IRBs to take responsibility	For: Research participants are supposed not to be able to absorb all research information and subject to the risks of necessary overdue pressure	Duty to protect research participants and afflicted population

6.4.3 Consent

Consent emerged as an important source for the generation of ethical problems and potential solutions for all of my different stakeholder groups. In Chapter 5, I have characterised the relationship between research participants/family members and study staff/research institutions, people's perception of consent and research in general, and the consent practice happening in the setting of REE. Ethical concerns in the consent practice in REEs are essentially about 2 main aspects including people's understanding and perception of research, and the informing practice of study staff with challenges caused by the setting of REEs. The following summary table will provide a snap-shot of all of the issues and challenges raised with corresponding solutions and values indicated in discussions on consent:

Challenges/Ethical problems	Solutions	Reasons (For/Against)	Principles/Values
<p>Understanding and cultural perception of patients and family members about research:</p> <p>Level of understanding</p> <p>Negative pre-conceived notions about research</p>	<p>Replace the word “nghiên cứu” and/or explain the research in different ways so that participants/family members understand basic concepts and procedures/interventions more easily.</p>	<p>For: educational level and/or medical knowledge of research participants/family members is still low; they are not familiar with new concepts such as voluntariness, randomization; they have negative associations of the word “nghiên cứu”.</p> <p>Against: Participants/family members have the right to know all the information to make their decision; involving legal issues if being charged of uninforming.</p>	<p>Duty to protect</p> <p>The right to being fully informed</p>
	<p>Explain, repeat the information provided and encourage research participants/family members to remain in the research</p>	<p>For: Participants need more information to understand clearly about what is being done on them and reassurance of whether it’s harmful or not.</p>	<p>To keep participants well-informed and assured about the research and the whole healthcare procedure.</p>
<p>Informing practice:</p> <p>Avoid the word “research”</p> <p>Increases anxiety associated with larger amounts of information provided</p> <p>Tension between providing full information the possibility of refusal to participate and the need to do research</p> <p>Lack of information</p> <p>Availability of time</p> <p>Therapeutic misconception</p>	<p>Flexibly adjust the type and amount of information provided</p>	<p>For: limitations of education level and medical knowledge, psychological fragility; familiarity of research concepts; the need to have research done to benefit society; the research itself benefit research participants individually.</p> <p>Against: the right to know all information of participants to make decision regardless of the fact that research sometimes cannot be done for not reaching targeted sample size.</p>	<p>Duty to protect</p> <p>The right to being fully informed</p> <p>The good for public health</p>

Conflict of duty	Having a third, independent party to obtain consent	A hard situation when research participants/family members usually trust physicians rather than an outsider	Equality in relationship to facilitate the decision making of participants/family members
Media role: distorted information of research, caused misunderstandings in public about research	Re-informing participants/family members Discreet in research information release	For: make people understand properly about research, reporting research's results are necessary for the benefit of society	Integrity of research information

At the specific level, some of the issues that were raised in the interviews are similar to ones addressed in other non-emergency research settings and general guidelines on research ethics; several are unique to the setting of REEs. However, when looking at all of them in their relation to relationship between participant-researcher and solutions proposed by respondents, it appears that consent process is not just an exercise of providing information, explaining and consenting, but a time when duties and expectations of involved parties are established. Given the unique characteristics of research subjects, family members, and researchers in the context of REEs and in this specific cultural and healthcare setting, the values that emerged from consent process are those of trust, duty to protect and the social value of research.

6.4.4 Summary

Reflecting on the findings in three empirical chapters, I have drawn the following 3 main conclusions for each of chapter:

- 1) Consent is a process whereby not only research information is provided but perceptions of the relationship, duties and expectations of involved parties are constructed towards involved parties including research host institutions, sponsors and study staff directly involved in the process. The values of trust, duty to protect and the social value of research are the key values serving as an explanatory account for what have been seen as ethically problematic and challenges in the consent practice of research in REEs, the overall relationship between involved parties in a research and all of possible solutions propounded for the problems and the practice.
- 2) What emerges as a big picture of international research collaboration in REEs reflected through the case of OUCRU and its research network is a type of

collaboration in which familiarity and trust are built through long-term partnerships with protective mechanisms such as research agreements or contracts in place. Most of the ethical problems and solutions raised in my interviews were directed towards to the ultimate goal of consensus among involved parties and the duty to protect the good of global health in the research setting of REEs.

- 3) The complex setting of REEs poses unique challenges in the process of IRB review. This calls for an improvement of research ethics review in which the nature of research ethics committees' position should be taken into consideration, and both research ethics committees and researchers would be the key components to bring about changes in this process. In solutions propounded for this improvement, two key values are drawn across all accounts provided by the stakeholders on research ethics review in the setting of REEs including openness for a common ground and the duty to protect research participants and afflicted population.

Across the three themes on consent, international research collaboration and IRB review, there emerges a tension in how to balance between what can be so called the interests at individual level and the social value of research.

In what follows, I will discuss the first three conclusions with their key values involved in their relation to research ethics in general and in particular how these are suggested to be understood and applied in the setting of research on REEs. In the discussion of each of the three conclusions, I will bring out the underlying issue of tension in the interests of individual and society as a whole, who both stand to the benefits of research, and its relevant implications for further deliberation.

6.5 Discussion:

6.5.1 Collaboration

As outlined in chapter 3, research collaborations in REEs appear to be complex, interconnected structures of relationships of involved stakeholders as portrayed for international scientific collaborations and health systems in general (Gilson 2003; Tindana 2013). This relationship structure is especially characterized by the involvement of community and public in general (Ezeome and Simon 2010). As a long-term research partner locating in a local hospital, OUCRU is in a unique position to trigger a quick response to emergency epidemics with local hospital partners. Thus research collaborations in REEs in this case can happen in the context of long established research institutions working in relatively stable populations (Parker 2014). Ethical challenges for establishing collaborative community in research in a public health emergency context involve defining the involved community in migratory epidemics, how and to what extent to make an engagement possible in response to the nature of rapid evolution of epidemics to ensure ethical research occurs (Emanuel et al. 2004; Calain et al. 2009; Ezeome and Simon 2010). Research collaboration in my study, however, presents other concerns and challenges in the nature of well-established collaborations with wider public and international outreach. What importantly stands out from all issues arising in this context and proposed solutions is a need for a parallel existence of a concatenation of measures for the stability and development of research collaborations in REEs. These include familiarity, trust, mutual understanding and protective mechanisms such as research agreements and “ombudsman”. In the next sections, I will focus on elaborating how these values and measures interweave with each other to bring about collaborations in research on REEs, and that in relation with the argument for the common good of

societies, I will show that the value of research collaborations in REEs is actually moving beyond typical notions of collaborations characterized by a “collaborative partnership” (Emanuel et al. 2004).

The concept of “trust” and collaborative partnership at the institutional macro-level

“Collaborative partnership” is seen as a benchmark in establishing research collaboration between researchers, sponsors in developed countries and researchers, policy makers and communities in developing countries (Emanuel et al. 2004). The concept is first developed in attempt to primarily minimize the possibility of exploitation with its focus on fairness, respect and joint working. In the paper arguing for an effective collaborative partnership, Ezeome et al. have made this concept generalizable for any party participating in the research conduct of acute epidemics with more focus on the value of engaging relevant parties in planning, research conduct and result application for mutual understanding of a shared account of vision and mission and benefit generating for afflicted population (Ezeome and Simon 2010). Towards this direction, engaging practice is widely opened to general public and media whose advocacy and support is crucial for research in REEs. Generally, the two accounts share the traits of engaging, respect, trust building and benefit generation for communities involved in research.

Principles	Benchmarks
Collaborative partnership	<p>Develop partnerships with researchers, makers of health policies, and the community.</p> <p>Involve partners in sharing responsibilities for determining the importance of health problem, assessing the value of research, planning, conducting, and overseeing research, and integrating research into the health-care system.</p> <p>Respect the community's values, culture, traditions, and social practices.</p> <p>Develop the capacity for researchers, makers of health policies, and the community to become full and equal partners in the research enterprise.</p> <p>Ensure that recruited participants and communities receive benefits from the conduct and results of research.</p> <p>Share fairly financial and other rewards of the research.</p>

(Source: Emanuel, E. J., D. Wendler, et al. (2004). "What makes clinical research in developing countries ethical? The benchmarks of ethical research." *The Journal of infectious diseases* 189: 930-937.)

Although much has been written about trust in the biomedical research setting, it is not clearly specified whether this concept should be understood at an interpersonal level between individuals or impersonal level between institutions. In my study, it appears that interpersonal and impersonal levels of trust are intertwined in relationships between individuals representative for groups of people/institutions and between institutions. For example, trust between “researchers” and community is not construed as an interpersonal relationship only. Or similarly when trust is mentioned in the form of “public trust” in relationships between public and institutions such as ethics committees and research institutions (TCPS 2 2010). Apparently, it would involve the idea of trust that is established between community and involved research institutions or group of researchers. Especially in an international collaborative context of research on REEs in which there is a variety of international and local institutions, the notion of trust should cover relationships between established institutions or groups of highly connected networking people and communities or the wider public. Now before going on to discuss how the concept of trust is applied at an institutional relationship level, it is necessary to say a bit more about “familiarity”

which is what stakeholders mention as a key component in their research collaborations in the studied context. If antecedents of a concept are defined as events that happen before the occurrence of a concept (Walker and Avant 1995), “familiarity”, drawing on my data, can be perceived as an antecedent of “trust” though the former does not necessarily result in the latter. Familiarity in some cases mentioned in my empirical data can bring mutual understanding between collaborators of what each party would require and how each would act in the collaboration. While this does not warrant a satisfaction for all involved parties, it increases the chance of positive interactions for potential collaborators bringing feelings of ease and security in jointly working in research projects through knowledge learnt from each other. While literature on research ethics is often concerned with the concept of “trust-building” in establishing an ethical research collaboration, a practical step involved in such a process of trust building like “familiarity” and its value is almost ignored. While trust between institutions and groups of people requires time and other mechanisms to promote accountability and reliance to develop, the value of familiarity in collaborative initiatives should be taken into account and practical steps to achieve it should be developed.

Research collaborations are in most cases established between institutions. These institutions work through such mechanisms as operating procedures, contracts, agreements and laws to establish and maintain collaborations. It is that these mechanisms inherent in any institution partly create and promote the characteristic of reliance of institutions. In discussion about the concept of “reliance” in the dimension of an organization based on such forms of mechanisms, reliance is attributed to “positive expectations come from the proven capability of the partners and/or the existing exchange standard observed by the partner” (Jiang et al. 2013). Capability of

a potential or current partner as evidenced either through their past relationship exchanges or proven through reliable sources of information of other partners contributes to the confidence of an organization that that partner can be relied on to fulfil expected outcomes (Jiang et al. 2013). This is consistent with what has been shown in my empirical data in the way that OUCRU and its partners have their research collaborations established and sustained through their institutional context, regulatory/protective measures and familiarity with which they feel confident about the collaborations. While it has also been shown that the level of trust is varied in each level of collaboration, for example between institutions and groups of people, or between individual researchers representative of their institution, collaboration still happens on the basis of familiarity, reliance and trust for a “mutually advantageous transaction” (Wertheimer 2010).

Weaving these elements back to the conceptual account of “collaborative partnership” aforesaid, it suggests that the construct of reliance and a combination of familiarity, reliance and trust be fully considered and specified when setting up research collaborations in the context of REEs particularly in order to produce a timely response to the REEs as there may be almost no time for a novel collaboration and building trust is a time-consuming task even for any well-established research collaboration.

One notable value that is crucial for an ethical scientific collaboration in the setting of REEs as discussed in the chapter on Collaboration is the value of “the good of global health”. In the interviews and anecdotal reports, this value is argued for its authority to override the validity of any collaboration that might impede progress in public health. It expands the scope of typically portrayed research collaborations which often concern participating actors only. As far as the duty to protect the global health by

minimizing the harms of a public health emergency remains its leading role in driving scientific collaborations in REEs, this value should be interwoven into any model of collaborations proposed and be counterbalanced with other embedded values.

6.5.2 IRB review

The findings of my research about research ethics review occurring with research projects on REEs are consistent in what have previously been discussed in my literature review, namely there were unnecessary delays in the review due to bureaucratic challenges caused by the requirement to obtain multiple ethical approvals and such constraints as the lack of time for a standard review and pressures placed upon RECs in acting expeditiously to the urgent nature of epidemic situation (Emmanuel et al. 2010, WHO meeting report 2009, Macklin R et al. 2009, Farrar 2014). Interestingly my data also reflect the fact that some representatives of IRBs in Viet Nam and in other countries recognize a need to implement clinical research and thus to act quickly upon epidemic events to benefit societies. In this direction, local IRBs have made an effort to be flexible, for example, giving approval while still being aware of the lack of scientific evidence and uncertainties about the epidemic. This implies that timeliness in the response is part of the duty to protect the public health and is valued sufficiently to compete with other scientific and ethical concerns at the level of individual patients. Speaking about the lack of guidance on the extent to which IRBs and national research community can facilitate research, stakeholders in my research suggest that the social value of research at global level should be taken into consideration when assessing the interests of individual patients.

What has been understated in the literature is how some of the characteristics of IRBs or RECs, particularly regarding their position, expertise and assigned responsibilities

result in a variety of limitations and pressures on IRBs in confronting an epidemic situation.

For its position and attached responsibilities, as discussed in Chapter 4 on Research ethics review, IRBs are bound by multiple requirements, regulatory and relationships. In discussing about bonds existing around ethics review structures, Guta et al. have pointed out that “Ethics review sits at the crossroads of power/knowledge, but within a much larger system of seemingly unrelated processes, systems, and rules” (Guta et al. 2013). There is further evidence and elaboration on the fact that the position of an IRB and its authority has increasingly invaded many aspects of research projects and research activities, which to some extent can be called as “ethics creep”¹⁶ (Haggerty 2004; Guta et al. 2013). Guta et al. concluded that there is a relationship between ethics review and power, knowledge and a larger system of ostensibly disassociated rules, processes and systems (Guta et al. 2013). Reflecting upon that this relation manifests in my empirical data as the “human nature” and “parochial independence” of IRBs, it suggests that we should look at IRB/REC and its relations with other stakeholders in the conduct of research to determine a full range of elements that may affect the IRB’s deliberations and its ability to cooperate with other parties in reviewing and overseeing research projects. Not only raised in my interviews with stakeholders in Viet Nam and Canada, parochialism is also captured in the form of local research ethics committees (LREC) established in the National Health Service (NHS) in UK in the report of the Ad Hoc Advisory Group on the operation of NHS

¹⁶ This concept is developed by Haggerty (2004) to explain for the increasing bureaucratization of IRBs/RECs and the expanding reach of ethics review.

Research Ethics Committees in 2005 (Department of Health 2005). Although the exact form of parochialism was not stated, nor supported by empirical data on how it would affect the deliberations and decision making of the LRECs in their ethics review and cooperation with other RECs, it was drawn from the fact that the LRECs were largely formed “from a relatively narrow spectrum of society, members tending to be professional in background and from an older age group” (Department of Health 2005, pg.10), and as such they appeared to be incongruent with the long held principles of independence and broad public representation of research ethics committees. In other words, they became “rather parochial, strongly influenced by association with particular research environments and disparate in direction and quality” (Department of Health 2005, pg.4). This is consistent with my findings on “parochialism” and suggests a connection between a narrow restriction in the outlook of RECs and how they perceive their independence. While solutions proposed for research ethics review in emergency epidemic setting and others mostly called for a general concept of being “independence” of IRBs/RECs indicating an ability to be free from conflicts of interest, addressing the issue of parochial independence as reflected in my study left unspecified. “Bureaucracy” or “over-regulation of research” is widely mentioned in papers and reports arising from this form of “independence”. In REE situations where many IRBs may need to be involved this is a particular problem, and calling for any solution which strives for common ground among multiple RECs would require another approach to how the nature of “independence” of RECs should be viewed in consideration of the value of achieving common ground of principles and values.

Having been discussed in Chapter 4 on Research ethics review, expertise in research areas under review, and in research ethics guidelines also appears to be an important

feature that might affect IRBs' competence in its review, oversight and relates to its integration with other IRBs and researchers. In reviewing research projects on REEs in particular, it is significant as stated by interviewed IRB members that IRBs should be able to recognize the emergency nature of such research in response to the epidemics of public health threat and to grasp as much as possible scientific information relevant to proposed interventions. While these two elements do not necessarily bring consistency in deliberations of IRBs, they are reported to accelerate the review process and decision making of the IRBs. However, enabling such a quick response is not perceived as the sole responsibility of the IRBs. It is shared by researchers who should raise the urgent nature of the situation and provide all available information for the review. Without this support, the review process may be impeded by unrealistic demands of the IRBs for what might be constituted as a meaningful protocol in their perspectives (Snider and Stroup 1997). The value of cooperation between IRBs is considered equally important in making a timely ethical review possible in the context of REEs. Nevertheless, opinions of "insiders" of IRBs show that parochiality which might be created by differences in working culture and in perspectives of standards and regulations IRBs is a major obstacle in this direction. This type of parochiality may cause concerns in any proposed solutions including options for a fast-track review approach (World Health Organization 2009) or top-down approach in which a prior approval in principle of a delegated centralized REC would be obtained and followed by specific considerations of each involved IRBs based at research sites to decide how the proposed research should be applied in their own sites (World Health Organization 2009; The Academy of Medical Sciences 2011). All of these measures once implemented without an agreement for a common

ground of both scientific and ethical perspectives are unlikely to speed up the research review process.

6.5.3 Consent

Obtaining informed consent has become a requirement for the ethical conduct of research involving human subjects worldwide. The requirement of obtaining consent is grounded on the fundamental ethical principle of respecting for patient autonomy (Norman 2011). Following from this principle, three constitutive components must be met: disclosure, capacity and voluntariness for a valid consent (Etchells et al. 1996). Descriptions of the process and nature of informed consent, however, vary in published national and international regulations and guidelines pertaining to research ethics. Its application also remains as one of the most controversial issues in bioethics, especially in the setting of REEs as appears in my interviews. As discussed in the chapter on Consent, obtaining consent in research projects on REEs presents a variety of ethical considerations and challenges based on identified factors that might influence and compromise the consent process in practice and the nature of research on such REEs. My findings are consistent with previous reports in the literature about obtaining consent in the context of disease outbreaks or acute epidemics. In particular, there are two main types of concerns. The first is how to return to patients for consent in the cases where clinical samples which were originally taken for public health purposes or from archived research samples taken for an antecedent research in which there was no plan for obtaining consent for a certain type of data that would be needed for future research. The second is when there are sources of vulnerability in the research context that might compromise the capacity for deliberations and decision making of research participants and family members. In both cases, arguments for

good research to be conducted for a timely and systematic response appeals to the value of the common good of the social value of research, the duty to protect research participants and the value of trust. In the first case, the use of clinical samples for future research and whether investigators should get back to patients for their consent are largely proposed to be subject to the review and decision of relevant research ethics committees and/or other advisory board representative for the engaged communities. And in fact, this solution has been applied in the three local hospitals that I have conducted my research. Nonetheless, responses of antagonists suggest that it is impractical when it took a long time to obtain the IRB's approval for the data collection, and during the lapsed time, procedures and quality of clinical samples collected as public health routine might not have met such stringent requirements as those applied in research. As far as research in epidemics would coordinate public health activities in determining causal agents and the magnitude of the epidemic to minimize possible harms of the public health emergencies, interviewees emphasized that this type of research needs to be approved quickly so that it can be built in the overall public health response for the common good of public health. While there is not any concern raised in relation to getting back to patients for consent in the first instance, lots of issues and considerations have been elaborated in the second. Consistent with assumptions and facts reported in literature about obtaining consent in the setting of REEs, there exists a concatenation of relationships coming on the scene in the interaction between research participants/family members and physician-researchers with other circumstantial factors that might affect the whole consent process and all involved relationships.

In general, it appears that consent is a process that involves not only researchers and research participants and/or family members, but other subjects including research

host institutions like local hospitals, study sponsors and other study staff. In Viet Nam, in places where community-based research was taking place, research relationships are extended to public health governing bodies and community members. All of these relationships in my interviews have been shown to affect the decision making of research participants or family members. As shown in the interviews with research participants, family members, Vietnamese researchers and foreign researchers based in Viet Nam, while full understanding of research information seems to be unattainable, consent is given mainly on the basis of trust, motivated by both self-interest of some immediate healthcare benefits and altruism through the awareness of research's social value. The trust between research participants/family members and physician-researchers are primarily grounded on the trust established in the relationship between patient and physician. While most literature on consent emphasize the trust between researchers and research participants/family members, in my research family members/ participants appear to place trust also on research host institutions, study sponsors and research governing bodies such as local IRBs and public health officials. The trust is manifested through the expectation that physician-researchers would not harm patients; that research host institutions and study sponsor are trustworthy names that usually provide good treatment to the patients, and that research governing bodies would protect the interests of patients through their review of research projects. From this perspective, the trust established through the consent process between research participants/family members and all involved parties is in the form of confident reliance (Baier 1986) which highlights the dependency and vulnerability of research participants/family members towards research parties and governing bodies. Being aware of the trust placed on them as patients towards physicians and local hospitals, physician-

researchers and local hospitals with their IRBs in my research have emphasized their accountability and the foremost duty to protect the safety of research participants and their responsibilities to protect their national public health. This is reflected through their review and selection of research projects that are considered to benefit and not to inflict harm on research participants. Autonomy of research participants or family members is in consequence not to be left alone in deciding the spectrum of risks involved in the research that they can bear. In other words, the decision to take part in the research by research participants and family members is not a validation of the ethics of that particular research. Regulation and requirements regarding responsibilities and accountability of physician-researchers appear to serve as an additional protective mechanism for research participants and family members. As suggested by the stakeholders in my research, when fully understanding is a condition that seems to be infeasible and ‘unrealistic’, not only in the context of research on REEs but other research settings, consent should not be regulated and relied on the decision making of research participants and family members. Other parties involved in research, especially, research ethics committees are integral in protecting research participants from any possible harm from research.

6.6 Solutions for identified ethical problems and challenges:

So far, my research has attempted to map out a range of issues arising in the context of research on rapidly evolving epidemics. What I will propose as solutions in this thesis accordingly will be general solutions for the three main themes discussed above. These solutions draw upon the views of key stakeholders about possible solutions to the ethical problems they identified, emerging key moral values across groups of stakeholders and my reflection on issues and challenges explored in the

research. They are built in light of the nature of the problems, challenges occurring in the research practice and practical conditions in the studied setting.

6.6.1 Establish and strengthen research collaboration on the basis of familiarity, trust, reliance and open involvement for the good of global health

As outlined in the chapter on Collaboration, clinical research on REEs involves a variety of stakeholders. These relationships occurring in both macro institutional and micro individual level are concatenated. While my data support the possibility that research on REEs could only be quickly triggered in long term already-established research collaborations between institutions and relevant public health sectors, research on REEs should be open to include key figures for additional support. These figures, as suggested in the case of Viet Nam, should include local hospitals with their public health support, public health representatives based at research areas/communities, local and international research institutions, local and international funders and sponsors, local and international research ethics committees and a large number of patients. Ideally, other medical and social forces including clinical community, scientific journals, national and international agencies and the public should also be involved to gain their support (Tran et al. 2009). Pharmaceutical companies also need to be taken into account for their role in supporting healthcare infrastructure and producing new drugs for clinical trials (Delva 2013) so long as any possible commercial interest has to be aligned with the good for global health. Setting up research collaboration would include creating familiarity with all potential collaborators and funders to facilitate mutual understanding, building of trust and setting up of an operating system which promotes reliance through mutual confidence

by proven capability (Blois 1999), ensured performance expectation (Voss et al. 1998) and positive outcomes (Anderson and Narus 1990). Familiarity and trust require time to be established, but can be built up and developed through other disease settings and collaborations in advance of REE. The long term collaboration model of OUCRU and its local and international research partners through a diversified profile of infectious diseases including REEs, or the establishment of International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) are exemplary cases. The consortium is a collaborative platform through which experts in REEs all over the world work towards the development of global, patient-oriented clinical research. Within these collaborations, reliance can be yielded through established agreements, standard operating procedures and transparency in working processes. Research partners would play supplementary role to each other. In other words, an approach to collegium in which all partners working in a framework of mutual understanding and respect towards shared goals should be adopted to build up research plans and achieve consensus among members. Any anticipatory research plan including having open access, wiki style protocols and case record forms (Tran et al. 2009; World Health Organization 2009), securing adequate fundings, pre-crisis in-principle ethics approvals, identified support laboratories and linked research centres (Tran et al. 2009) can only established based on such an collaborative framework.

6.6.2 Enhance research review process and research oversight of research ethics committees (RECs)

With respect to REC's research review process and research oversight, taking into consideration issues, challenges and solutions raised by the IRBs' members and other key stakeholders in the interviews, I propose a number of suggestions in addressing

these issues and challenges. Inasmuch as the two values “openness towards shared principles/ethical frameworks” and “duty to protect” are regarded by interviewees as important to the role of RECs in the context of REE, proposals relating to providing necessary training, developing communication, and strengthening research oversight as detailed in the following paragraphs can be considered.

6.6.2.1 Provide necessary scientific and ethics training to RECs and build up an appropriate model for ethics review in REEs

Recognising that RECs need to be sensitized and involved in any anticipatory plan for a timely response to epidemic situation, training on scientific knowledge and research ethics that might be applied and considered in the complexity of the disease situation is required for RECs’ members for their mutual understanding and support of research in the setting. Calling on non-members with special expertise is another way for enhanced scrutiny and attention to relevant aspects of the study (Tansey et al. 2010), as well as for diversified perspectives. Training would also help RECs to decide and adopt which approach or model of ethical review would be useful and suitable to their context. Proposals for research ethics review in emergencies have brought up 3 key elements: proportionality, special scrutiny and expedited review (Levine et al. 2004; Tansey et al. 2010; TCPS 2 2010) for a warrant in the quality of review yet creating flexibility for RECs during the time of public emergencies. While those proposals are widely applied in the US and Canada, a framework for streamlining ethics review into a ‘single research regulator’ applied in UK is another step forward in reducing unnecessary bureaucracy in regulation and governance while facilitating high-quality health research for public benefit (The Academy of Medical Sciences 2011). All of those proposals aforementioned should be considered for application in Viet Nam and

other countries where clinical research proves to be useful not only for future patients but also for current medical resources and patients or afflicted populations. Again, how to decide what fits into the medical and research system and how to build up an appropriate framework as well as to deploy it in detail require ongoing training for all REC members on aspects specific to the research context.

6.6.2.2 Develop communication between RECs

International collaborative research is increasing and especially becomes crucial in research on REEs. While the model of 'single research regulator' is in its experimental process and a controversial topic across countries, current procedure applied in research ethics review which involves seeking ethical approval from individual local committees is currently inevitable in multisite research. Developing communication between RECs appears to be an effective way to improve mutual understanding and recognition among RECs, which can help to avoid unnecessary bureaucratic delays, inconsistencies among RECs, money and energy as reported in my research and dispersedly in studies into the current multiple review system (Gold and Dewa 2005; The Academy of Medical Sciences 2011). Communication between RECs can be facilitated by researchers as in-between contacts and sources of information about the research projects and local contexts. While other proponents of developing communication between RECs into an end of aim to develop consensus among RECs, leading to forms like 'centralized IRB', based on what my research data suggest, other proponents of 'reasonable disagreement' (Richardson 1990; Emanuel et al. 2004), and antagonistic view of 'moral authority of consensus' (Moreno 1988), I would argue for a form of cooperative, collegial discussion between RECs to recognize latent values and ways to mutually facilitate good research.

6.6.2.3 Develop better communication between RECs and investigators

As mentioned above as a way to facilitate cooperation between RECs and suggested by respondents in my research as an approach to impulse and facilitate the review of RECs on research on REEs for a rapid response, communication between researchers and RECs should be established and maintained throughout the research collaboration. On the part of RECs, effective communication strategies with researchers will help the RECs to improve transparency in their decisions, understand practical challenges in doing research in the local context, develop expertise in a particular topic area, understand researchers' perspectives and make researchers mutually understand challenges and duties of RECs. This mutual understanding would eventually place both RECs and researchers in an engaged process whereby research participants are better protected and research can be conducted effectively without being subject to unnecessary delays, misunderstanding and uncertainties.

6.6.2.4 Strengthen research oversight for approved research projects

A proportionate approach to risk (Tansey et al. 2010; The Academy of Medical Sciences 2011) should be considered in the research oversight of RECs. In research on REEs, this should involve 1) enhancing ongoing assessment of risks and benefits of a novel intervention for an epidemic to quickly achieve understanding of the disease and proposed interventions, and 2) simplify procedures for safety reporting when appropriate (e.g. reduce duplicating and over-reporting of all adverse events, changes in drug safety profile). This would help to relieve RECs from being overloaded with administration, focus on genuine risks, terminate the research if it proves to bring harm or be ineffective, and finally provide evidence to inform public

health practice in a timely manner. In the setting of REEs in which there is a lack of scientific information about the disease and safety information of experimental interventions, enhanced monitoring of research projects, instead of delaying the conduct of research then missing research opportunities into the diseases, would enable RECs to keep up with their ultimate duty in REE context, which is to safeguard both the well-being of research participants and the good of public health.

6.6.3 Consent process: duty to protect research participants and develop prosocial behaviour

When research participants/family members are subject to possible sources of vulnerability in the context of REEs as outlined above, the consent process should aim to safeguard the safety and the rights of research participants and benefits of afflicted population. This duty should be taken on by RECs/IRBs, physician-researchers, local and international research institutions and other entities involved in the research in designing, reviewing and implementing research projects. At the same time, the consent process should be developed in a way that will enhance "voluntary actions that are intended to help or benefit another individual or group of individuals" (Eisenberg and Mussen 1989) of research participants, family members and community. This would involve public education about research, for example, the nature and meaning of research and how research would aim to benefit population. As suggested by respondents in my research, sensitizing populations with research information and engaging research participants and communities in the research process, should also be taken into account in any plan for REEs. However, community or public favor for research should not be equated with ethical acceptability for the research project. Support of community, governmental public health sectors and host institutions for research should not be used in a way that might

coerce individuals. Rather, these supports should be employed to enhance trust between research participants/family members and researchers and of research participants/family members in the research. While the consent process may last for a finite period, trust and prosocial behavior requires time to be established. Other strategies to maintain the trust and nurture prosocial behavior for research, as a result, should also be developed as well. Reporting research's result to research participants, family members and community is one of these strategies. Patient and public involvement in research can be considered as well in how their experiences can help in improving the quality of research, e.g. consent process, testing procedure, research visits, and information exchange during this involvement process can help them be familiarized with research in general.

6.7 Limitations of this research

Before bringing this thesis to a conclusion, I would like to outline some of the potential limitations of the research and return briefly to the question of reflexivity with which this chapter began.

In consideration reflexive concerns throughout the research and the contribution of this thesis in the study of ethics of research practice on REEs and other healthcare settings in general, I will present a number of limitations of this research and make suggestions for further research required as a result of the findings.

The first limitation during data collection that respondents were asked about actual ethical problems or challenges that they confronted in some clinical studies on REEs which some of them had completed 3 years before the interview took place. This results in some limitations. First, some respondents could not recall issues or past

events. Second, respondents' recall is subject to bias. They may remember things differently from what those things actually were.

The second limitation lies in the interview method that I adopted: I did not let the interviewees know specifically what questions or topics were to be asked. This method was a part of my methodological intention to enable respondents to talk freely about diverse problems they had encountered and not be confined to a topic identified elsewhere in relevant literature. It however created some difficulty for respondents to relate to moral values or ethical principles to provide elaboration on what are ethical problems and solutions within the short-time frame of an interview. Developing an account of ethical problems that might arise in research requires some knowledge of ethics, an overview of relevant research practice, the issues for discussion, and time for thinking. While most of respondents are not ethicists or not well-trained in research ethics, and had been concerned in only a certain part of the research, some even have low education level (patients and family members), having to recall the research practice and relate this to their experiences to build up a coherent constructed account of ethical problems, arguments and solutions during the restricted time in an interview was difficult. In addition it was necessary to also compare with other disease settings to be able to provide an account of what ethical problems were considered unique to the studied setting. Ethical problems, arguments and solutions were sometimes consequently limited, incoherent and not developed to a deeper level of argument by appealing to various relevant principles and values.

The third limitation that I want to address is using the approach of broad words like "challenges" or "difficulties" in asking about ethical considerations. On one hand, using these terms was intended to broaden the account of issues raised by respondents in cases they were not familiar with the term "ethical issues" and/or confused with

what should or should not be counted as ethical issues. These difficulties and challenges may be genuine ethical problems that they might not perceive as such. However, this method resulted in the reporting of non-ethical scenarios from their narratives such as technical challenges in developing laboratory tests, difficulties at times in contacting laboratory staff for sample delivery at night shift, or the father or mother could not arrange their work to visit their child in the hospital regularly. Though these types of information contribute to the overall understanding of the context, it took quite an amount of time in the interviews to clarify the issues, with and less time available for identifying ethical issues.

Finally, while recalling past events as mentioned above poses limitation in the reconstruction of ethical issues, constructing hypothetical issues based on actual current events also occurs in the interviews is also worth considering in data analysis and presentation. These hypothetical issues may not happen in the present and there may be no direct evidence or detailed elaboration of how an undesirable consequence is assumed to have occurred (Cavender and Kahane 1998). An example of this is competition in research agendas between government and international experts is supposed to lead to the fact that the national government may cease the other party's research. In other words, these issues are drawn from non-direct experience, and their presence is more meaningful in a study investigating the reasoning of a group of people than in the type of empirical research examining actual ethical issues.

6.8 Summary of key contributions of this thesis and future research

This thesis set out to identify and describe the ethical considerations unique to research in rapidly evolving infectious disease epidemics using the case of OUCRU-Viet Nam and its international research network. Given the lack of empirical literature

and international guidelines mapping on a wide range of ethical issues and good research practice for clinical studies conducted in the REE context, this work is important in informing the local and international scientific community, especially who are in the front line of such situation, and public of major ethical considerations and possible solutions for addressing the issues and developing good research practice in the field. To my knowledge, this research is the first empirical project aimed to elicit ethical issues in the setting of REEs by eliciting perspectives of a broad range of key stakeholders directly involved in such epidemics. My research shows that investigating ethical issues from multiple perspectives of key figures involved in the research practice would provide a better understanding of the issues arising through the analysis into the complexity of views with subjective meanings and moral values that people assign to their various experiences of the studied context. Furthermore, this empirical research provides an account of recommendations and views built on experiences of both stakeholders and the researcher on what should be established as good research practice in the research context of REEs, which may be applicable to other research settings as well.

There are other benefits of empirical research into the ethical conduct of a certain research practice through speaking to key stakeholders. First, it provides an account of actual ethical issues and solutions which are context-dependent and tailored to real options in reality. For example, community engagement or local cultural perception about research (e.g. perception of blood) have been raised in literature as issues in research in REEs in which there is a migration of affected population and different perceptions of blood taken would serve as constraints to research. These issues, however, in the context of Viet Nam and other countries, as outlined in previous empirical chapters, might not be a problem or manifest in different ways. Second,

empirical research provides rich accounts of the context and processes occurring in the studied setting. Issues in consent are an example. Without talking with study doctors, study nurses, research participants and family members, we may not have an overview of how obtaining consent has actually been performed in research on REE involving informing with flexibility in types of research information, encouraging, persuading, and significant issues related to vulnerability, responsiveness to the misconception of research participants, or intense sampling which scarcely addressed or neglected in the literature of relevance. Or the different views expressed about equality in the partnership and the general partnership between local and foreign research institutions reveals which elements are involved in long term research collaborations, for example, familiarity, trust and reliance, and how these could facilitate a rapid response in research in REEs. Without this understanding, ethical perspectives about the partnership and solutions put forward to addressing any issue arising in this domain are still narrowed or confused with such concepts as trust, or the value of engagement to enhance trustworthiness.

On a general level, findings from my research suggest that the issues and their relative importance were raised and valued differently between key stakeholder groups depending on the stakeholder's specific role and research experience. Some of the issues which were raised relate to all health related research while some very important considerations were unique to the setting of REEs. Research in REEs is characterized by a complex, interconnected structure of collaborations of involved local and international research stakeholders, research ethics committees, research participants, community and governmental public health sectors.

The findings of this research would serve as basic step for further empirical studies and normative studies into ethical issues and research ethics in the context of public

health emergencies like REEs. In terms of developing a framework for good research practice in the context of REEs, the next steps for further empirical ethics research would possibly involve disseminating findings of this research and a form of ‘moral conversation’ in which researchers will develop a practice space, e.g. a discussion group, meeting, with relevant stakeholders to build the framework or policy (Dunn et al. 2012). These conversations can take place through a model of specification of a detailed account of ethical issues specific to the studied setting and the evaluation of possible solutions based on the content of ethical norms and upheld moral values specified and tailored to the situation (Richardson 1990). With respect to normative ethics research, further research on ethical theories relevant and applicable is needed to arrive at a convincing philosophical account of arguments for the ethical conduct of research in the setting of REEs. While it may be argued that this normative work may lack of support of empirical evidence to fit different perspectives and thus to actually convince involved agents, it still holds its position in providing justificatory forces in considering and arguing for a comprehensive look at the issues in discussion in the combination of ongoing provision of further empirical evidence. In areas where the empirical findings of this thesis are applicable, they can be used to inform the normative work in developing an appropriate framework for the solution of problems at issue. This, in discussing about each of the three levels of collaborations, I have pointed out areas which would require further work on developing informed and solid framework for identified issues.

Despite of limitations outlined in the research, I hope this thesis has contributed to the understanding of research practice and ethical considerations arising in the context of REEs. For hospitals, research institutions, and the public health sector, in the front

line of such public health emergencies, I hope findings of this thesis will help to inform their work and facilitate the development of solutions specific to the setting.

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Appendix 1: List of interviewees

No.	Respondents	Study role	Gender	Location
1	PI4	Principal Investigator, Expatriate	Male	OUCRU HCMC
2	PI13	Principal Investigator, Vietnamese	Male	OUCRU HCMC
3	PI8	Principal Investigator, Expatriate	Male	OUCRU HCMC
4	PI11	Principal Investigator, Vietnamese	Male	OUCRU HCMC
5	Study doctor 1	Study doctor, Vietnamese	Male	HTD
6	Study doctor 2	Study doctor, Vietnamese	Male	HTD
7	Study doctor 3	Study doctor, Vietnamese	Male	HTD
8	Study doctor 4	Study doctor, Vietnamese	Female	HTD
9	SN1	Study nurse, Vietnamese	Female	HTD
10	SN2	Study nurse, Vietnamese	Female	HTD
11	SN3	Study nurse, Vietnamese	Female	HTD
12	IRB1	IRB member, Vietnamese	Female	HTD
13	IRB2	IRB member, Vietnamese	Male	HTD
14	Study Sponsor 1	Study sponsor, Expatriate	Female	OUCRU HCMC
15	P1	Research subject, Vietnamese	Male	HTD
16	P2	Research subject, Vietnamese	Male	HTD
17	P3	Research subject, Vietnamese	Male	HTD
18	FM1	Family member, Vietnamese	Male	HTD
19	FM3	Family member, Vietnamese	Female	HTD
20	FM4	Family member, Vietnamese	Male	HTD
21	Study doctor 1	Study doctor, Vietnamese	Female	CH2
22	Study doctor 2	Study doctor, Vietnamese	Female	CH2
23	Study doctor	Study doctor, Vietnamese	Female	CH2

	3			
24	Study doctor 4	Study doctor, Vietnamese	Male	CH2
25	SN1	Study nurse, Vietnamese	Female	CH2
26	SN2	Study nurse, Vietnamese	Female	CH2
27	IRB1	IRB member, Vietnamese	Male	CH2
28	IRB2	IRB member, Vietnamese	Male	CH2
29	IRB3	IRB member, Vietnamese	Male	CH2
30	FM1	Family member, Vietnamese	Female	CH2
31	FM2	Family member, Vietnamese	Female	CH2
32	FM3	Family member, Vietnamese	Female	CH2
33	FM4	Family member, Vietnamese	Female	CH2
34	FM5	Family member, Vietnamese	Male	CH2
35	FM6	Family member, Vietnamese	Male	CH2
36	FM7	Family member, Vietnamese	Male	CH2
37	PI1	Principal Investigator, Expatriate	Male	OUCRU Ha Noi
38	PI3	Principal Investigator, Expatriate	Female	OUCRU Ha Noi
39	PI5	Principal Investigator, Expatriate	Male	OUCRU Ha Noi
40	PI16	Co-Investigator, Vietnamese	Male	NHTD
41	Study doctor 1	Study doctor, Vietnamese	Female	NHTD
42	Study doctor 2	Study doctor, Vietnamese	Male	NHTD
43	Study doctor 3	Study doctor, Vietnamese	Female	NHTD
44	SN1	Study nurse, Vietnamese	Female	NHTD
45	SN2	Study nurse, Vietnamese	Female	NHTD
46	SN3	Study nurse, Vietnamese	Female	NHTD
47	IRB1	IRB member, Vietnamese	Male	NHTD
48	IRB2	IRB member, Vietnamese	Male	NHTD
49	P1	Research subject, Vietnamese	Male	NHTD
50	P2	Research subject, Vietnamese	Female	NHTD

51	P3	Research subject, Vietnamese	Female	NHTD
52	P4	Research subject, Vietnamese	Female	NHTD
53	FM1	Family member, Vietnamese	Female	NHTD
54	FM2	Family member, Vietnamese	Female	NHTD
55	Funder 1	Study funder, British	Male	Wellcome Trust, UK
56	PI9	Expert in public health and research on infectious diseases, Swiss	Female	WHO, Geneva
57	PI14	Expert in public health and research on infectious diseases, Japanese	Female	WHO, Geneva
58	Policy maker	Policy maker, British	Male	Health Protection Agency, UK
59	PI2	Investigator, British	Male	UK
60	PI6	Investigator, Canadian	Male	Canada
61	PI7	Investigator/Ethics consultant, British	Female	UK
62	PI10	Investigator, Chinese	Male	Hongkong, China
63	PI12	Investigator, Chinese	Male	Beijing, China
64	PI15	Investigator/Member of research ethics committee	Male	Australia

Appendix 2: Consent form for H1N1 influenza study

National Hospital for Tropical Diseases

COMMITMENT FORM

Full name:

Occupation:

Home address:

Phone number:

After being informed by doctor of the necessity of PCR testing for influenza A/H1N1 to help the diagnosis, treatment and research on the disease, I agree to do the testing and comply with all regulations of the National Hospital for Tropical Diseases when I receive healthcare and treatment at the Hospital.

Ha Noi, (date)/ (month)/ 2010

Signature

(Sign and write full name)

Note: Commitment form used in influenza research at NHTD in 2010 before the date signed on official consent form designed in the study.

Appendix 3: Consent form for medical interventions

Health Service:..... Socialist Republic of Viet Nam Code: 03/BV-01
Hospital:..... Independence – Freedom – Happiness Admission no.:...
.....

COMMITMENT FORM FOR ACCEPTANCE OF SURGERY, INTERVENTION AND ANAESTHESIA

Full name: Age:
..... Male/Female
Ethnic: Vietnamese overseas:
Occupation: Work place:
Address:
I am patient/representative of patient's family/full name:
is currently treated at Ward:..... Hospital:

After being informed by doctor of my disease status/my family member/risks incurred for not having surgery, intervention, anaesthesia and possible risks caused by the disease, by operation, intervention, anaesthesia, I voluntarily write this commitment paper:

- Agree to have surgery, intervention, anaesthesia, and leave this paper as proof.
- Do not agree to have surgery, intervention, anaesthesia, and leave this paper as proof.

(Sentence no.1 and no.2 are directly written by patients, representative of patient)

.....

Date.....month.....year.....

Patient/Representative

Instruction: Print in A5 in landscape orientation

Full name:.....

Note: Standard form issued by the Ministry of Health accompanied with Decision no. 4069/2001/QĐ-BYT dated 28 September 2001 on document and patient record forms.

Appendix 4: Study Information Sheet and Consent forms

Template Information Sheets and Consent Form

OXTREC Reference: 33-11

These are template information sheets that will be adjusted following consultation with local informants, to ensure that they are culturally appropriate and understandable. None of the essential information will be altered. Final consent forms can be provided to OXTREC if required

Information Sheet for study team (investigators, study doctors, study nurses)

Title of the Study: The ethics of research in rapidly evolving infectious disease epidemics: an international perspective.

OXTREC Reference: 33-11

Introduction and summary

You are invited to take part in this research study that aims to identify the ethical issues that you or your study team members have encountered and to know how you and your study team members have addressed (or would address) these issues during research conducted in rapidly evolving epidemics, including SARS, bird flu H5N1, swine flu H1N1, dengue and extensively drug resistant microorganisms. The information you and your colleagues provide will be complemented by information provided by other people including research participants, their families, communities, and representatives of the ethical review boards and study funders. This information will help us understand the ethical dilemmas arising at the frontline of these rapidly evolving epidemics and will help us to develop an ethical framework appropriate for emergency epidemic research across cultures in international settings. This study is part of a Doctor of Philosophy study funded by the Wellcome Trust in the Department of Public Health, University of Oxford and the Li Ka Shing Foundation. If you agree to participate, I would like to interview you in a quiet setting of your choice with a voice recorder. The interview may take up to one hour. Your personal information and the interview will be kept confidential; however, anonymised excerpts from the interview may be used in the academic reports of this study.

Objective

The objective of this study is to interview approximately 50 people who are involved in research in rapidly evolving infectious disease epidemics worldwide to identify common ethical issues uniquely arose due to the urgency and magnitude of these epidemics on individual and public health. Our goal is to develop an ethical framework that appropriately addresses the unique issues, taking into account different socio-cultural factors, different healthcare systems and resources in a broader global perspective with the goal to facilitate critical research that are performed in these settings.

Investigators

Ms. Nguyen Thi Cam Binh, DPhil student, Oxford University Clinical Research Unit, Ho Chi Minh City, Viet Nam.

Supervisors:

1. Professor Michael Parker, The Ethox Centre, Department of Public Health, University of Oxford, United Kingdom.
2. Professor Jeremy Farrar, Oxford University Clinical Research Unit, Viet Nam
3. Dr. Thuy Le, Oxford University Clinical Research Unit, Viet Nam.
4. Dr. Philippe Calain, Medecins Sans Frontieres, Switzerland

Participants

People directly involved in research projects during the aforementioned epidemics from Asia, South America and Africa will be invited to participate. These will include study investigators, study doctors, study nurses, patients, their family members, members of study sponsors, of ethical review boards, and of the host community.

Methods

An initial interview lasting up to one hour will be conducted in a suitable location (work office, home, or other meeting venues). The interview will be recorded. The interview will be in English or Vietnamese, however if you prefer the interview in your native language, an experienced and professional interpreter will be arranged. A re-interview and/or a focus group interview may be additionally requested to further discuss specific issues that are brought up during the first interview.

Privacy

All potentially identifiable information (your name, position, other contact information) with the exception of your study role will be removed from the transcripts. The recordings and transcripts of the information you provide will be kept in a locked cabinet, and access will be restricted to only the investigators. Only the interviewer will know which interviewee said what. We will not publish the interviews; however, some anonymised excerpts may be used in academic reports of this study to accurately illustrate your point. If this is done, a piece of text from your interview will appear together with a brief description of your research role (for instance, 'study nurse'), and a code for the interview (for instance, interview No.1).

Additional Information

Your participation in this research project is entirely voluntary, and there are no consequences if you decide not to participate. If during the interview or at a later date

you would like to withdraw from the study, I will terminate the interview and will destroy the recording session at any time. If you would like to withdraw from the study, please contact Ms. Nguyen Thi Cam Binh (contact details below).

Contact Information

If you would like more information about this research project before deciding to participate, or if you have any questions or comments, please contact Ms. Nguyen Thi Cam Binh (+84 (0)989991091) or by email (binhntc@oucru.org).

Template Information Sheet for members of Research Ethics Committees (REC)

Title of the Study: The ethics of research in rapidly evolving infectious disease epidemics: an international perspective.

OXTREC Reference: 33-11

Introduction and summary

You are invited to take part in this research study that aims to identify the ethical issues that Research Ethics Committees have encountered in the review of research on rapidly evolving epidemics including SARS, bird flu H5N1, swine flu H1N1, dengue, and extensively drug resistant microorganisms and to know how you and members of your committee have addressed (or would address) these issues. The information you and your colleagues provide will be complemented by information provided by other people including study investigators, study patients, their families, communities, and study funders. This information will help us understand the ethical dilemmas arising at the frontline of these rapidly evolving epidemics and will later help us to develop an ethical framework appropriate for emergency epidemic research across cultures in international settings. This study is part of a Doctor of Philosophy study funded by the Wellcome Trust in the Department of Public Health, University of Oxford and the Li Ka Shing Foundation. If you agree to participate, I would like to interview you in a private setting of your choice with a voice recorder. The interview may take up to one hour. Your personal information and the interview will be kept confidential; however, anonymised excerpts from the interview may be used in the academic reports of this study.

Objective

The objective of this study is to interview approximately 50 people who are involved in research in rapidly evolving infectious disease epidemics worldwide to identify common ethical issues uniquely arose due to the urgency and magnitude of these epidemics on individual and public health. Our goal is to develop an ethical framework that appropriately addresses the unique issues, taking into account different socio-cultural factors, different healthcare systems and resources in a broader global perspective with the goal to facilitate critical research that are performed in these settings.

Investigators

Ms. Nguyen Thi Cam Binh, DPhil student, Oxford University Clinical Research Unit, Ho Chi Minh City, Viet Nam.

Supervisors:

1. Professor Michael Parker, The Ethox Centre, Department of Public Health, University of Oxford, United Kingdom.
2. Professor Jeremy Farrar, Oxford University Clinical Research Unit, Viet Nam
3. Dr Thuy Le, Oxford University Clinical Research Unit, Viet Nam.
4. Dr. Philippe Calain, Medecins Sans Frontieres, Switzerland

Participants

People directly involved in research projects during the aforementioned epidemics from Asia, South America and Africa will be invited to participate. These will include study investigators, study doctors, study nurses, patients, their family members, members of study sponsors, of ethical review boards, and of the host community. Members of local, national and international ethical review boards who have reviewed these research studies and have experiences reviewing research projects in rapidly evolving epidemics, for instance, Oxford Tropical Research Ethics Committee (OXTREC), are invited to participate.

Methods

An initial interview lasting up to one hour will be conducted in a suitable location (work office, home, or other meeting venues). The interview will be recorded. The interview will be in English or Vietnamese, however if you prefer the interview in your native language, an experienced and professional interpreter will be arranged. A re-interview and/or a focus group interview may be additionally requested to further discuss specific issues that are brought up during the first interview.

Privacy

All potentially identifiable information (your name, position, other contact information) with the exception of your study role will be removed from the transcripts. The recordings and transcripts of the information you provide will be kept in a locked cabinet, and access will be restricted to only the investigators. Only the interviewer will know which interviewee said what. We will not publish the interviews; however, some anonymised excerpts may be used in academic reports of this study to accurately illustrate your point. If this is done, a piece of text from your interview will appear together with a brief description of your research role (for

instance, ‘member of research ethics committee’), and a code for the interview (for instance, interview No.1).

Additional Information

Your participation in this research project is entirely voluntary, and there are no consequences if you decide not to participate. If during the interview or at a later date you would like to withdraw from the study, I will terminate the interview and will destroy the recording session at any time. If you would like to withdraw from the study, please contact Ms. Nguyen Thi Cam Binh (contact details below).

Contact Information

If you would like more information about this research project before deciding to participate, or if you have any questions or comments, please contact Ms. Nguyen Thi Cam Binh ((+84 (0)989991091) or by email (binhntc@oucru.org).

Template Information Sheet for Representatives of Funding

Body/Sponsors

Title of the Study: The ethics of research in rapidly evolving infectious disease epidemics: an international perspective.

OXTREC Reference: 33-11

Introduction and summary

You are invited to take part in this research study that aims to identify the ethical issues that research funders/sponsors might have encountered in relation to the conduct of research on rapidly evolving epidemics, including SARS, bird flu H5N1, swine flu H1N1, dengue and extensively drug resistant microorganisms. The information you and your colleagues provide will complement information provided by other people including study investigators, research participants, their families, communities, and representatives of the ethical review boards. This information will help us understand the ethical dilemmas arising at the frontline of these rapidly evolving epidemics and will later help us to develop an ethical framework appropriate for emergency epidemic research across cultures in international settings. This study is part of a Doctor of Philosophy study funded by the Wellcome Trust in the Department of Public Health, University of Oxford and the Li Ka Shing Foundation. If you agree to participate, I would like to interview you in a private setting of your choice with a voice recorder. The interview may take up to one hour. Your personal information and the interview will be kept confidential; however, anonymised excerpts from the interview may be used in the academic reports of this study.

Objective

The objective of this study is to interview approximately 50 people who are involved in research in rapidly evolving infectious disease epidemics worldwide to identify common ethical issues uniquely arose due to the urgency and magnitude of these epidemics on individual and public health. Our goal is to develop an ethical framework that appropriately addresses the unique issues, taking into account different socio-cultural factors, different healthcare systems and resources in a broader global perspective with the goal to facilitate critical research that are performed in these settings.

Investigators

Ms. Nguyen Thi Cam Binh, DPhil student, Oxford University Clinical Research Unit, Ho Chi Minh City, Viet Nam.

Supervisors:

1. Professor Michael Parker, The Ethox Centre, Department of Public Health, University of Oxford, United Kingdom.
2. Professor Jeremy Farrar, Oxford University Clinical Research Unit, Viet Nam
3. Dr Thuy Le, Oxford University Clinical Research Unit, Viet Nam
4. Dr. Philippe Calain, Medecins Sans Frontieres, Switzerland

Participants

People directly involved in research projects during the aforementioned epidemics from Asia, South America and Africa will be invited to participate. These will include study investigators, study doctors, study nurses, patients, their family members, members of study sponsors, of ethical review boards, and of the host community. Representatives of the study funders and sponsors, including the Wellcome Trust, UK; Medical Research Councils, UK; the National Institutes of Health, USA; World Health Organization (WHO); Medicins sans Frontieres Switzerland; International Red Cross, will be invited to participate.

Methods

An initial interview lasting up to one hour will be conducted in a suitable location (work office, home, or other meeting venues). The interview will be recorded. The interview will be in English or Vietnamese, however if you prefer the interview in your native language, an experienced and professional interpreter will be arranged. A re-interview and/or a focus group interview may be additionally requested to further discuss specific issues that are brought up during the first interview.

Privacy

All potentially identifiable information (your name, position, other contact information) with the exception of your study role will be removed from the transcripts. The recordings and transcripts of the information you provide will be kept in a locked cabinet, and access will be restricted to only the investigators. Only the interviewer will know which interviewee said what. We will not publish the interviews; however, some anonymised excerpts may be used in academic reports of this study to accurately illustrate your point. If this is done, a piece of text from your interview will appear together with a brief description of your research role (for

instance, ‘study sponsor/funder’), and a code for the interview (for instance, interview No.1).

Additional Information

Your participation in this research project is entirely voluntary, and there are no consequences if you decide not to participate. If during the interview or at a later date you would like to withdraw from the study, I will terminate the interview and will destroy the recording session at any time. If you would like to withdraw from the study, please contact Ms. Nguyen Thi Cam Binh (contact details below).

Contact Information

If you would like more information about this research project before deciding to participate, or if you have any questions or comments, please contact Ms. Nguyen Thi Cam Binh ((+84 (0)989991091) or by email (binhntc@oucru.org).

Template Information Sheet for research participants, their family members, and representatives of their communities

Title of the Study: The ethics of research in rapidly evolving infectious disease epidemics: an international perspective.

OXTREC Reference: 33-11

Introduction and summary

You are invited to take part in this research study that aims to explore the ethical issues arising in research on rapidly evolving epidemics including SARS, bird flu H5N1, swine flu H1N1, dengue, and very drug resistant microorganisms. The study aims to develop an ethical framework and guidelines for good practice in this kind of research. We would like to interview you to find out your views about the issues you think are important about participating in research projects of this kind, and how you/your family/community would like or would have liked these issues to be addressed if they arose during participation in research of rapidly evolving epidemics. The information you provide will be complemented by information provided by interviews with other people including study investigators, members of the ethical review boards, and representatives of funding bodies. Together, this information will help us understand the ethical dilemmas arising at the frontline of these rapidly evolving epidemics and will later help us to develop ethical principles and procedures appropriate for emergency epidemic research across cultures in international settings. This study is part of a PhD study funded by the Wellcome Trust in the Department of Public Health, University of Oxford and the Li Ka Shing Foundation. If you agree to participate, I would like to interview you in a setting of your choice with a voice recorder. The interview may take up to one hour. Your personal information and the interview will not be revealed to anyone who are not part of this study; however, unidentified phrases from the interview may be used in the academic reports of this study.

Objective

The objective of this study is to interview approximately 50 people who are involved in research in rapidly evolving infectious disease epidemics worldwide to identify common ethical issues uniquely arose due to the urgency and magnitude of these epidemics on a patient and the public. Our goal is to develop some guiding principles

and procedures that appropriately addresses the unique issues, taking into account the different socio-cultural factors, different healthcare systems and resources in a broader global perspective with the goal to facilitate critical research that are performed in these settings.

Investigators

Ms. Nguyen Thi Cam Binh, DPhil student, Oxford University Clinical Research Unit, Ho Chi Minh City, Viet Nam.

Supervisors:

1. Professor Michael Parker, The Ethox Centre, Department of Public Health, University of Oxford, United Kingdom.
2. Professor Jeremy Farrar, Oxford University Clinical Research Unit, Viet Nam
3. Dr Thuy Le, Oxford University Clinical Research Unit, Viet Nam
4. Dr Philippe Calain, Medecins Sans Frontieres, Switzerland.

Participants

People directly involved in research projects during the aforementioned epidemics from Asia, South America and Africa will be invited to participate. These will include study investigators, study doctors, study nurses, research patients, their family members, members of study sponsors, of ethical review boards, and of the host community. You, a member of your family, and a representative of your community are invited to participate in this project because you have participated in a research projects during these infectious disease epidemics.

Methods

An initial interview lasting up to one hour will be conducted in a suitable location (work office, home, or other meeting venues). The interview will be recorded. The interview will be in English or Vietnamese, however if you prefer the interview in your native language, an experienced and professional interpreter will be arranged. A re-interview and/or a focus group interview may be additionally requested to further discuss specific issues that are brought up during the first interview.

Privacy

All potentially identifiable information (your name, position, other contact information) with the exception of your role as a research participant will be removed from all published papers. The voice recordings and paper transcripts of the information you provide will be kept in a locked cabinet, and access will be restricted to only the investigators. Only the interviewer will know which interviewee said what.

We will not publish the interviews; however, some unidentified phrases may be used in academic reports of this study to accurately illustrate your point. If this is done, a piece of text from your interview will appear together with a brief description of your research role (for instance, ‘research participant/family member/representative of host community’), and a code for the interview (for instance, interview No.1).

Additional Information

Your participation in this research project is entirely voluntary, and there are no consequences if you decide not to participate. If during the interview or at a later date you would like to withdraw from the study, I will terminate the interview and will destroy the recording session at any time. If you would like to withdraw from the study, please contact Ms. Nguyen Thi Cam Binh (contact details below).

Contact Information

If you would like more information about this research project before deciding to participate, or if you have any questions or comments, please contact Ms. Nguyen Thi Cam Binh ((+84 (0)989991091) or by email (binhntc@oucru.org).

Information Sheet for International Experts

Title of the Study: The ethics of research in rapidly evolving infectious disease epidemics: an international perspective.

OXTREC Reference: 33-11

Introduction and summary

You are invited to take part in this research study that aims to identify the ethical issues that you or your study team members have encountered and to know how you and your study team members have addressed (or would address) these issues during research conducted in rapidly evolving epidemics, including SARS, bird flu H5N1, swine flu H1N1, dengue and extensively drug resistant microorganisms. The information you and your colleagues provide will be complemented by information provided by other people including research participants, their families, communities, and representatives of the ethical review boards and study funders. This information will help us understand the ethical dilemmas arising at the frontline of these rapidly evolving epidemics and will help us to develop an ethical framework appropriate for emergency epidemic research across cultures in international settings. This study is part of a Doctor of Philosophy study funded by the Wellcome Trust in the Department of Public Health, University of Oxford and the Li Ka Shing Foundation. If you agree to participate, I would like to interview you in a quiet setting of your choice with a voice recorder. The interview may take up to one hour. Your personal information and the interview will be kept confidential; however, anonymised excerpts from the interview may be used in the academic reports of this study.

Objective

The objective of this study is to interview approximately 50 people who are involved in research in rapidly evolving infectious disease epidemics worldwide to identify common ethical issues uniquely arose due to the urgency and magnitude of these epidemics on individual and public health. Our goal is to develop an ethical framework that appropriately addresses the unique issues, taking into account different socio-cultural factors, different healthcare systems and resources in a broader global perspective with the goal to facilitate critical research that are performed in these settings.

Investigators

Ms. Nguyen Thi Cam Binh, DPhil student, Oxford University Clinical Research Unit, Ho Chi Minh City, Viet Nam.

Supervisors:

1. Professor Michael Parker, The Ethox Centre, Department of Public Health, University of Oxford, United Kingdom.
2. Professor Jeremy Farrar, Oxford University Clinical Research Unit, Viet Nam
3. Dr. Thuy Le, Oxford University Clinical Research Unit, Viet Nam.
4. Dr. Philippe Calain, Medecins Sans Frontieres, Switzerland

Participants

International experts who have been involved in international collaborative research and directly worked with Vietnamese partners or who have been part of a collaboration with Oxford University Clinical Research Unit (OUCRU), Viet Nam as part of the same research project. These will include investigators, policy makers, sponsors/funders, and ethics advisors.

Methods

An initial interview lasting up to one hour will be conducted in a suitable location (work office, home, or other meeting venues). The interview will be recorded. The interview will be in English or Vietnamese, however if you prefer the interview in your native language, an experienced and professional interpreter will be arranged. A re-interview and/or a focus group interview may be additionally requested to further discuss specific issues that are brought up during the first interview.

Privacy

All potentially identifiable information (your name, position, other contact information) with the exception of your study role will be removed from the transcripts. The recordings and transcripts of the information you provide will be kept in a locked cabinet, and access will be restricted to only the investigators. Only the interviewer will know which interviewee said what. We will not publish the interviews; however, some anonymised excerpts may be used in academic reports of this study to accurately illustrate your point. If this is done, a piece of text from your interview will appear together with a brief description of your research role (for instance, 'study nurse'), and a code for the interview (for instance, interview No.1).

Additional Information

Your participation in this research project is entirely voluntary, and there are no consequences if you decide not to participate. If during the interview or at a later date you would like to withdraw from the study, I will terminate the interview and will destroy the recording session at any time. If you would like to withdraw from the study, please contact Ms. Nguyen Thi Cam Binh (contact details below).

Contact Information

If you would like more information about this research project before deciding to participate, or if you have any questions or comments, please contact Ms. Nguyen Thi Cam Binh (+84 (0)989991091) or by email (binhntc@oucru.org).

Consent form

Full Title: The ethics of research in rapidly evolving infectious disease epidemics: an international perspective.

OXTREC Reference: 33-11

Have you been provided with sufficient information about the study? Yes No

Have you had an opportunity to ask questions and discuss this study? Yes No

Have you received satisfactory answers to all your questions? Yes No

Do you understand that your participation is voluntary, and that you are free to withdraw from the study at any time?

Yes No

Do you agree to take part in this study? Yes No

Signature.....Date.....

Name in block letters

.....

Investigator Statement

I confirm that I have carefully explained the proposed study to the participant.

Signature.....Date.....

Name in block letters

.....

Appendix 3 Guide for semi-structured interviews

A. Pilot interview guide:

A survey aimed at increasing our understanding of ethical issues identified by study staff involved in research projects at OUCRU and HTD and how this issues evolved during the response to the Influenza 2009H1N1 pandemic

Objectives:

1. To describe the ethical challenges encountered by study staff during a pandemic and document some of the important practical ethical issues presented by research on emerging infections.
2. To document some of the approaches and methods used by study teams to find solutions to address these challenges in the context of a rapidly emerging problem.
3. To explore views about potential resolutions for such ethical challenges

Participants: Vietnamese and international investigators, study doctors, nurses, coordinators and laboratory technicians participating in research projects during the Influenza pandemic

Method:

Standardized Open-ended Interview and Informal Conversational Interview will be used in combination.

These structured interviews will collect information on what sort of ethical issues study members encountered and how they addressed these issues as they arose in the context of research conducted during the 2009H1N1 influenza pandemic. The information will be used to help evaluate the reality of such a response in the practical setting of a hospital and research institute at the frontline of an epidemic.. This will help to establish future research ethics studies aimed at developing a framework for study staff to engage in and identify solutions for ethical issues arising in epidemic research

1) What roles have you taken in H1N1 influenza pandemic research?

1. Investigator
2. Study doctor
3. Study nurse
4. Coordinator
5. Lab Technician
6. Other

1) What was involved in your role?

2) In what ways did the influenza pandemic make your work be more difficult or challenging? Can you tell me the reasons for this?

3) Now going back to each of the work that you have described in your role, what have you found to be difficult/challenging aspects or potentially important issues in each area of your work in the setting of the pandemic?

Try to test and expand the following issues:

IRB Review

Individual informed consent

Collection and Storage of biological specimens

Duty to care

Standard of care

Personal fears of dealing with the pandemic at work or at home

4) Have there been situations in which you have faced difficult decisions because of tensions between your different roles, e.g. doctor and investigator, investigator and study doctor?

- 5) In your experience, which of the following have been helpful to you in identifying issues including ethical considerations?
1. Comments/recommendations of Institutional Review Board(s)
 2. From ethical issues arising in conducting research
 3. From surmises inferred from the nature of research and activities planned to implement the research
 4. From trainings in research ethics and good clinical practice
 5. Self acquisition from international and/or national research ethics guidelines in research
 6. From experiences of colleagues who are not study members
 7. From reports of monitor and auditor
 8. From discussion with study team
 9. From discussions with senior staff
 10. From discussions with the Directors of Wards, Hospitals or Research Institutions
 11. From discussions with family and friends away from work
 12. The media
 13. Other sources: _____
- 6) In practice, can you identify any ways in which you/your study team resolved each of the issues?
- 7) Do you think these resolutions were reasonable? In your viewpoint and experience, is there any better way to resolve each of these issues?
- 8) It is likely that Vietnam will experience future epidemics. Are there any lessons you have learnt from your experiences which might help guide you and others in the future.
- 9) Do you have any other thoughts or suggestions or comments which I have not covered.

B. Interview guides for Phase 1 in Viet nam:

INTERVIEW GUIDANCE FOR STUDY STAFF

Demographic Information	
1. Full name:	2. Gender: <input type="radio"/> Male <input type="radio"/> Female
3. Interview date: [][]/[][]/[][] Date Month Year	4. Nationality:
5. Age:	6. Ethnicity:
7. Study role:	8. Employer:
Questions:	
General information about the research and research work	
1) Which emergency epidemic research project/s have you been involved in (H1N1, H5N1, SARS)?	
2) Have you worked full time for research or do you have another job while partaking in the research project? What work takes up most of your time?	
3) Can you describe how participating in these research projects affect your work?	
4) Does the research involve any collaboration? Who are the collaborative partners (national and international?) in the projects? And what role do they play in the research?	
Experience in research participation	
Pre-study	
Study Planning	
1) What is your participation in planning research in rapidly evolving epidemics? Can you briefly describe the work that you have done?	
2) What is your experience in planning research on rapidly evolving epidemics in terms of ethical considerations or issues or advantages when taking into account of special characteristics such as its wide spread, sudden onset, short in duration and unpredictable? Can you give me specific examples?	
3) Why do you see them as difficulties or challenges or issues?	
4) How did you overcome these challenges? Can you give me specific examples? If nothing could be done, why not?	
5) Do you have suggestions to resolve the issues with respect to the nature of the evolving	

situation in an epidemic?

- 6) In what way do you think the nature of rapidly evolving in an epidemic can facilitate your work?

[Probe the participants around such processes: research design and development, ethics review, plans for collaboration, community and research subject approach)

During the study

- 7) What type of work have you involved in during the implementation/execution of the research?
- 8) Can you describe your experience in the implementation/execution of the research in terms of ethical considerations or issues and also any advantage under the setting of rapid evolvement and emergency of the epidemics? Can you give me specific examples?
- 9) Why do you see them as difficulties or challenges or issues?
- 10) How did you overcome these challenges? Can you give me specific examples?

If nothing could be done, why not?

- 11) Do you have suggestions to resolve the issues with respect to the nature of the evolving situation in an epidemic?

- 12) In what way do you think the nature of rapidly evolving in an epidemic can facilitate your work?

[Probe the participants around such processes: research subject recruitment, things happening with research subjects, any of their considerations about the research process]

Post study

- 13) Can you describe your experience of the work you have done after the research was completed or terminated?

Do you have any ethical concern about or find it challenging? If yes, why?

- 14) What things do you think should be done after the research is completed or terminated?

Do you have any ethical concern about it or find it challenging? If yes, why?

- 15) In what way do you think the nature of rapidly evolving in an epidemic can facilitate your work?

- 16) How did you overcome these challenges? Can you give me specific examples?

If nothing could be done, why not?

- 17) Do you have any suggestion to improve the situation?

[Probe the participants around such processes: research result reporting, publication, any activities that they have done after the completion of the study]

Is there any other issue in research in rapidly evolving epidemic you have experienced or

think of which you would like to talk about? Why is it an issue/challenge/difficulty? What did you do about it? How do you suggest it should be improved?

INTERVIEW GUIDANCE FOR STUDY SPONSORS/FUNDERS

Demographic Information	
1. Full name:	2. Gender: <input type="radio"/> Male <input type="radio"/> Female
3. Interview date: [][]/[][]/[][] <div style="text-align: center; font-size: small;">Date Month Year</div>	
4. Age:	5. Nationality:
6. Working position:	7. Working place:
Questions:	
<p>Background:</p> <ol style="list-style-type: none"> 1) Can you briefly describe your professional background? 2) Can you describe briefly the research on rapidly evolving epidemics that your institution has sponsored/funded? 3) Can you briefly describe the role and responsibility of your institution as a sponsor/funder in the research? 4) How did the decision made in sponsoring/funding the research project in emergency epidemics? <p>Experience in sponsoring/funding research</p> <ol style="list-style-type: none"> 5) Can you describe your experience in sponsoring/funding the research in rapidly evolving epidemics in terms of ethical considerations, issues and advantages with respect to the nature of rapidly evolving of the epidemics? 6) Why does the sponsoring/funding committee see them as ethical considerations/issues/advantages? 7) How did the committee resolve the problems? If nothing could be done, why not? 8) Did you find the solutions satisfied? If not, do you have any other suggestion? <p>Is there any other issue in research in rapidly evolving epidemic you have experienced or think of which you would like to talk about? Why is it an issue/challenge/difficulty? What did you do about it? How do you suggest it should be improved?</p>	

INTERVIEW GUIDANCE FOR RESEARCH PARTICIPANTS OF EPIDEMIC RESEARCH

Demographic Information	
1. Full name:	2. Gender: <input type="radio"/> Male <input type="radio"/> Female
3. Interview date: [][]/[][]/[][] <div style="text-align: center; font-size: small; margin-top: 5px;">Date Month Year</div>	
4. Age:	5. Ethnicity:
Questions:	
<p>General information about the research</p> <p>1) Which emergency epidemic research project/s have you been involved in (H1N1, H5N1, SARS)?</p> <p>2) How did you know about the research?</p> <p>3) Can you briefly tell me what you know about the research that you have participated?</p> <p>4) What made you decide to participate in the research?</p> <p>5) Have you participated in other research? Can you briefly tell me what that research is about?</p> <p>Experience in research participation</p> <p>6) Can you describe how you were approached for the research participation?</p> <p>7) Can you describe what you were required to do with your participation in the research?</p> <p>8) What is your experience in participating in such emergency research in terms of difficulties or issues or advantages?</p> <p style="margin-left: 20px;">If the interviewee participated in other research out of rapidly evolving epidemic setting, ask them:</p> <p style="margin-left: 20px;">How do you find participating in emergency research different from other research you have involved?</p> <p>9) In what way, do you see them as issues/difficulties and advantages?</p> <p>10) How were the issues/challenges overcome/resolved?</p> <p style="margin-left: 20px;">If nothing could be done, why not?</p> <p>11) Do you find the solutions satisfied? If not, how do you want them to be improved?</p> <p>12) What is your expectation from participating in the research in emergency epidemics?</p> <p style="margin-left: 20px;">Do you think the research has met your expectations?</p>	

If yes, in what way?/If no, in what way?

Is there any other issue in research in rapidly evolving epidemic you have experienced or think of which you would like to talk about? Why is it an issue/challenge/difficulty? What did you do about it? How do you suggest it should be improved?

INTERVIEW GUIDANCE FOR IRB MEMBERS

Demographic Information	
1. Full name:	2. Gender: <input type="radio"/> Male <input type="radio"/> Female
3. Interview date: [__ __]/[__ __]/[__ __] <div style="text-align: center; font-size: small;">Date Month Year</div>	
4. Age:	5. Ethnicity:
6. Employer:	
Questions:	
Background:	
<ol style="list-style-type: none"> 1) Can you briefly describe your professional background? 2) Can you briefly describe the role and responsibility of the ethics committee in research? 3) What is your role in the research ethics committee? How long have you been in the committee and have you received any particular training for your work as a member of the research ethics committee? 4) What rapidly evolving epidemic do the reviewed research projects were on? (H1N1, H5N1, SARS, etc) 	
Experience in research ethics review and oversight	
<ol style="list-style-type: none"> 5) Can you describe your experience in reviewing and overseeing the research in each of the rapidly evolving epidemics in terms of difficulties, challenges, issues and advantages with respect to the nature of rapidly evolving of the epidemics? 6) Why does the committee see them as difficulties/challenges/issues/advantages? 7) How did the committee resolve the problems? If nothing could be done, why not? 8) Did you find the solutions satisfied? If not, do you have any other suggestion? 	
Issues raised in the research projects	
<ol style="list-style-type: none"> 9) Can you describe ethical issues or considerations raised by the nature of emergency and rapid evolvement of the epidemics in the research projects that the committee has been reviewed? 10) Why does the committee see them as ethical issues or considerations? 11) In what way does the committee suggest the issues to be resolved? 12) Did you find the solutions satisfied? If not, do you have any suggestion to improve them? 	
Is there any other issue in research in rapidly evolving epidemic you have experienced	

**or think of which you would like to talk about? Why is it an issue/challenge/difficulty?
What did you do about it? How do you suggest it should be improved?**

INTERVIEW GUIDANCE FOR FAMILY MEMBERS

Demographic Information	
1. Full name:	2. Gender: <input type="radio"/> Male <input type="radio"/> Female
3. Interview date: [__][__]/[__][__]/[__][__] <div style="text-align: center; font-size: small; margin-top: 5px;">Date Month Year</div>	
4. Age:	5. Ethnicity:
6. Relationship to the research subject:	
Questions:	
General information about the research	
1) Which emergency epidemic research project/s has your family member involved in (H1N1, H5N1, SARS)?	
2) How did you know about the research?	
3) Can you briefly tell me what you know about the research that your family member has participated?	
4) Did you family member involve in any other research out of emergency epidemics?	
Experience in research participation	
5) Can you describe how you and your family member were approached for the research participation?	
6) Can you describe what you were required to do with your family member's participation in the research?	
7) Did you have any concerns for your family member being in the emergency epidemic research?	
8) What made you decide for her/him to participate in the research in rapidly evolving epidemics?	
9) What is your experience in letting your family member participate in such emergency research in terms of difficulties or issues or advantages?	
If their family member participated in other research out of rapidly evolving epidemic setting, ask them:	
How do you find participating in emergency research different from other research your family member has involved?	
10) In what way, do you see them as issues/difficulties and advantages?	
11) How were the issues/challenges overcome/resolved?	

If nothing could be done, why not?

12) Do you find the solutions satisfied? If not, how do you want them to be improved?

13) What is your expectation from letting your family member participate in the research in emergency epidemics? Do you think the research has met your expectations?

If yes, in what way?/If no, in what way?

Is there any other issue in research in rapidly evolving epidemic you have experienced or think of which you would like to talk about? Why is it an issue/challenge/difficulty? What did you do about it? How do you suggest it should be improved?

C. Topic guides and interview guides for Phase 2 with international experts

Topic guides for investigators

The interview will focus on experience of investigators on 4 main areas. However, in order to ensure the flexibility in the type of issues and issues of significance perceived by the respondents, questions about their work experience and general experience of ethical considerations are still posed to the interviewees to open following discussions.

Topics to cover:

- General information about the research and research work
- Experience in research response in epidemic situation, research participation and ethical considerations in general (asking ethical considerations in general at this stage would also help respondents prepare and recall ethical considerations they have experienced in following focused topics)
- Research subjects and family members: ability to give consent, community engagement
- Experience of research role in relation to other health initiatives in response to epidemic situation
- Impact of collaboration to research and ethical considerations raised in the dynamics of that collaboration

Suggested semi-structured questions:

General information about the research and research work

- 1) Which emergency epidemic research project/s have you been involved in (H1N1, H5N1, SARS, HFMD)?
- 2) Apart from doing research, what other types of work have you done?
- 3) Can you tell me about your experience of both working in the research and covering other work as you have mentioned?
- 4) Does the research involve any collaboration? Who are the collaborative partners (national and international?) in the projects? And what role do they play in the research?

Experience in research participation

- 5) Can you describe briefly the work that you have been involved when taking part in research in rapidly evolving epidemics?

- 6) What is your experience of research activities, especially clinical research involving human subjects in response to rapidly evolving epidemics in general?
- 7) In the situation of such emergency epidemics, what is your experience of ethical considerations arising in implementing research into such epidemics?

Now I would like to discuss with you further about 4 following topics:

Research subjects and family members

- 8) What is your experience of the ability of research subjects and family members to give consent to research on rapidly evolving epidemics?
- 9) What types of ethical considerations should be raised in relation to the ability of research subjects and family members to give consent to research in the setting of rapidly evolving epidemics?
- 10) How do you think these issues can be resolved?
- 11) Is there any other ethical consideration that you might think of in relation to research participants participating in emergency epidemic research? How do you think the issues can be resolved?
- 12) There is opinion that community engagement is imperative in research on rapidly evolving epidemics, and that community engagement is suggested as an ethical responsibility of investigators in research in general, what is your experience of community engagement in this emergency epidemic setting?

Relation between medical care, public health and research

- 13) How do you think about the relation between medical care, public health and research in response to rapidly evolving epidemics, especially research involving human subjects?
- 14) How do you think the public health and other medical practice and policies would in any way affect research activities on emergency epidemics, especially clinical research involving human subjects?
- 15) How do you think the research would in any way affect other health initiatives in response to such emergency epidemics?
- 16) Opinions have been raised that there should be a balance between public health practice and research in terms of priority and the rigor of applied standards, how do you think about this?

Collaboration

17) What is your experience of local and international collaboration in the research response to rapidly evolving epidemics in terms of the level of collaboration and the dynamics of that collaboration?

18) In what aspects the collaboration would affect research in rapidly involving epidemics?

19) Would the collaboration in research response in the setting of emergency epidemics raise any ethical consideration? If yes, what it is and how would you suggest it to be resolved?

(Probe them on: the nature of collaboration, level of understanding, conflict of interest and benefit sharing, scientific integrity, power balance between relevant parties)

IRB/IEC ethics review and oversight

20) What is your experience of ethics review and oversight process that IRBs or IECs applied to international collaborative research projects in response to the setting of rapidly evolving epidemics?

21) Would each of any process that you have described raise any ethical consideration? If yes, what it is and in what way do you suggest the issues to be resolved?

Probe them on: response of the involved IRBs, appropriateness of existing IRB review and oversight mechanisms towards research activities in emergency epidemics, ethical dilemmas caused by different requirements of different local and international IRBs, and how to address different requirements and ethical dilemmas, the impact and binding of public health policy on research proposals and their feasibility.

22) In your opinion, what elements would affect the decision of IRBs/IECs in reviewing an international collaborative research project on rapidly emerging epidemics? And in what way?

Is there any other issue in research in rapidly evolving epidemic you have experienced or think of which you would like to talk about? Why is it an issue/challenge/difficulty? What did you do about it? How do you suggest it should be improved?

TOPIC GUIDES FOR POLICY MAKERS

Topics to cover:

- Experience in discussing and decision making public health/health policies in response to the setting of rapidly evolving epidemics to understand about general principles and other factors that might influence the decision making (lack of evidence, uncertainties, international collaboration, public health interventions, norms and standards required by relevant international and local research guidelines) and how they might influence in the decision making.
- Perceptions on the role of research and research standards in relation to public health and medical care in the epidemic response
- Interaction of research to other health related initiatives and vice versa in response to emergency epidemic settings.
- Impact of collaboration on the policy making and ethical considerations raised in the dynamics of that collaboration

Suggested semi-structured questions:

Experience of policy making in response to epidemic setting

- 1) Which rapidly evolving epidemics have you involved in the policy making?
- 2) What elements would be taken into consideration in making policies in response to such rapidly evolving epidemics?
- 3) Can you describe your experience in discussing and making policies in such emergency epidemic response?

Overview of research activities in emergency epidemics

- 4) How do you situate research in the overall response to rapidly evolving epidemics?
- 5) What is your opinion about the research response to rapidly evolving epidemics that you have experienced?

Relation between medical care, public health and research

- 6) How do you think about the relation between medical care, public health and research in response to rapidly evolving epidemics, especially research involving human subjects?

- 7) How do you think about the public health policies and other health related policies would in any way affect research activities on emergency epidemics, especially clinical research involving human subjects?
- 8) How do you think the research would in any way affect the making and applying health related policies in response to such emergency epidemics?
- 9) Opinions have been raised that there should be a balance between public health practice and research in terms of priority and the rigor of applied standards, how do you think about this?

Collaboration

- 10) What is your experience of collaboration in the research response to rapidly evolving epidemics in terms of the level of collaboration and the dynamics of that collaboration?
- 11) Would the collaboration with international partners in any way affect the making and applying research related policies in response to the emergency epidemics? If yes, in what way?
- 12) Would the collaboration in research response in the setting of emergency epidemics cause any ethical consideration? If yes, what it is and how would you suggest it to be resolved?

Is there any other issue in research in rapidly evolving epidemic you have experienced or think of which you would like to talk about? Why is it an issue/challenge/difficulty? What did you do about it? How do you suggest it should be improved?

TOPIC GUIDES FOR IRB MEMBERS

Topics to cover:

- Roles and responsibilities of the IRB members
- Their role and types of work involve in their role
- Experience of reviewing clinical research projects in rapidly evolving epidemics, especially those conducted in international collaboration (to understand about factors/elements involving in their review, difficulties/challenges, their priorities and working principles)
- Experience of ethical considerations raised by the research in rapidly evolving epidemics, especially in international collaborative research projects (international collaboration, available public health interventions, culture, norms and standards required by relevant international and local research guidelines).
- Suggestions of ways to address ethical considerations.

Suggested semi-structured questions:

Experience in research review and oversight

- 1) What is your experience of ethics reviewing and overseeing international collaborative research projects in rapidly evolving epidemics?
- 2) What is your opinion about the ethics review and oversight process that have been applied to international collaborative research in response to rapidly evolving epidemics?
- 3) Do you have any ethical consideration for ethics review and oversight process which have been applied to international collaborative clinical research on such emergency epidemics?

If yes, what it is and in what way do you suggest the issues to be resolved?

IRB decision making process

- 4) In the setting of rapidly evolving epidemics where there is lack of evidence about the diseases, and uncertainties about the epidemic situation and proposed treatments, how would the final decision be reached among IRB members?
- 5) What is your opinion about the decision making process(es) of IRBs that you have described in response to the setting of emergency epidemics?

Multiple ethics review

- 6) In the context of emergency epidemics, what is your opinion about having multiple IRB reviews in reviewing international collaborative research projects?
- 7) Would this multiple review raise any ethical consideration in the research response to rapidly evolving epidemics? If yes, what it is and in what way do you suggest the issues to be resolved?

Research subjects and family members

- 8) How do you think about the ability of research subjects and family members to give consent to research on rapidly evolving epidemics?
- 9) What types of ethical considerations should be raised in relation to the ability of research subjects and family members to give consent to research in the setting of rapidly evolving epidemics?
How do you think these issues can be resolved?
- 10) Is there any other ethical consideration that might arise in relation to research participants participating in emergency epidemic research? How do you think the issues can be resolved?
- 11) There is opinion that community engagement is imperative in research on rapidly evolving epidemics, and that community engagement is suggested as an ethical responsibility of investigators in research in general, what is your experience of community engagement in this emergency epidemic setting?

Issues raised in the research projects

- 12) Can you describe other ethical issues or considerations raised by the nature of emergency and rapid evolution of the epidemics in the research projects that the committee has been reviewed?
- 13) Why does the committee see them as ethical issues or considerations?
- 14) In what way does the committee suggest the issues to be resolved?
- 15) Did you find the solutions satisfied? If not, do you have any suggestion to improve them?

Is there any other issue in research in rapidly evolving epidemic you have experienced or think of which you would like to talk about? Why is it an issue/challenge/difficulty? What did you do about it? How do you suggest it should be improved?

TOPIC GUIDES FOR ETHICS CONSULTANT

Topics to cover:

- Roles and responsibilities of the ethics consultant
- Their role and types of work involve in their role
- Experience of reviewing clinical research projects in rapidly evolving epidemics, especially those conducted in international collaboration (what ethical aspects are reviewed and their perceptions on how the ethical principles should be interpreted and applied)
- Experience of ethical considerations raised by the research in rapidly evolving epidemics, especially in international collaborative research projects (international collaboration, available public health interventions, culture, norms and standards required by relevant international and local research guidelines).
- Suggestions of ways to address ethical considerations.

Suggested semi-structured questions:

Experience in research ethics review and consulting

- 1) What is your experience of ethics reviewing and providing ethical guidelines in international collaborative research projects in rapidly evolving epidemics in terms of difficulties/challenges and advantages if there is any?
- 2) In what aspects do you think ethics review and oversight research on rapidly evolving epidemics might be different from other research settings?
- 3) What ethical aspects that you think should be particularly paid attention to when reviewing an international collaborative research project on emergency epidemics?

Now I would like to discuss with you further about 3 following topics:

Research subjects and family members

- 4) How do you think about the ability of research subjects and family members to give consent to research on rapidly evolving epidemics?
- 5) What types of ethical considerations should be raised in relation to the ability of research subjects and family members to give consent to research in the setting of rapidly evolving epidemics?
How do you think these issues can be resolved?

- 6) Is there any other ethical consideration that might arise in relation to research participants participating in emergency epidemic research? How do you think the issues can be resolved?
- 7) There is opinion that community engagement is imperative in research on rapidly evolving epidemics, and that community engagement is suggested as an ethical responsibility of investigators in research in general, what is your experience of community engagement in this emergency epidemic setting?

IRB/IEC ethics review and oversight

- 8) What do you think about ethics review and oversight process that IRBs or IECs applied to international collaborative research projects in response to the setting of rapidly evolving epidemics?
- 9) Would each of any process that you have described raise any ethical consideration? If yes, what it is and in what way do you suggest the issues to be resolved?

Probe them on:

- ✓ Decision making pattern of the IRB/IEC while there is a lack of evidence and uncertainties resulted in disagreements among IRB members and differences in the response of IRBs/IECs
 - ✓ Multiple review by multiple IRBs/IECs
 - ✓ Review pattern, e.g. a combination of scientific and ethical review
- 10) In your opinion, what elements would affect the decision of IRBs/IECs in reviewing an international collaborative research project on rapidly emerging epidemics? And in what way?

Collaboration

- 11) What is your experience of local and international collaboration in the research response to rapidly evolving epidemics in terms of the level of collaboration and the dynamics of that collaboration?
- 12) In what aspects the collaboration would affect research in rapidly involving epidemics?
- 13) Would the collaboration in research response in the setting of emergency epidemics raise any ethical consideration? If yes, what it is and how would you suggest it to be resolved?

(Probe them on: the nature of collaboration, level of understanding, conflict of interest and benefit sharing, scientific integrity, power balance between relevant parties)

Is there any other issue in research in rapidly evolving epidemic you have experienced or think of which you would like to talk about? Why is it an issue/challenge/difficulty? What did you do about it? How do you suggest it should be improved?

Topic guides for study sponsors/funders

Research experience of sponsors or funders is very dependent on their devolved responsibilities and their delegated work. The interview questions should be open and flexible to their work they have involved. However, two groups of experience will be focused on:

- 1) Experience of applying international normative and regulatory guidelines into local practice and in the context of evolving epidemics
- 2) Experience of local and international research collaboration under the setting of rapidly evolving epidemics

Suggested semi-structured questions:

Background:

- 1) Can you briefly describe your professional background?
- 2) Can you describe briefly the research on rapidly evolving epidemics that your institution has sponsored/funded?
- 3) Can you briefly describe the role and responsibility of your institution as a sponsor/funder in the research?

Experience in sponsoring/funding research

Sponsoring/Funding research projects:

- 4) What elements would be taken into consideration when making decision on sponsoring/funding research projects on rapidly evolving epidemics?
- 5) Can you describe your experience in sponsoring/funding the research in rapidly evolving epidemics in terms of ethical considerations, issues and advantages with respect to the nature of rapidly evolving of the epidemics?

Probe them on:

- Experience of applying international normative and regulatory guidelines into local practice and in the context of evolving epidemics
 - Experience of local and international research collaboration under the setting of such rapidly evolving epidemics?
- 6) Why does the sponsoring/funding committee see them as ethical considerations/issues/advantages?
 - 7) How did the committee resolve the problems? If nothing could be done, why not?
 - 8) Did you find the solutions satisfied? If not, do you have any other suggestion?

Is there any other issue in research in rapidly evolving epidemic you have experienced or think of which you would like to talk about? Why is it an issue/challenge/difficulty? What did you do about it? How do you suggest it should be improved?