SIDCER

Globalizing Ethics for Health Research

FERCAP/SIDCER Handbook of Case Studies on Ethical Issues in Health Research

Forum for Ethical Review Committees in the Asian & Western Pacific Region

www.fercap-sidcer.org

FERCAP/SIDCER

HANDBOOK OF CASE STUDIES ON ETHICAL ISSUES IN HEALTH RESEARCH

Forum for Ethical Review Committees in the Asian and Western Pacific Region (FERCAP)
& Strategic Initiative for Developing Capacity in Ethical Review (SIDCER)
2012

FERCAP/SIDCER

HANDBOOK OF CASE STUDIES ON ETHICAL ISSUES IN HEALTH RESEARCH

Published by the **Forum for Ethical Review Committees in the Asian and Western Pacific Region (FERCAP) & Strategic Initiative for Developing Capacity in Ethical Review (SIDCER)**
WHO-TDR Clinical Coordination and Training Center (CCTC)
Thammasat University (Rangsit Campus)
Pathumthani 12121, Thailand
Website: http://www.fercap-sidcer.org

Book cover template: Arnie Angelo S. Manzano
Layout: Atoy M. Navarro

Prepared and printed by **FERCAP & SIDCER**

Printed in Thailand

Table of Contents

Background of the Handbook 3
Atoy M. Navarro

PART 1

Role of Research Ethics Committees and the Application of Ethical Principles 9
Cristina E. Torres, Ph.D.

Clinical Trial and Ethical Considerations 17
Juntra Karbwang-Laothavorn, M.D., Ph.D.

Review of Ethical Principles in Applied Social Science Research on Health 33
Cristina E. Torres, Ph.D.

PART 2

Selected Clinical Trial Case Studies 37

Selected Social Research Case Studies 49

Discussion of Short Case Studies 57

Discussion of Clinical Trial Case Studies 65

Discussion of Social Research Case Studies 75

BACKGROUND OF THE HANDBOOK

Atoy M. Navarro

This handbook is borne out of the need to develop training materials in reviewing different types of health research for ethics committee (EC)/institutional review board (IRB) members. Responding to this need, the *Forum for Ethical Review Committees in the Asian & Western Pacific* (FERCAP), *Strategic Initiative for Developing Capacity in Ethical Review* (SIDCER), and the *National Research Council of Thailand* (NRCT) organized a *Workshop on Ethical Issues in Different Types of Health Research* at *Chulalongkorn University* (CU) last August 23-24, 2012. The workshop, which was hosted by the CU Faculty of Medicine IRB, served as a venue for different institutions concerned with health research (Table 1) to discuss ethical issues in clinical trials (Phases I-IV), pediatric studies, oncology research, genetics studies, psychiatric studies, social and behavior research, traditional medicine research, and international health research by using actual case studies from selected Thai ECs/IRBs (Table 2).

Table 1
List of Institutions That Participated in the Workshop

#	Institutions	Representatives
01	Royal Thai Army Medical Department Institutional Review Board	▪ Col. Dr. Sahaphol Anannamcharoen ▪ Col. Dr. Yawana Tanapat

Table 1 List of Institutions That Participated in the Workshop		
#	**ECs/IRBs**	**Representatives**
02	Faculty of Medicine, Chulalongkorn University Institutional Review Board	▪ Assist. Prof. Dr. Anan Chongthaleong ▪ Assist. Prof. Dr. Prapapan Rajatapiti ▪ Prof. Dr. Tada Sueblinvong ▪ Assoc. Prof. Sopit Thamaree ▪ Assoc. Prof. Dr. Wasee Tulvatana ▪ Assist. Prof. Dr. Apichai Vasuratna
03	Department for Development of Traditional and Alternative Medicine (DTAM), Traditional and Alternative Ethics Committee (TAMEC), Ministry of Public Health (MOPH) - Thailand	▪ Dr. Vichai Chokevivat
04	Ethics Committee of the Faculty of Tropical Medicine, Mahidol University	▪ Prof. Dr. Krisana Pengsaa ▪ Mr. Noppajakkr Sonthinen
05	Faculty of Medicine Research Ethics Committee, Chiang Mai University	▪ Assoc. Prof. Dr. Kittipat Charoenkwan
06	The Ethical Review Committee for Research Involving Human Research Subjects, Health Science Group, Chulalongkorn University (ECCU)	▪ Prof. Dr. Sirikul Isaranuruk ▪ Dr. Kriangkrai Lerdthusnee

Table 1 **List of Institutions That Participated in the Workshop**		
#	**ECs/IRBs**	**Representatives**
07	Khon Kaen University Ethics Committee for Human Research (KKU EC)	▪ Assist. Prof. Dr. Ratana Komwilaisuk ▪ Assist. Prof. Dr. Supatra Porasuphatana ▪ Assoc. Prof. Dr. Kwanchanok Yimtae
08	Siriraj Institutional Review Board (SIRB), Faculty of Medicine, Siriraj Hospital, Mahidol University	▪ Assoc. Prof. Dr. Winai Ratanasuwan ▪ Prof. Dr. Jarupim Soongswang
09	Faculty of Medicine (Number 1 Human Ethics Committee), Thammasat University	▪ Prof. Dr. Surasak Buranatrevedh
10	FERCAP and SIDCER	▪ Prof. Dr. Juntra Karbwang-Laothavorn ▪ Mr. Atoy M. Navarro ▪ Prof. Dr. Cristina E. Torres

Table 2 **List of ECs/IRBs That Submitted Case Studies for the Workshop and Handbook**		
#	**ECs/IRBs**	**Representatives**
01	Royal Thai Army Medical Department Institutional Review Board	▪ Assoc. Prof. Dr. Sangkae Chamnanvanakij ▪ Assoc. Prof. Dr. Suthee Panichkul
02	Faculty of Medicine, Chulalongkorn University Institutional Review Board	▪ Assoc. Prof. Sopit Thamaree

Table 2 List of ECs/IRBs That Submitted Case Studies for the Workshop and Handbook		
#	**ECs/IRBs**	**Representatives**
03	Faculty of Medicine Research Ethics Committee, Chiang Mai University	▪ Assoc. Prof. Dr. Kittipat Charoenkwan
04	The Ethical Review Committee for Research Involving Human Research Subjects, Health Science Group, Chulalongkorn University (ECCU)	▪ Prof. Dr. Sirikul Isaranuruk ▪ Dr. Kriangkrai Lerdthusnee
05	Khon Kaen University Ethics Committee for Human Research (KKU EC)	▪ Assist. Prof. Dr. Ratana Komwilaisuk ▪ Assist. Prof. Dr. Supatra Porasuphatana ▪ Assoc. Prof. Dr. Kwanchanok Yimtae
06	Siriraj Institutional Review Board (SIRB), Faculty of Medicine, Siriraj Hospital, Mahidol University	▪ Prof. Dr. Jarupim Soongswang
07	Faculty of Medicine (Number 1 Human Ethics Committee), Thammasat University	▪ Prof. Dr. Surasak Buranatrevedh

The output of the workshop served as the foundation for this handbook. Through the Thai ECs/IRBs, permission was given by the principal investigators of the protocols used during the workshop so that anonymized and modified case studies will form part of this handbook. Thai EC/IRB members also helped in rewriting some of the case studies. In addition to these case studies, this handbook also included anonymized and modified cases studies from two Chinese ECs/IRBs, namely, the EC of the

First Affiliated Hospital, Nanjing Medical University, Jiangsu Province Hospital and the IRB of the First Affiliated Hospital of Zhejiang Chinese Medicine University.

To properly contextualize these case studies in relation to larger ethical issues in health research, articles dealing with the role of ECs/IRBs and the application of ethical principles in health research by Prof. Dr. Cristina E. Torres, clinical trials and ethical considerations by Prof. Dr. Juntra Karbwang-Laothavorn, and ethical review of applied social science research on health by Dr. Torres were included to comprise Part 1 of this handbook. Shorter case studies were incorporated in these essays while the rest of the case studies were selected for longer presentation in Part 2 of this handbook. Points for discussion identified in the presentation of the short and selected case studies were also elaborated in Part 2 of this handbook.

With the publication of this handbook, FERCAP and SIDCER hope to provide a useful material for EC/IRB members as they tackle various ethical issues in health research.

ROLE OF RESEARCH ETHICS COMMITTEES AND THE APPLICATION OF ETHICAL PRINCIPLES

Cristina E. Torres, Ph.D.

An institutional review board (IRB) or a research ethics committee (REC) is an "independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects" (ICH-GCP E6: 1.31).

It is an important stakeholder in clinical trials and its roles and functions are defined in Chapter 3 of ICH-GCP E6. The following case studies illustrate the important role that RECs play in clinical trials.

Case Study 1: Role of the REC

18 November 2012. Company ABC is the sponsor for a Phase III trial on an investigational new drug for treatment of tuberculosis. Site YZ has already recruited 60% of the patients for the study. Today, the clinical monitor who is currently on site for the routine monitoring visit calls the sponsor to seek advice. During the review of the study documents/investigator file, he noted that the renewal of the approval of the local REC

was not on file. When he asked the principal investigator (PI), he was told that the new approval had not yet been received. The last approval covered the period 15/09/2011 to 30/09/2012.

Points for Discussion

1. What will be your advice to the monitor?
2. Would you consider any GCP finding in under such conditions? If so, formulate your finding.
3. Can the study continue? Discuss new enrolment and follow up of patients.
4. What corrective action should be done by the Investigator related to the local ethics committee?

The approval was finally obtained, but after enquiry, it seems that the REC didn't have a lay person and there were no minutes of the meeting.

5. What should the sponsor do, considering that they have more projects that would need to be submitted to this ethics committee?

Case Study 2: Emergency Room Research

An REC approved the protocol and informed consent form (ICF) for a randomized double blind clinical trial about the emergency use of an investigational drug vs. placebo in comatose patients.

The monitor went to the site for the monitoring visit and called the sponsor because she found that a patient's husband had given consent to enroll his comatose wife.

As sponsor, you checked the REC approval and found out that the REC only approved a patient consent form. There was no consent form for a legally acceptable representative.

Points for Discussion

1. What should the sponsor (project manager) do next?
2. What did the IRB miss when it reviewed the protocol?
3. Identify the IRB deficiencies and what corrective action should be done?
4. Identify the IRB SOP issues.

Case Study 3: Scientific Soundness

A newly formed company prepared a protocol with the objective of proving the health benefits of water processed by an imported machine to HIV positive patients. They chose a sanitary engineer as PI and submitted the protocol to the hospital REC. Since the investigational product was water, the REC approved the protocol and ICF immediately.

Points for Discussion

1. What are the GCP issues related to the case study?
2. What is the role of sponsor, role of investigator, and role of IRB?
3. Was the hasty approval justified?
4. What information should the REC require in the protocol? In the ICF?
5. What kind of investigator expertise does the protocol require?

Case Study 4: Conflict of Interest

An epidemiologist member of the REC is the thesis adviser of a post-graduate student who submitted a protocol about the community directed intervention in malaria prevention and control. The epidemiologist member is appointed as primary reviewer of the protocol due to his expertise and publications about malaria prevention.

Points for Discussion

1. Is he the appropriate reviewer for this protocol? Explain your answer.
2. If not, who should review this protocol?
3. Will this protocol qualify for expedited review? How should this protocol be reviewed?

Case Study 5: Research on Healthy Volunteers

The hospital researchers recruit healthy volunteers for bioequivalence studies of generic drugs as required by local regulatory authorities. The ICF mentions that volunteers will get free treatment in addition to $100 for participation. It also mentions that volunteers will get the opportunity to stay overnight at the newly renovated hospital ward with high technology audio visual room where they can play the latest computer games and watch popular movies.

Points for Discussion

1. If you are an REC member, will you approve the ICF? Explain your decision.
2. Are there risks involved when healthy volunteers are recruited to join the study? What safeguards should be in place to protect health volunteers from harm?
3. What are the benefits of this study? Would you consider the compensation given as undue inducement?

Case Study 6: Observational Study

A protocol is submitted to the REC by a local pharmaceutical sponsor about a generic drug to address mild to moderate hypertension. The sponsor classifies this study as observational in nature and would encourage study physicians to prescribe this drug to their patients. The protocol requires a wash-out period of one week before the patients will start taking the

new drug. Each physician investigator will record patient data in the case report form and will be paid $30 for each patient recruited into the study. The REC grants a waiver of consent for this protocol since it is an observational study.

Points for Discussion

1. What are the risks to participants who join this study?
2. What are the benefits to participants?
3. Is it appropriate to waive informed consent?
4. Is it appropriate for a study physician to change the medication of a patient whose current drugs are effective to address his hypertension?

Case Study 7: Behavioural Research

A medical anthropologist submits a protocol to the REC about developing an educational intervention for HIV prevention among sex workers in an Asian city. The first part of the protocol is about conducting focus group discussion (FGD) among sex workers to determine their knowledge, attitudes, and practices about HIV prevention. Based on the FGD results, a questionnaire about knowledge, attitudes, and practices of sex workers about HIV will be formulated that will become the baseline before conducting the educational intervention. The outcome measure is to determine if there has been an increase in HIV among the cohort of volunteers in the intervention group.

Points for Discussion

1. What protocol related documents should the REC require for this study?
2. How should vulnerability be addressed?
3. How can social risks be minimized?
4. Should informed consent be waived for this study?

5. Can social scientists check medical records of the participants to check if there has been an increase in the incidence of HIV?

Case Study 8: Traditional Medicine

A traditional medicine doctor wants to conduct a study about a herbal product that can address constipation. He decides to do it among hospital in-patients and proposes to do the study in the intensive care unit (ICU) where many patients experience constipation.

Points for Discussion

1. Is it appropriate to do the study in the ICU?
2. Should some patients who are active in the study die, should the PI report this as serious adverse event (SAE)?
3. Is there any other place where this study can be done?

Case Study 9: Recruitment and Informed Consent

A group of social scientists wants to conduct a multi-country study about knowledge, attitudes, and practices related to vasectomy in Asia. Each study group will submit their protocol to an REC in their country. The protocol proposes that participating social scientists prepare a list of prospective participants from the medical records of the hospitals in the cities where they live. Then, they would call up men who underwent vasectomy to get their consent to be interviewed. A standard ICF was prepared that was to be administered orally. The standard questionnaire was also submitted to the REC.

Points for Discussion

1. Should the IRB approve this study?
2. Does the study qualify for expedited review?

3. What are your suggestions to make the study more ethical?

Case Study 10: Post-Trial Access

One of the participants of a Phase II herbal medicine study for HIV sent a complaint to the REC. He has been recruited in this study since July 2010 until July 2011. After the protocol has been closed, he continued to receive the herbal extract study drug. In December 2011, his renal function started to deteriorate. T he renal function test was re-evaluated in March 2012 and he has been diagnosed to have renal failure.

Points for Discussion

1. Should the investigator continue to provide the investigational drug to the patient after the study is over?
2. Should post trial access be required by the REC in the consent form?
3. What is the accountability of the Investigator for the renal failure? What is the accountability of the REC? What is the accountability of the funder for this study?

CLINICAL TRIAL AND ETHICAL CONSIDERATIONS

Juntra Karbwang-Laothavorn, M.D., Ph.D.

- **Clinical Trial Overview**
- **Ethical Considerations in Clinical Trial**
- **EC Considerations for Ethical Clinical Trial**

I. Clinical Trial Overview

Definition of Clinical Trial (from ICH GCP E6)
"Any investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy."

The Principles
Clinical trials should be designed, conducted, analyzed, and reported according to sound scientific and ethical principles to achieve their objectives. The design and performance of each trial must be clearly described in a clinical trial protocol. A statement of the ethical concerns should be included in the protocol and it should indicate how these concerns have been addressed.

Classification of Clinical Trials

Clinical trials can be classified according to the types of study or the phases of clinical product development.

Types of Study Based on ICH GCP E 8

1. Human pharmacology: The objectives are to assess tolerance, to define pharmacokinetics/pharmacodynamics, to explore drug metabolism and drug interactions, and to estimate activity.
2. Therapeutic exploratory: The objectives are to explore the use of the targeted indication, to estimate dosage for subsequent studies, and to provide basis for confirmatory study design, endpoints, and methodologies.
3. Therapeutic confirmatory: The objectives are to confirm efficacy, to establish safety profile of the investigational product, to provide an adequate basis for assessing the benefit/risk relationship to support licensing, and to establish dose-response relationship.
4. Therapeutic use: The objectives are to refine understanding of benefit/risk relationship in general or special populations and/or environments, to identify less common adverse reactions, and to refine dosing recommendation.

Phases of Clinical Product Development

Clinical product development is a logical, step-wise investigation in which information from prior studies should influence the plan and design of later studies.

Initial trials provide an early evaluation of short-term safety and tolerability as well as pharmacodynamic and pharmacokinetic information needed to choose a suitable dosage range and dose schedule for initial exploratory therapeutic trials. The results of exploratory trials will be used to plan confirmatory studies in which generally, more diverse patients will be recruited, the sample size is larger, and study duration is normally longer.

However, a new data may suggest the need for additional studies that are typically part of earlier phases. For example, drug concentraton data in a Phase III trial may suggest a need for a drug-drug interaction study (human pharmacology study). Adverse effects or efficacy data may suggest the need for further dose finding study (therapeutic exploratory) and/or additional non-clinical studies (animal toxicology). It is thus important to recognize that one type of trial may occur in several phases and the sequential phases do not imply a fixed order of studies required.

Phase I (First Time in Human)
Studies in this phase of development usually have non-therapeutic objectives, thus, normally are conducted in healthy volunteer subjects. However, the studies of drugs with significant potential toxicity (*e.g.*, cytotoxic drugs) are normally conducted in patients.

The primary objective of the studies in this phase is to determine the safety (*i.e.*, adverse reactions that can be expected) and tolerability of the dose range expected to be used in later clinical studies. The other objective is to determine the basic clinical pharmacology of the drug—pharmacokinetics (characterization of a drug's absorption, distribution, metabolism, and excretion) and pharmacodynamics. This information is important for the future development and use of the drug, as well as in determining the relationship of blood levels and adverse-effects.

The design of the study can be open, baseline controlled. Randomization and blinding may be used to improve the validity of observations.

The starting dose depends on the information from pre-clinical studies. For example, the starting dose is based on one-tenth of the dose that caused 10% mortality in rodents, etc.

Phase II (Therapeutic Exploratory)
The primary objective of this phase is to explore therapeutic efficacy in patients. An important goal for this phase is to determine the dose(s) and regimen for Phase III trials.

Additional objectives may include evaluation of potential study endpoints, therapeutic regimens (including concomitant medications) and target populations (*e.g.*, mild *versus* severe disease) for further study in Phase II or III. These objectives may be served by exploratory analyses, examining subsets of data, and by including multiple endpoints in trials.

The study designs employed in this phase include concurrent controls and comparisons with baseline status. Early studies often utilize dose escalation designs to give an early estimate of dose response. Subsequent trials are usually randomized and concurrently controlled to evaluate the efficacy of the drug and its safety for a particular therapeutic indication. Studies in Phase II are typically conducted in a group of patients who are selected by relatively narrow criteria**,** leading to a relatively homogeneous population and are closely monitored.

Doses used in Phase II are usually less than the highest doses used in Phase I.

Phase III (Therapeutic Confirmatory)
The studies in this phase are designed to confirm the preliminary evidence accumulated in Phase II that a drug is safe and effective for use in the intended indication and recipient population. The studies are definitive steps in the evaluation of the new product intended to provide an adequate basis for marketing approval. The purpose is to determine the efficacy and safety (incidence of adverse-effects and the severity) of the new drug/vaccine relative to existing standards.

Studies in Phase III may also further explore the dose-response relationship, or explore the drug's use in wider populations, in different stages of disease, or in combination with another drug.

Phase IV (Variety of Studies: Therapeutic Use)
Studies in Phase IV are all studies (other than routine surveillance) conducted after drug approval and related to the approved indication. They are studies that are considered to be important for optimizing the use of the product according to its approved indication, but they are not necessary for marketing approval. They may be of any type but should have valid scientific objectives and must be ethically justifiable. Commonly conducted studies include additional drug-drug interaction, dose-response or safety studies, and studies designed to support use under the approved indication (*e.g.*, mortality/morbidity studies and epidemiological studies).

II. Ethical Considerations in Clinical Trial

Ethical issues in clinical trials are important and need to be recognized and addressed when planning the study.

Ethical standards have been defined in relation to scientific design of the study, minimizing risks and maximizing benefits to create a favourable risk-benefit ratio, appropriate selection and recruitment of study participants, adequacy of medical care during the study and post-trial periods, compensation for any inconvenience and injury associated with the trial, protection of participant privacy and confidentiality, provision for proper informed consent, and a prior review and approval by ethics committees (ECs).

The ethical issues in clinical trial are commonly seen in the study design of a specific trial in a specific circumstance, selection of

subjects, selection of control group, and estimation of sample size. The discussion will confine to these four aspects.

Study Design

The purpose of clinical trial is to evaluate the safety and efficacy of the intervention (drug, vaccine or diagnostics). The data collected can be independent data where each group of subjects receives different intervention, or paired data where the evaluation on each individual subject is carried out in more than once.

The appropriate study design should be chosen to provide the desired information. The validity of the results depends on the extent to which investigators have been able to avoid all possible sources of bias. The techniques commonly used to minimize bias are randomization, blinding, and the use of control group.

Randomization is the means to ensure the independent allocation of subject to the trial; all subjects have the same chance to treatment assignment. Randomization removes any chance of allocation bias. For randomization to be ethical, the stage of 'equipoise' is required.

Blinding is an important means of reducing or minimizing the risk of biased study outcomes. The blinding can be a single blind (subjects do not know treatment assignment) or double blind (both subject and investigator do not know the treatment assignment).

Using control group will allow an objective evaluation of the effect of intervention, if any. However, selection of control group should be appropriate with adequate numbers of subjects included to achieve the study objectives.

Examples of study design include parallel group, cross-over, factorial, dose escalation, and fixed dose-dose response.

Selection of Subjects

In early trials, the subjects may be limited to a narrow range with strict selection criteria. When drug/vaccine development proceeds, the subject should be broadened to reflect the target population.

For a drug expected to be used in children, it is ethically appropriate to begin with older children before extending the trial to younger children and then infants.

For vulnerable subjects to be included in the clinical trial, ethical justification of their involvement is required to affirm that the research could not be carried out equally well with less vulnerable subjects.

Selection of Control Group

Trials should have an adequate control group. Comparisons may be made with placebo, no treatment, and different active controls or of different doses of the drug/vaccine under investigation. The choice of the comparator depends, among other things, on the objective of the trial.

The use of placebo or no treatment is limited to the situations where no current proven treatment exists or where it is necessary for scientifically sound methodological reasons. However, it should not put subjects to any risk of serious or irreversible condition.

There is an exception, in the case where current proven treatment is known to have severe toxicity that patients refuse to use it, placebo may be acceptable as control group.

As a general rule, it is not ethically acceptable to use placebo-controlled trial design when effective therapy that is known to prevent death or irreversible morbidity exists.

In other situations where therapy is directed at less serious conditions, placebo control group may be used as internal evidence of assay sensitivity.[1] In a three-arm trial design, placebo and active control are used to assess if the test drug is ineffective or the trial lacks assay sensitivity. When a difference is demonstrated, it is interpretable without reference to external findings.

In a dose-response study, placebo as an additional group permits an estimate of the total pharmacologically mediated effect of test doses. When all doses produce similar effects, placebo group can assist in the interpretation that they are equally effective or equally ineffective.

In any placebo-control study, unbalanced randomization (*e.g.*, 2:1 or 3:1 study drug to placebo) is recommended.

Sample Size

The sample size is ethically and scientifically important. Too small sample size may not allow detecting anything significance and type II error (false negative) may occur. On the other hand, too large sample size raises ethical issues, as subjects are exposed to risk unnecessary, as well as unnecessary waste of resources.

The size of a trial is influenced by the disease to be investigated, the objective of the study, and the study endpoints.

[1] *Assay sensitivity* is a property of a clinical trial defined as the ability to distinguish an effective treatment from a less effective or ineffective treatment (ICH E10).

Study endpoints should be chosen to assess drug/vaccine effects that are related to efficacy and safety. Selection of primary endpoint should be based on the primary objective of the trial and should reflect clinically relevant effects. A surrogate endpoint may be used as primary endpoint when it is likely to predict clinical outcome. The measurements of the endpoints should be validated prior to use to ensure the accuracy, precision and reproducibility.

In clinical trials involving the comparison of two independent quantitative data sets, the sample size required depends on clinically meaningful difference to be detected, standard deviation of the variable, power, and the nominated significance level.

When very small difference in measurement can be detected, it is important to distinguish between statistical significance and clinical significance. In this case, the decision on clinical meaningful difference must be defined.

III. EC Considerations for Ethical Clinical Trial

Prior ethical review and approval of a clinical trial protocol is a universally required standard. It is thus, important that EC members commit to timely review, thoroughness and objectivity, competency, impartiality in review, managing conflict of interest, and maintaining confidentiality of reviewed documents. To demonstrate their competency in ethical review for clinical trial, at a minimum, they should have training in good clinical practice (GCP) and research ethics.

In reviewing a clinical protocol, EC members should base their decisions on the submitted information with reference to international acceptable standards. In deciding if a clinical trial is

ethical, the members should consider, but not limited to, the following important issues:

Scientific Merit of the Study and the Effect of the Study on the Health of Research Subjects (*i.e.*, potential harm and benefit)
In ethically acceptable research, risks have been minimized (both by preventing potential harms and minimizing their negative impacts should they occur) and are reasonable in relation to the potential benefits of the study. EC members should be aware that the nature of the risks may differ according to the type of clinical trial as well as the location of the trial to be conducted. For example, risk of pneumonia in Europe is considered lower in comparison with Africa where there is limited health care facility available and accessible and thus, high mortality. EC members should recognize that risks can occur in different dimensions including physical, social, financial, or psychological. When assess risk, the probability, duration, and the magnitude of the effect should be taken into account. Furthermore, harm may occur either at an individual level or at the family or population level. Similarly, consideration for benefit should be carried out on different dimensions as well as probability, duration and magnitude. It is important that EC members recognize the limitations of their knowledge and seek external inputs when necessary, particularly in relation to trial involves people whose experiences may differ significantly from those of the EC members.

Vulnerability of Subjects
EC members must recognize the vulnerability of the subjects in the protocol they review. It is thus, important that EC members are aware of the definition of vulnerability. The ICH GCP describes vulnerable subjects as individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members

of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dentistry, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, individuals who are politically powerless, members of communities unfamiliar with modern medical concepts and those incapable of giving consent. Subjects who have serious, potentially disabling or life-threatening diseases should be considered as highly vulnerable.

EC members need to evaluate whether the subjects in the proposal under review is vulnerable or not. EC members should assess whether the research could be carried out equally well with less vulnerable subjects. EC members need to evaluate whether the knowledge gain from research will lead to improve health problems that are characteristics of the vulnerable subjects or not. EC members must pay attention to the appropriateness of protection that is being proposed by the investigator. For example, provision for counseling in the case of HIV study or lawyer in the case of drug addict subjects (this has been done in HIV vaccine trial in drug addict subjects). From the experience in FERCAP surveys in the past 8 years, the most common finding in protocol review is the deficiency in recognizing vulnerability of the subjects, specifically chronic diseases such as chronic obstructive lung disease, chronic kidney or liver failure, etc., and the incurable disease such as cancer, HIV patients, etc.

Study Design

EC members should evaluate if the design of the study is appropriate and can yield the desired information. EC members must assess carefully whether the chosen study design has avoided all possible bias or not. When there is a control group, randomization and blinding should be used; if not, justification should be provided by the investigator and evaluated by EC members. In some case where blinding is not possible, EC members should assess its justification.

In the case of placebo control trial, the design is always double blind randomized. The purpose is to control for placebo effect as well as control for all potential influences on the actual course of the disease. Blinding is intended to minimize the potential biases resulting from differences in management, assessment and interpretation of study results.

Selection of Subjects (inclusion/exclusion/withdrawal criteria)

EC members should assess the appropriateness of subject selection. EC members assess the inclusion criteria if the chosen population is likely to yield the answers seek. No subject with undue risk or vulnerability should be included in clinical trial unless reasonably justifiable and risks involved can be satisfactorily managed. EC members should also examine the withdrawal criteria if the criteria have provided sufficient protection for those who may experience unexpectedly high risk as a result of errors in initial judgment on their risk or adverse effects from the intervention. The criteria should assure EC members that all conditions have been covered and that the subjects will be withdrawn from intervention at an appropriate time to prevent undue risk.

Selection of Control Group

EC members should pay particular attention when the trial proposed to use placebo or no-treatment as control group.

When evaluating the efficacy of a new drug, the Declaration of Helsinki states that it should be compared with the best current proven intervention. It also states clearly that a placebo may be used only when no current proven intervention exist or when there are compelling and scientifically sound methodological reasons, provided that the patients who receive placebo will not be subject to any serious risk or irreversible harm. From the scientific methodological perspective, some conditions may require the use of placebo comparator to prove absolute efficacy of a new therapy (*e.g.*, new drugs for some chronic conditions with waxing and waning symptoms with high rate of placebo response). The fundamental ethical principle underlying the application of this standard is the avoidance of exploitation, particularly for individuals or communities who may be vulnerable because of their socio-economic status. Extreme care must be taken to avoid abuse of using placebo option. When the trial objective is to measure absolute effect size, placebo control is likely to play a significant role, either alone or in combination with other concurrent control such as active control and/or dose response. However, when there is effective therapy that is known to prevent death or irreversible morbidity, the use of placebo control is not ethically acceptable.

Sample Size

Clinical trials often involve the comparison of new intervention with the best available treatment or placebo in a sample of subjects, and the difference between the two treatment groups is analyzed using a hypothesis testing. When reviewing sample size, EC members need to assess that the sample size is large enough to detect a treatment effect (if any), at a given significance level. The common mistake in sample size calculation is that the investigator fails to distinguish between statistical significance and clinical relevance. Another common mistake is the use of one-sided or two-sided testing which can result in different sample size. If the direction of hypothesis

testing is known, one-sided testing should be used. The examples below will demonstrate these points.

Example: An active control trial of a new drug for dyspeptic symptoms is submitted to EC for review and approval. In the sample size section, the investigator described as following: Drug X *versus* ranitidine hydrochloride (standard treatment), using 1-10 pain scale, the accuracy of measurement is 0.5 (*i.e.*, the difference can be detected at 0.5), the statistical significance level (α) at 5%, and power (1-β) at 80%, the standard deviation with both treatment estimated to be 1.73.

Issues of statistical significance or clinical significance:
If a difference in pain rating of 0.5 points is used (measurement with accuracy and precision—statistical significance), the sample size required using 2-sided test would be **188**.

However, if a difference in pain rating of 1.5 points is considered as clinically meaningful, the sample size required using 2-sided test would be **21** (reduced by 9-fold).

Issues of using one or two-sided test:
If the hypothesis testing is that either treatment can either be more effective, and clinical meaningful difference is 1.5, then the 2-sided test is used, the sample size required would be **21**.

However, if new drug is expected to be more effective (direction of hypothesis testing is known), and clinical meaningful difference is 1.5, one-sided test is used and the sample size required would be **8** (sample size will be reduced by almost 3-fold).

Investigator Competence
The competence of the investigator can be assessed on two dimensions: technical and ethics. Technical can be evaluated by

education, knowledge, certification, and experience. In addition to their technical competence, the investigator must have clinical trial competence, the EC members assess from the information presented in the protocol if the investigator has performed a competent systematic review of current knowledge and previous trials, to be certain that the planned study is justified. For clinical trial, training in GCP is required.

With regard to ethics dimension that relate to compassion and responsiveness, the assessment is limited to the evidence of ethics training, which may not be sufficient to support the competency of investigator on this aspect. However, the history of violating GCP in the past trials may provide EC members with some ideas on how much of the oversights should be required.

Conclusion

Clinical trials should be designed, conducted, analyzed, and reported according to sound scientific and ethical principles to achieve their objectives.

The ethical issues in clinical trial are commonly seen in study design, selection of subjects, selection of control group, and estimation of sample size.

The appropriate study design should be chosen to provide the desired information. The validity of the results depends on the extent to which investigators have been able to avoid all possible sources of bias. EC members should evaluate whether the chosen study design has avoided all possible bias or not.

In early product development, the subjects may be limited to a narrow range with strict selection criteria. When development proceeds, the subject should be broadened to reflect the target

population. EC members need to evaluate whether trial subjects under review are vulnerable and assess whether the research could be carried out equally well with less vulnerable subjects.

Trials should have an adequate control group. Comparisons may be made with placebo, but its use is limited to situations where no current proven treatment exists, or where it is necessary for scientifically sound methodological reasons. However, it should not put subjects to any risk of serious or irreversible condition.

The sample size should be sufficient to answer the questions. Too small sample size may not allow detecting anything significance and type II error (false negative) may occur. Too large sample size raises ethical issues, as subjects are exposed to risk unnecessary.

References

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: General Considerations for Clinical Trials (E8), dated 17 July 1997.

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Choice of Control Group and Related Issues in Clinical Trials (E10), dated 20 July 2000.

Smith FG and Smith JE. Key Topics in Clinical Research: A User Guide to Researching, Analyzing, and Publishing Clinical Data. Oxford: Bios Scientific Publishers Limited, 2003.

Piantadosi S. Clinical Trials: A Methodologic Perspective. New York: John Wiley & Sons, Inc., 1997.

REVIEW OF ETHICAL ISSUES IN APPLIED SOCIAL SCIENCE RESEARCH ON HEALTH

Cristina E. Torres, Ph.D.

Social research aims to understand social phenomenon as this occurs in the context of individuals, groups, institutions or societies. It includes various disciplines which share in its aims and methods in order to analyze a wide range of social phenomena that range from individual perception and experiences in case studies to description of large populations in surveys. In the field of health, applied social science research has been widely used "to predict or influence health outcomes, risks, or protective factors" as well as "the impact of illness or risk for illness on behavioral or social functioning" (US NIH Office of Behavioral and Social Sciences Research).

One way of differentiation is by means of the method used: 1. Quantitative social research; 2. Qualitative social research; 3. Combination of both methods.

1. Quantitative research makes use of quantifiable evidence to describe social phenomena to provide generalizable information/conclusions; makes use of statistical tools; and includes a data analysis plan in the protocol that would ensure validity and reliability of data. Often times, it makes use of simple random sampling or stratified random sampling techniques.

2. Qualitative research analyzes a particular context or setting to understand social phenomena. It makes use of methods like direct observation, key informant interview, and focus group discussion to describe specific contexts to provide sufficient detailed account or analysis with emphasis on "subjective accuracy over generality." There is no intention to draw generalizable conclusions and its rigor is not based on sample size but on quality and credible data collection techniques and analysis plan.

   Its findings/outcomes may be applied to other similar circumstances.

   The scientific review of social research should look at the consistency of study objectives with the research methodology, analysis plan, and research outcomes to ensure scientific soundness of the protocol. The protocol should also include literature review and an ethical consideration section.

   Some types of social research (health related, research on vulnerable populations, etc.) are submitted to research ethics committee (REC) for review, while other types (public opinion surveys, observation of public behavior, etc.) are exempt from ethics review. The main issue about this differentiation is confidentiality of the type of information being collected. Social research that involves collection of information that are private and confidential in nature are reviewed by RECs to ensure confidentiality protection of participants to prevent stigmatization due to possible public disclosure.

Ethical Guidance in Social Research

1. The conduct of social research should generally comply with relevant international norms and standards (Declaration of Helsinki, CIOMS, and codes of conduct of professional organizations in social sciences) about human research.
2. Social research protocols should be scientifically sound to ensure that the study objectives are consistent with the choice of study methodologies that would achieve the desired research outcomes.
3. The inclusion/exclusion criteria should be appropriate and clearly stated in the protocol to ensure fair selection of participants and inclusion of vulnerable participants is justified.
4. Social research about sensitive topics that may involve emotional and other social risks should describe clearly in the protocol how distress will be managed.
5. Researchers should have training on what topics can cause distress and how to address them.
6. The researcher should explain in the protocol the ethical means of getting access to a database of probable research participants (persons with HIV, STD, etc.) and how recruitment will be done.
7. When the study involves vulnerable participants (HIV-AIDS patients, drug addicts, victims of disasters, sexual abuse, etc.), the protocol should explain how social risks will be addressed and how valid consent would be obtained.
8. The protocol, when necessary, should describe the confidentiality measures that will be adopted to address stigma and social risk issues.
9. Researchers should have training in confidentiality protection when the research involves topics that may cause stigma or other social risks.

10. Participants should be informed about any potential to be identified in the research results.
11. The researcher should provide opportunities for participants to comment on the accuracy or completeness of interview transcripts before completing analysis.
12. The individual and community benefits (counseling, knowledge sharing, access to social services, technology transfer, etc.) from study participation should be described in the protocol and researchers should ensure their compliance during the conduct of the study.
13. Debriefing sessions should be held with the study participants or community to validate data and share study results.
14. Publication about the study results should use pseudonyms when referring to names of persons or places and avoid any identifier that may cause stigma to the study participants.
15. The informed consent process (written, oral or waived) should be appropriate to study topic (sensitive issues) and the type of data collection method (questionnaire, interview, observation, etc.) that is used in the protocol.
16. The informed consent process should take into consideration relevant cultural contexts and values, as well as vulnerability issues of participants (tribal populations, children, elderly, etc.) who will be recruited into the study and adequate measures should be adopted to protect them.
17. When the protocol involves access to information about secondary subjects (persons about whom information is derived from primary participants), consent from secondary subjects may be necessary and may be required by the ethics review committee.
18. The informed consent form of protocols about sensitive issues should disclose confidentiality risks and identify who has access to coded information.

SELECTED CLINICAL TRIAL CASE STUDIES

- Allergic Rhinitis (children, no treatment as comparator)
- Tics (children, placebo control trial)
- Measles vaccine (healthy children, active comparator)
- Oncology patients (open label, add on adjunct therapy)
- Myelodysplastic syndromes and iron overload (placebo control trial)

<u>Case Study 1</u>: Efficacy of Saline Nasal Irrigation in Children with Allergic Rhinitis

Allergic rhinitis is a condition associated with inflammation of the nasal membranes and is characterized by a symptom complex of one or a combination of the following symptoms: sneezing, nasal congestion, nasal itching, and rhinorrhea. The symptoms may last hours or days. It is an extremely common condition, affecting approximately 10-15% of the population worldwide with higher prevalence in children than adult. Onset of the condition is common in childhood with the age range of 8-11 years.

Allergic rhinitis is not considered as a life-threatening condition but it can impair quality of life. However, the condition may become life threatening if it coexists with severe asthma. Allergen avoidance is the most effective treatment. However

some allergen cannot be avoided. Decongestant, antihistamine or topical nasal steroids has been proposed as an option for treatment of allergic rhinitis in children. Nasal saline irrigation is an effective adjunct treatment in allergic rhinitis, it is postulated that the procedure removes crust and decreases amount of allergen and mediators. A bolus use of nasal saline irrigation has been shown to be effective in seasonal allergic rhinitis, but inadequate data to support the efficacy of this procedure in perennial allergic rhinitis, which is the most common type of allergic rhinitis in Thailand. The risks of nasal saline irrigation include discomfort, nosebleed, infective rhino sinusitis and aspiration.

The objective of the study is to evaluate the efficacy of saline nasal irrigation in pediatric patients with allergic rhinitis. The evaluation will be based on the amount of antihistamine and decongestant used (medication score), total nasal symptom score (TNSS) and the quality of life score.

The study design is a parallel-randomized controlled trial between the use of normal saline nasal (NSS) irrigation and without nasal irrigation in allergic rhinitis children for 8 weeks. The allergic rhinitis patients at the age of 5-15 years with moderately severe symptoms (based on TNSS) will be invited to join the study. The clinical diagnosis will be confirmed by skin prick test with aeroallergen or by serum specific (*i.e.*, at specified clinics). The patients who receive intranasal corticosteroid within 2 weeks, or NSS irrigation within 2 months, uncontrolled asthma or infective rhinitis, sinusitis will be excluded. Withdrawal or termination criteria include patients who cannot tolerate saline nasal irrigation, patient whose rhinitis becomes more severe and requires intranasal corticosteroid or antibiotic.

Sample size: Based on data from the previous study, TNSS of 10 in pediatric allergic rhinitis patients without saline nasal irrigation

was higher than the ones with saline nasal irrigation (TNSS = 6). Standard deviation of 4, 95% confident interval (type I error = 0.05, 2-sided) and 80% power (type II error = 0.20) are used for sample size calculation for this study. The sample size calculated is 17 patients for each group. With provision of 30% withdrawals, the samples size becomes 22 per group.

Methodology: 180 ml sterile 0.9% normal saline solution will be used to irrigate on each side of nasal cavity twice a day. The study team will demonstrate how to do nasal irrigation procedure during the first visit. The caregivers and or the patients then will perform the procedure at home.

Evaluation: Symptoms score of the week prior to each visit (week 2, 4 and 8) medication score, quality of life score, and complications (*e.g.*, epistaxis, nasal congestion, etc.) will be evaluated between the two groups.

Points for Discussion

1. Inclusion/exclusion criteria – are they appropriate?
2. The risk of intervention procedure – how to minimize the risk?
3. Sample size – is it appropriate?
4. Is there any vulnerability issue?
5. What are the important information and procedure that must be disclosed in the consent form?
6. Should there be compensation for travel and time loss during follow-up visits and study related injury?

Case Study 2: Dose Optimization Study of a Newly Registered Drug

A proposed study aims to find a better dose of transdermal MED patch for Tourette syndrome (TS). The approved registered dose (1 mg per patch per week) is shown to be generally well tolerated and effective in 70% of children patients. The side-effects of MED patch include rash, dizziness, drowsiness, dry mouth, headache, fainting, nausea, vomiting, and weakness.

TS is a neuropsychiatric disorder with onset in childhood and the symptoms can last for a lifetime. However, in approximately 50% of the patients, the symptoms disappear by the age of 18. The disease is characterized by multiple physical and vocal tics. By the nature of this disease, the symptoms typically wax and wane. Some patients do not need treatment while some may require medication to control the symptoms. The etiology of this disease is unknown but it seems to be associated with genetic and environmental factors. Currently, there is no specific treatment for the disease. Treatment of TS is symptomatic such as neuroleptic blockers of dopamine receptor (D2). However, the side-effect of the treatment could be severe and difficult to treat such as tardive dyskinesia (repetitive, involuntary, purposeless movements).

The objective of the study is to compare 3 different dosage regimens of this drug, in addition to a placebo arm at 1:1:1:1 ratio for the treatment of Tourette syndrome. The proposed doses are as follows: 1 mg, 1.5 mg and 2 mg per patch per week. The duration of treatment is 8 weeks and the duration of the study is 1 year. The sample size is 1600, divided into 400 patients per group.

The design of the study is a prospective, randomized, double blind, placebo controlled trial in children with diagnosis of

Tourette syndrome. Children who are 6-18 years, with weight between 20-40 kg with TS will be invited to join the study. Hematological and biochemical tests will be performed prior to recruitment. The patients will be excluded if the laboratory values are abnormal. The children will have physical examination by a Pediatrician prior to treatment and weekly for 8 weeks. The weekly evaluation of the tics will be conducted by using the Yale Global Tic Severity Scale (YGTSS). The adverse-effects will be assessed through a diary and validated by the pediatrician during the weekly follow-up.

Points for Discussion

1. Is the design of the study appropriate?
2. Is Placebo justified? If so, what protection can you provide to the placebo group?
3. Is there any vulnerability issue?
4. What is the type of informed consent?
5. Is risk/benefit assessment justifiable?
6. What are the important information and procedure that should be disclosed in the consent form?

Case Study 3: Clinical Trial of New Route of Measles Vaccine Administration

A prospective, opened, randomized, comparative study of two administrative routes of measles vaccine (subcutaneous and aerosol) in school children with low or absent serum antibody levels.

In the past, measles occurred predominantly in children under five years old. However, there has been an upward shift in the ages of those infected with the measles virus. Missed vaccination at the age for the first dose or the failure to response to the first dose may be responsible for this change. It is thus, a policy in many countries to vaccinate the school age children to ensure sufficient antibody level.

Several studies have shown that subcutaneous standard titre measles vaccines can boost antibody levels among children whose pre-vaccination antibody level is low (*e.g.*, <200 mIU). However, after revaccination of schoolchildren or young adults, antibody levels drop again in approximately 40% of children within 1-3 years.

Aerosol administration of the vaccine has theoretical advantages as it mimics the natural route of measles infection, potentially inducing local respiratory tract immunity. The measles vaccine virus could multiply locally without being neutralized by low levels of antibody. It is attractive to health professionals and parents because it is non-invasive and avoids the risk of transmission of infection by needles.

The objective of the study is to compare the serological response at 3 weeks, 12 and 24 months post-vaccination of measles vaccine administered by the subcutaneous or aerosol route in

previously vaccinated schoolchildren who have low or absent antibody levels.

The design of the study is a prospective, randomized, controlled trial in children with low or absent serum antibody levels. The school children aged 5-9 years who are due for the booster dose of measles vaccine will be asked to provide a salivary sample for salivary measles-specific IgG. Those who are negative for salivary measles-specific IgG will be asked for informed consent and randomized into one of the two groups: aerosol or subcutaneous route (standard) of administration. The 5 ml of blood and saliva will be taken on the vaccination day as well as during follow-up at 3 weeks, 12 and 24 months after the follow-up. Local anesthetic pads will be used to reduce discomfort during blood taking. Salivary samples will be obtained using a simple sponge device. Children (and their caretakers) in each group will be asked to complete a pictorial calendar of adverse reactions to vaccination for 3 weeks after vaccination. The children will have physical examination by the doctor for upper respiratory track infection during the follow-up visits. The study will be carried out in school facility. The duration of participation is 24 months.

Points for Discussion

1. Is the study justified?
2. Is there any vulnerability issue?
3. Is risk/benefit assessment justifiable?
4. What is the type of informed consent?
5. What are the important information and procedure that must be disclosed in the consent form?

<u>Case Study 4</u>: Phase II Clinical Trial of Vitamin X in Oncological Patients

A Phase II, open labeled, non-randomized study of active form of vitamin X in combination with standard chemotherapy to evaluate tumor response in patients with advanced, intrahepatic cholangiocarcinoma is submitted to the institutional review board (IRB) for review and approval.

Rationale: The incidence of cholangiocarcinoma in the research community is high. The most effective treatment is surgical removal in early stage patient. However most patients present to the hospital in advanced stage, which is inoperable. There is no standard chemotherapy regimen for advanced stage. The life expectancy after being diagnosed is 12 weeks.

The oral active form of oral vitamin X has been approved for more than 30 years as a supplementary treatment for patients with vitamin X deficiency. The recommended dose is 0.25 μg per day orally.

In vitro study, active form of Vitamin X was proved to control or decrease tumor cell growth in many tumor cells that have positive vitamin X receptors. In an animal study, chemotherapy plus active form of vitamin X can better control tumor growth than chemotherapy alone. There were some evidences in phase I-II studies of active form of vitamin X in combination with chemotherapy in the treatment of prostate cancers and hepatic cancers. The patients could tolerate to an intermittent high dose (2.8 μg /kg/day) for three days and positive trend to prolong life. The most common adverse effect is hypercalcemia. Other toxicities when using in combination with other chemotherapeutic drugs are mild as grade 1-2 and are similar to those using chemotherapeutic drugs alone.

In this study, investigator will prescribe oral active Vitamin X 12 µg for three days in combination with every cycle of chemotherapy for 6 months. Drug level, adverse effects, and tumor growth will be monitored every month for 6 months. Treatment will be provided free of charge. This study received co-funding supports from pharmaceutical company, university and other government agencies. There is no insurance coverage for compensation.

Points for Discussion

1. Is the study justified?
2. Is there any vulnerability issue?
3. Is risk/benefit assessment justifiable?
4. What is the type of informed consent?
5. What are the important information and procedure that must be disclosed in the consent form?

Case Study 5: Oral Iron Chelating Agent for the Treatment of Iron Overload in Patients with Myelodysplastic Syndromes (MDS)

A randomized double-blind, placebo-controlled clinical trial using a new oral iron chelating agent in patients with myelodysplastic syndromes and iron overload has been submitted to an IRB.

MDS are clonal stem cell disorders characterized by ineffective hematopoiesis (process by which immature precursor cells develop into mature blood cells) in one or more cell lineage and has the potential to evolve into acute myeloid leukemia (AML). MDS are frequently characterized by anemia and transfusion dependency. Blood transfusion is one of the treatments for MDS. In low-risk patients, transfusion dependency can be long lasting, leading to iron overload. Heart failure, liver dysfunction, cirrhosis and endocrinopathies have been described in multi-transfused MDS patients.

DFR is a rationally-designed oral iron chelator, administered once daily and has been recently released on the market for the treatment of secondary iron overload in transfusion-dependent anemias. Its usefulness has been tested in a cohort of MDS patients, yielding good data on efficacy and safety in older population. Its adverse effects are generally mild, consisting mainly of nausea, diarrhea and a self-limiting serum creatinine increase, thus making this agent possibly the most suitable for chelation therapy in the MDS population.

The primary objective of the study in this country is to compare **DFR** to placebo for event-free survival (a composite primary endpoint including death and non-fatal events elated to cardiac and liver function, and transformation to AML) in low and intermediate-1 risk MDS patients with transfusion iron overload.

The design of this study is a prospective, randomized, double-blind, placebo-controlled with a 2:1 (active: placebo). Two interim analyses for efficacy and safety will be carried out and a DSMB will be set up. The recruitment period is planned to last 24 months. The end of study is expected to occur 5 years after first patient first visit when 244 events for the composite primary endpoint have been observed.

The end of study treatment may occur if a patient meets any non-fatal component of the composite primary endpoint. His/her individual randomized study treatment will be unblinded and discontinued at the time. The subsequent iron chelation treatment is subject to patient's and the investigator's decision. Patients will continue to be followed every 6 months for iron chelation therapies and overall survival once he/she discontinues from the study treatment.

Points for Discussion

1. Is the use of placebo control justifiable?
2. If placebo control trial is not justifiable, what would be the study design that could allow evaluation of this drug in this country.

SELECTED SOCIAL RESEARCH CASE STUDIES

Case Study 1: Baseline Study towards Development of an Effective Intervention for Reduction of Intimate Partner Violence

1. Research Objectives

1.1. To describe the causes and manifestations of intimate partner violence

1.2. To study how partners manage or resolve problems

1.3. To determine the effectiveness of a model intervention program for reduction of intimate partner violence (IPV)

2. Study Design

2.1. Qualitative method will be used: In-depth interview of abused females and perpetrator males involved in intimate partner violence

2.2. Quasi-experimental design will be used to determine the effectiveness of a model intervention for IPV

3. Participants: Inclusion & Exclusion Criteria

Participants will be married or cohabiting couples who had intimate partner violence experience.

Inclusion & Exclusion criteria

3.1. Inclusion criteria

- Participants will be married or cohabiting couples who had intimate partner violence
- Aged 18 and older

- Female are assessed by HITS screening (score > 10)
- Those who agree to participate in intervention program.

3.2. Exclusion criteria

- Those with psychiatric disorders
- Those with drug abuse history
- Those not willing to sign the consent forms

4. Research Methodology

4.1. Sample & sampling technique

Qualitative studies generally focus on in-depth probing of a relatively small number of cases selected through purposive sampling. In qualitative inquiry, the goal is richness of information so as to illuminate the questions under study.

For the quantitative methodology, data will be collected from patient history record in 3 hospitals for 6 months.

4.2. Data collection

The personal interview: Talking face to face with respondents on highly sensitive matters requires sensitivity, skill, and the ability to interpret and respond to both verbal and nonverbal cues. In depth semi-structured interviews of participants will be used.

5. Data Analysis

5.1. Qualitative analysis: Content analysis consists of data immersion, data coding, data display, data reduction, interpretation/conclusion drawing.

5.2. Descriptive statistics including frequencies and percentages will be used for socio-demographic data.

5.3. Inferential statistics: chi-square, t-tests, and logistic regression will be carried out to formally test for statistical differences between the study and control group.

6. Outcomes

6.1. The study will provide insights into intimate partner violence, including prevalence and characteristics of violence, risk and protective factors for IPV, health consequences, couple's responses and solutions to violence, and perpetrator and victim voices will be heard.

6.2. The interventions will be useful for abused women and perpetrator men, their family members, and community.

6.3. There is a new model as appropriate for using multi-component approach that addresses change at the victim, perpetrator, and at the community level.

Points for Discussion

1. Is the design of the study appropriate?
2. What are different types of vulnerability in this study?
3. What types of consent forms are needed for this study?
4. What are the risks in this study?
5. What are the benefits of this study?

Case Study 2: Pesticide Exposure of Families in an Agricultural Community

1. Research Objectives

1.1. To evaluate the risk of pesticide exposure among people living in an agricultural community

1.2. To determine the relationship between environmental media (*e.g.*, air, dust, drinking water) and the urinary pesticide levels in people living in an agricultural community.

1.3. To identify environmental factors that contribute to pesticide exposure.

2. Study Design

The study is designed as a cross sectional study in which pesticide exposure in an agricultural community will be determined.

All questionnaires will be administered and samples will be collected from one agricultural community during the season of high pesticide use.

3. Participants: Inclusion & Exclusion Criteria

All of participants will be living in the area for more than 1 year.

This study will select the household as follows:

3.1. Occupational family (farm family) group

Inclusion criteria

- The housing location is within the agricultural community.
- The household has one of the following members: a child, a member of working age, or an elderly
- Live on land used for chili farming
- One of member of the household works in agriculture or in commercial pesticide application.

- Healthy children with ages between 2-5 years old who have no undesirable health diseases.
- Healthy working age people with ages between 15-59 years old who have no undesirable health diseases.
- Healthy elderly people who are more than 60 years old who have no undesirable health diseases.

Exclusion criteria

- Live outside the study area.
- Nobody in the household working in agriculture or commercial pesticide application.
- Unwilling to give urine or environment samples.

3.2. Non-occupational family (non-farm family) group

Inclusion criteria

- The housing location is within the agricultural community.
- The household has one of the following members: a child, a member of working age, or an elderly
- Live on land that not used for farming
- Nobody in the household works in agriculture or in commercial pesticide application
- Healthy children with ages between 2-5 years old who have no undesirable health diseases.
- Healthy working age people with ages between 15-59 years old who have no undesirable health diseases.
- Healthy elderly people with ages more than 60 years old who have no undesirable health diseases.

Exclusion criteria

- Live outside the study area.
- One of their families is farmer or working in agriculture or commercial pesticide application
- Unwilling to give urine or environment samples.

3.3. The population will be analyzed separately according to 3 groups:

- Preschool children (aged 2-5).
- Working age (aged 15-59).
- Elderly people (aged more than 60).

4. Research Methodology

4.1. Sample & sampling method

The number of households should be 54 samples per group (non-occupational family/farm family).

This study will use random sampling technique for selecting the sampling units (household). Then, the purposive sampling technique will be used to classify households. Because, for non-occupational family group, the household should not be use any pesticide for agricultural application and should not have a farmer in the family. Study household selection will be dependent on the residence location and separated into 3 levels.

Level 1: far from the agricultural farm less than 50 m.

Level 2: far from the agricultural farm 50-100 m.

Level 3: far from the agricultural farm 101-150 m.

The Geographic Information System (GIS) will be used for the sampling location.

4.2. Sample collection

- The questionnaire will be administered to each participant on the first visit.
- Air samples will be prepared using NIOSH method 5600.
- Water samples will be collected on the second visit. The water sample to be collected will be approximately 1 liter from each unique drinking water source.
- Surface residues will be collected from common areas from the participant's entire household on the second visit.

- Hands and feet will be wiped for the presence of pesticide residues using the gauze pads moistened with 40% isopropanol.
- Urine will be collected during the first visit. The participant will be asked to collect the urine sample (50 ml) in the morning on the second visit.

5. Data Analysis

5.1. Exposure assessment

An individual exposure to pesticide via inhalation, ingestion and dermal contact will be estimated by calculating average daily doses.

For non-cancer effect, risk assessment considers the period of time over which exposure occurred. Average exposures or dose over the period of exposure is sufficient for the assessment.

5.2. Risk characterization

The risk characterization combines and uses appropriate method to analyze the essential information from hazard identification, dose-response assessment, and exposure assessment to make risk estimates for the exposure scenarios of interest.

5.3. Aggregate risk characterization

The hazard quotients are combined to form a Hazard Index (HI) which assumes that the effects of the different compounds and effects are additive.

5.4. Statistical analysis

SPSS for windows (version 16) will be used for statistical analysis. The descriptive statistics will be used to describe mean, median and percentage for general information. Correlation between each exposure route and DAPs concentration will be conducted.

6. Outcomes

The pesticide exposure patterns in people living in agricultural community will be explored and associated to their behaviors to assess the human health risk of people living in this area. The evaluated information can be manipulated for risk management and risk communication to prevent or reduce risk to local community.

Points for Discussion

1. Is the design of the study appropriate?
2. What types of consent forms are needed for this study?
3. What are the risks in this study?
4. What are the benefits of this study?

DISCUSSION OF SHORT CASE STUDIES

Case Study 1: Role of the Research Ethics Committee (REC)

1. The monitor should advise the investigator to submit the progress report required for continuing review by the local ethics committee to keep the protocol approval updated.
2. Failure by the Investigator to submit an annual progress report on time is a GCP deviation/violation which states that "the investigator should submit written summaries of the trial status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC" (4.10.1).
3. Enrolment of new subjects should be suspended until the approval of the progress report by the local ethics committee. Follow up of patients enrolled in the study may continue, in order not to endanger the safety of those who have been previously enrolled.
4. The Investigator should submit a protocol deviation report to the local ethics committee and report all interim study related activities from the due date of the progress report until the date of continuing review approval.
5. The sponsor should communicate with the local ethics committee about the need to comply with the GCP requirements to include "at least one member whose primary area of interest is in a nonscientific area" (3.2.1) and that it "should maintain written records of its activities and minutes of its meetings" (3.3.2).

Case Study 2: Emergency Room Research

1. The sponsor should prepare a separate informed consent form for a legally acceptable representative and submit this to the ethics committee as amendment. The protocol deviation of making the husband sign the patient consent form should be likewise be reported to the REC.
2. The REC overlooked the need for a separate consent form from a legally acceptable representative, considering that the protocol was about emergency room research that presented the possibility that some patients were in a comatose stage.
3. The REC, when it reviews the protocol, should ensure that all relevant consent forms (including separate assent forms, etc.) have been submitted for approval.
4. The REC standard operating procedures (SOPs) should provide guidelines which types of protocols should require separate consent forms from legally acceptable representatives and assent forms from vulnerable participants.

Case Study 3: Scientific Soundness

1. GCP requires that "clinical trials should be scientifically sound, and described in a clear, detailed protocol" (2.5). The protocol should contain complete information about the machine that treats the water, what change it brings about to justify its potential health benefit claims for HIV patients. Likewise the study team should include a medical doctor to comply with the provision that "the medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician" (2.7).
2. It is the responsibility of the sponsor to "designate appropriately qualified medical personnel who will be readily available to advise on trial related medical questions

or problems" (5.3). It is the responsibility of the Investigator to ensure that a qualified physician is part of the team (4.3.1) and it is the REC's responsibility "to safeguard the rights, safety, and well-being of all trial subjects, with special attention paid to trials that may include vulnerable subjects," like HIV patients (3.1.1).

3. The hasty REC approval, without sufficient information is not justified.
4. The protocol should describe how the machine treated water will provide health benefits to persons with HIV. The ICF should also contain this information.
5. The protocol requires the inclusion of an infectious disease physician who has experience with HIV treatments.

Case Study 4: Conflict of Interest

1. The epidemiologist REC member should not be the appropriate reviewer due to his conflict of interest, since he is also the adviser of the post graduate student. He must have played a significant role in conceptualizing the study and may even be included as a co-author in future publications.
2. Another member, with experience in community research or malaria interventions may be assigned as primary reviewer.
3. Expedited review should only be used for minimal risk protocols. The review channel (expedited or full board) for this malaria community directed intervention will depend on several factors that could elevate the levels of risks involved in the study:
    i. Types of intervention used in the study (treatments, educational activities, etc.)
    ii. Study site (whether it will be implemented among tribal or marginalized groups like migrant workers who may be classified as vulnerable populations, etc.)

Case Study 5: Research on Healthy Volunteers

1. Presumably, the informed consent form will contain information about the $100 payment to healthy volunteers and the privilege of staying in the newly renovated ward with high technology features and games. Highlighting such features may constitute undue inducement for healthy volunteers to take forgranted the health risks involved and focus on the short term inducement being offered.
2. The ICF should mention the risks involved related to study procedures (blood draw, injections, overnight stay, etc.). There should be a provision in the protocol to exclude participants who have enrolled in a bioequivalence study during the previous 6 months to avoid frequent volunteers who do it for monetary reasons.
3. The ICF should state that the study has no health benefits to healthy volunteers. The REC should recommend the appropriate amount to compensate the volunteers based on local practice.

Case Study 6: Observational Study

1. If this is an observational study, the doctor should prescribe the investigational drug based on his clinical judgment, not based on the incentive provided by the local pharmaceutical company or the promotional activities of the sponsor. Once the physician allows himself to be affected by the marketing objectives of the sponsor, his conflict of interest could influence his clinical judgment that would constitute potential risks to his patients in an observational study. The washout period that the study requires when there is a change in drug prescription is another potential source of risk.
2. The generic drug, if it has been proven to be bioequivalent of the branded drug may be cheaper.

3. Informed consent should not be waived. The patient, even in real world conditions, should be given full information about the drug, its health benefits and side effects, and should give consent to allow the investigator to use his/her data for the study.
4. The study physician should have good clinical or economic reasons to change the drug of a patient whose study medication currently addresses his/her hypertension. The change in drug prescription should not be based on the physician's desire to facilitate patient recruitment into the observational study.

Case Study 7: Behavioural Research

1. The investigator should submit the protocol, the consent forms, the study instruments (questionnaire, interview guide, FGD guide, etc.), advertisements and other recruitment materials for REC approval.
2. Since the study will be done among sex workers, vulnerability issues should be identified in the various stages of the research process. Recruitment of potential participants should be done by someone who enjoys the trust of sex workers, like a health personnel who is familiar with their health conditions or a fellow sex worker who has been recruited into the study, making use of the snowball recruitment method.
3. The protocol should also contain a data confidentiality plan to protect the privacy of sex workers and minimize potential social risks, like stigma, legal consequences, etc. The research staff should have additional training in confidentiality protection.
4. The sex workers need to be informed that their data will be used for a study and informed consent should not be waived. The signature in the informed consent form may be

waived if participants in the study raise the issue that they do not want to be identified.

5. Social scientists need permission from the health facility to access medical records of patients and need informed consent from the participants of the study.

Case Study 8: Traditional Medicine

1. Constipation is not a high risk condition and can be treated outside the hospital. Patients in the intensive care unit are high risk patients and constitute a vulnerable population whose recruitment is regulated by laws and guidelines. The protocol needs to justify the use of ICU patients in the study, and its main consideration should not be the convenience of recruitment. The ethical standard is to explore doing the study with less vulnerable groups first, since doing it in the ICU will elevate the levels of risks, such as herbal drug effects that may exacerbate the health conditions of the ICU patients.
2. Death is classified as a serious adverse event that should be reported.
3. This study can be done at the surgery department with patients with less serious health conditions or at the outpatient department.

Case Study 9: Recruitment and Informed Consent

1. The study should be revised before it is approved. Recruitment of potential participants is an important ethical issue. The social scientist cannot just look at medical records of vasectomized men to come up with a list of potential participants whom they would call to get their consent to be interviewed.
2. The study does not qualify for expedited review due to stigma attached to vasectomy in many cultures. The

vulnerability of vasectomized men, who will be interviewed, elevates the level of risk of the study.

3. The recruitment and consent procedures should be revised. One possible recruitment procedure is to ask the medical doctor who performed the vasectomy to recruit potential participants. Or the snowball recruitment method can be used, making use of a patient to recruit other patients.

Case Study 10: Post-Trial Access

1. Since this is a Phase II study, it means that the study drug is at the early stages of clinical trial where there may not be sufficient evidence of safety and efficacy of the herbal extract. The sponsor and the investigator should wait for favorable results of clinical trials before accommodating the patient request for post trial access.
2. Post trial access is mandated by the Declaration of Helsinki. But the investigator and the ethics committee should consider various factors and specific patient conditions in requiring post trial access. The clinical trial should have favorable outcomes related to safety and efficacy for patient use. The physician should use his/her clinical practice judgment to decide if the patient will benefit from the drug. The study team should include, not only a pharmacologist who develops herbal extracts, but should also include an HIV specialist who can make medical decisions about appropriate prescribing of the study drug.
3. The investigator, the REC, the institution and the funder have the moral responsibility to help the patient who experienced renal failure to deal with his conditions as defined by local laws, regulations and guidelines.

DISCUSSION OF CLINICAL TRIAL CASE STUDIES

- Allergic Rhinitis (children, no treatment as comparator)
- Tics (children, placebo control trial)
- Measles vaccine (healthy children, active comparator)
- Oncology patients (open label, add on adjunct therapy)
- Myelodysplastic syndromes and iron overload (placebo control trial)

<u>Case Study 1</u>: Efficacy of Saline Nasal Irrigation in Children with Allergic Rhinitis

Children with allergic rhinitis may be treated by different expertise (*i.e.*, ENT specialist or pediatrician or expert in allergy and immunology). Each expertise may have their treatment preference that is related to their experiences. Inputs from these experts will broaden the understanding of the study rational and design, which will result in a better analysis of benefit and risk involved in the study.

The patients with allergic rhinitis may present with different symptoms such as itchy nose, sneezing, nasal congestion, rhinorrhea, etc. However, patients that would benefit from saline nasal irrigations are those with rhinorrhea and crust. Furthermore, the children with clef palate are at risk for using saline irrigation. In this study, the inclusion criteria, therefore,

should be only children who may benefit from nasal irrigation, i.e., patients with rhinorrhea and crust. This will enhance the chance of detecting the efficacy of nasal irrigation, if any. The children with cleft palate should be excluded to avoid the risk of complications.

The intervention with a large amount of saline irrigation into each side of the nasal cavity within a short period of time could cause discomfort to children. It is thus important that the caregivers/patients are trained until they are able to perform the procedure properly. The appropriate posture for nasal irrigation to minimize aspiration during the procedure should be emphasized during training. The performance of caregivers/ patients on nasal irrigation should be verified and documented by the investigator.

The data from previous studies demonstrated that the ones without nasal irrigation had higher TNSS, which suggests that the direction of hypothesis testing is known; therefore, the one-sided test should be applied for sample size estimation. This would significantly improve the power of hypothesis testing and, thus, reduce the sample size. However, if the investigator is uncertain about the information from the previous studies, a two-sided test could be used as proposed. A more important issue is the lack of information on the difference of TNSS that would have clinical significance, which is essential for a meaningful estimation of sample size.

The study includes children of age 5-15 years is justified at the onset of allergic rhinitis is common in childhood within this range. It is thus necessary to include children in this study since it could benefit this age group.

The informed consent and assent should include the possibility of risk associated with the nasal irrigation procedure, including the

aspiration during the procedure as well as bleeding and nasal congestion. The statement on the responsibility of the caregivers should be included to ensure that no one without proper training from the investigator team be allowed to do the procedure on their behaves, as this would increase the risk of aspiration, epistaxis or discomfort from rapid irrigation of large amount of NSS.

The study involves 3 follow-up visits for the purpose of research. The participants' travel expenses and time loss should be compensated. Provision of expenses for medical care should be made to cover possible risk(s) from the procedure.

Case Study 2: Dose Optimization Study of a Newly Registered Drug

This type of study demonstrates that even after marketing approval, there may be a need for further dose finding studies that might improve efficacy. The use of placebo is acceptable in this study as the symptoms in TS can wax and wane. It is also the case that not all TS patients require treatment. The use of placebo is scientifically sound to determine the efficacy of the drug. The patients with placebo will not likely be subject to serious risk or irreversible harm. However, the placebo group is at risk of having tics more than the group with the active intervention; thus, the placebo group should have special protection. One measure is to lessen the number of patients in the placebo arm. Changing the ratio of the active intervention to placebo should be considered such as 2:2:2:1 or 3.3.3.1 ratio instead of 1:1:1:1 as proposed. In addition, the use of DSMB to monitor the safety of the participants and to have early termination if the primary endpoint has been achieved would be another measure to protect the placebo group. Furthermore, post-trial treatment using the approved dose of transdermal MED patch should be given to the placebo group at the end of the trial.

The study includes children age 6-18 is justified due to the nature of disease that commonly occurs in early childhood. Although the symptoms can last a lifetime, half of the patients will not have symptoms by the age of 18. It is essential to include children in this study since it could benefit this age group. Perhaps the study should be first performed in older children (say, 15-18 years of age).

The information that should be included in the informed consent process is as follows: an explanation of the nature of the disease, disclosure that the intervention drug is not a specific treatment

for the disease but is a symptomatic treatment, probability of being assigned to the placebo arm.

Case Study 3: Clinical Trial of New Route of Measles Vaccine Administration

The study proposed to compare the effectiveness of a new route (aerosol) of measles vaccine to the conventional route (subcutaneous) in a prospective, randomized, controlled trial of school children whose antibody title is low. Expertise in clinical immunology and pediatrics would be required to guide the review of this type of trial.

According to the clinical immunologist, the aerosol route mimics the natural infection and can induce local respiratory immunity. Contrary to the subcutaneous route of administration, the aerosol measles vaccine virus could multiply locally without being neutralized by low levels of antibody. It is reasonable to expect that aerosol vaccination will generate immunity both locally in the respiratory mucosa as well as systemically, and result in higher antibody production than that achieve through the subcutaneous route. The study is responsive to an important health need because subcutaneous route does not seem to be effective enough to maintain the protective antibody level required to protect children from measles.

The subjects in this trial are vulnerable. However, the study could not be performed in other less vulnerable group, the purpose of the trial is specific for the benefit of children in the proposed age group and under this condition i.e. low antibody to measles. The benefit could be for both the research subjects and the future children. The study is justified in spite of having a long follow-up period with several investigations. However, the subjects are school children and the study will be performed in school facilities, the concern is that the school children may be under the influence or pressure from the teachers if they are involved with the process of screening.

Risk involved in this study is blood taking, which may have psychological impact to the children. The investigator proposed to minimize this risk by using local anesthetic pads to reduce pain or discomfort from blood taking procedure. Furthermore, aerosol vaccine may not induce sufficient antibody to protect them from infection. The investigator proposed examine the participants for upper respiratory infection during the follow-up: 3, 12 and 24 months, but whether the duration of follow-up is long enough or not, is a concern for both safety and efficacy evaluation. A longer period may be required as according to the data from revaccination of school children or young adults, antibody levels drop again in approximately 40% of children within 1-3 years. The study is of the exploratory type. The location of the trial is at a school facility so the potential risk of aerosol administration to subjects with an undiagnosed allergy or asthma is not known. Potential participants with a known history of allergy or asthma should be excluded from the study. To address such safety concerns a medical emergency kit must be available at the study site in order to ensure prompt action should a medical emergency arise.

The vaccine has the potential to directly benefit the participants, but the efficacy is still questionable. The post-study benefits should be considered for the research participants receiving the aerosol.

This study requires both assent (the age depends on the requirement of the country performing the study) and informed consent. Important information and procedures that must be disclosed in the consent form include the chance of being randomized into the aerosol measles vaccination group in which the efficacy and safety are still not known (but potentially more effective than the conventional route), the long follow up period (24 months), 4 times blood taking of 5 mls, and if they disagree to participate, they will still receive routine vaccination.

Case Study 4: Phase II Clinical Trial of Vitamin X in Oncological Patients

This study examines the efficacy of the active form of vitamin X in combination with standard chemotherapy to evaluate tumor response in patients with advanced, intrahepatic cholangiocarcinoma. Cholangiocarcionoma is a serious condition with a short life expectancy following diagnosis. The active form of vitamin X has a positive trend to prolong life in other types of cancer. The study is responsive to a well-defined health need. It is worth exploring the complementary effect of this add-on treatment on this serious disease. However, a placebo-control study design should be considered as it will be more informative and the result can be interpretable. Placebo-controlled trials will provide the maximum ability to distinguish adverse effects caused by a drug from those resulting from the underlying disease or intercurrent illness, as well as the evidence of improved clinical outcomes. This is an add-on therapy, thus, placebo is ethical justifiable.

The patients in this study are terminal staged cancer patients and thus they should be considered highly vulnerable. It is important to consider performing this study in less vulnerable patients perhaps in cholangiocarcinoma patients at earlier stage inoperable but having fewer complications. The inclusion/ exclusion/withdrawal criteria and screening procedures must be stringent and should be clearly defined in the protocol.

The risk of the study is that the proposed design is unlikely a conclusive response to the study question due to the many factors that could affect disease progress and survival in this group of patients. The results will not be highly difficult to interpret. The study design appears unsound and the selection of the patient population appears unethical.

<u>Case Study 5</u>: Oral Iron Chelating Agent for the Treatment of Iron Overload in Patients with Myelodysplastic Syndromes (MDS)

The use of placebo control in this study is not justifiable because the drug has been registered in many countries already. The test intervention's efficacy has been shown to work as an oral iron chelator for secondary iron overload. Many studies using this intervention have already been performed in patients with MDS in other countries. The use of placebo will deprive treatment to some patients who would likely benefit from the test intervention. As stated in the *Declaration of Helsinki*, the use of placebo should be restricted to studies where no standard treatment is available or for specifically justified methodological reasons. In this country standard treatment for iron overload is not regularly used. The test intervention, however, has been demonstrated to be effective and safe. There is no reason to prove its efficacy as an iron chelator. Rather this study should focus on demonstrating the test intervention's validity in this country's MDS population to support a national application for marketing authorization.

The real objective of the study in this country is to (re)confirm the efficacy and safety of DFR. An open trial with the registered dosage could provide desired information.

DISCUSSION OF SOCIAL RESEARCH CASE STUDIES

Case Study 1: Baseline Study towards Development of an Effective Intervention for Reduction of Intimate Partner Violence

1. The study makes use of both the qualitative and quantitative methods. The qualitative method of using in-depth interview is appropriate to be able to describe the causes, manifestations, experiences of couples involved in intimate partner violence (IPV). In this component of the study, both female victims and male perpetrators are participants. The quantitative component will involve collection of data from 3 hospitals for 6 months. Presumably, the hospital records would consist of women treated in emergency rooms or admitted into hospitals as a consequence of intimate partner violence.
2. Couples involved in IPV are vulnerable participants. In countries where there are laws for the protection of women, partner battering is a crime and subject to legal litigation and sanctions. The male perpetrators may be charged with illegal acts by their female partners who are victims of IPV. There is also the element of social stigma for participants in this study, considering the abnormal conditions of couple relationships and the possible underlying psychological reasons for IPV.
3. Different consent forms are required in this study: a. Consent forms for the in-depth interview from both female and male couples who will participate; b. Consent forms for

the use of medical records from women treated in emergency rooms or admitted into hospitals as a consequence of intimate partner violence. The investigator may request for a waiver of consent, if the health providers of female victims in IPV will agree to provide anonymized data sets and the investigators will not follow up or interview these women. However, it is only the research ethics committee that reviews this protocol can grant the waiver of consent.

4. The risks of this study are related to the legal and social vulnerability of participants, including the potential worsening of IPV as a result of participation in this study. For the participants who will be interviewed, it is important to get consent from the couple. The investigators should draw up a confidentiality plan in the protocol that describes how privacy of information will be protected. Contingency measures should also be descibed in case IPV gets worse or when a couple refuses counseling or other means to mitigate violence.
5. The benefit of the study is the possibility of being able to develop effective interventions to address IPV that could directly benefit the couple to be able to resolve their IPV issues.

<u>Case Study 2</u>: Pesticide Exposure of Families in an Agricultural Community

1. The study design is appropriate for an environmental study as it makes use of households within an agricultural community as the units of analysis and identifies the members of the household from whom samples will be taken. Water and residue samples will likewise be collected and analyzed from the houses of the respondents.
2. The consent form from the household head should identify all information or data needed and samples to be collected from each household. Collection of urine and other individual samples from each member of the household requires a separate consent form from each individual member.
3. The investigator should identify potential socio-political and economic risks of the study related to the site where it will be implemented and discuss how these will be mitigated. Referral for health care should also be provided to participants who are at risk for adverse events caused by exposure to pesticide.
4. Since environmental impact of pesticide is a public health issue, the study team should share the results with the community to provide them with proper information about environmental risks and mitigation measures. In addition, the study team should conduct an educational intervention to improve community knowledge, attitudes and practices related to pesticide exposure. These measures should be included and described in the protocol when it is submitted to a research ethics committee.