Perspectives on Ethical Review

A Casebook for Reflecting on Challenges and Aspirations for Improving the Role and Function of Ethics Committees and Ethical Review Systems

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The Strategic Initiative for Developing Capacity in Ethical Review
(SIDCER)

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The Strategic Initiative for Developing Capacity in Ethical Review
(SIDCER)
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This book is presented to Dr. Angela Bowen
in appreciation of her vision and guidance
in the MFES Fellowship Program.

Foreword

The creation of this casebook is a wonderful expression of friendship, and it will become a source of motivation for future professionals to share in the learning of the Fellows Program.

The Fellows Program envisioned by Dr. Juntra and myself in 2002 has succeeded beyond our most optimistic expectations and hopes. The Program has grown to include an alumni organization known as the Middleton International Fellows Association (MIFA), which aspires to provide graduate Fellows with an information network that can be of worldwide impact.

Alongside the key achievement of promoting ethical medical research, two other important results should be noted. Firstly, the value of members from so many different countries and cultures coming together as one to reach common goals. Secondly, the close and lasting international friendships that continue to this day and promise to flourish in the years ahead.

I am enormously proud to be recognized by you in this sharing of perspectives as well as the commitment to common progress as expressed in this casebook. Thank you all and, in appreciating the achievements of this casebook, let us continue to respect our friendships and honor our shared goals.

Angela J. Bowen, M.D.
President, Middleton Foundation for Ethical Studies (MFES)

Introduction
The Origins of These Perspectives

This casebook presents ten recent examples of studies that have aspired to improve healthcare in Asia while at the same time challenging local ethics committees to provide an appropriate consideration and guidance. A synopsis of the proposed research is presented as well as the challenges the ethics committees addressed. This is then followed with the perspectives of the ethics committees that framed the discussions.

The casebook wants to demonstrate that perspectives matter: perspectives from varying research protocol types that ethics committees regularly address, perspectives from specific settings and cultural backgrounds, but mostly perspectives out of which ethical issues and challenges arise and are addressed. The authors here provide perspectives on research proposals made to their committees. They have highlighted the scientific frameworks as well as health issues the protocols intend to address; and they have sought to bring to the fore the salient ethical questions to which their committees provided a response.

This casebook is intended as a pedagogic tool for teaching research ethics, for training new as well as established members of ethics committees, and for critically approaching ethical review practices. But even more so, this casebook is intended to share and grow perspectives on, and appreciation for, health research ethics as seen through the eyes of ethics committees. This is intended to be a book that is shared among students, among professors, among researchers, and among members of ethics committees. But principally this book is intended to be shared by friends, and shared as an appreciation of that friendship we achieve when we collectively reflect on ethics.

Promoting human subjects protections in health research underlies the objectives and work of the Forum for Ethical Review Committees in Asia and the Western Pacific (FERCAP). Over the course of the past sixteen years, FERCAP has focused on building the capacity of ethics committees to contribute to research carried out on human subjects such that the research takes into consideration the dignity, values, and needs of individuals and communities. We cannot afford affluent research institutions and projects focused on scientific advancement without reflecting sufficiently on, and acting resolutely toward, understanding the impact of research on the subjects that offer their participation.

The work of FERCAP has helped to bring to light differences in the standards and practices of ethical review as well as the impact of these differences on the progress of health research and, eventually, public health itself. Obstacles to much needed research should be recognized and removed. This is an ethical requirement. Research is needed to prevent or alleviate suffering brought about by disease. Even the threat of disease induces suffering.

However, we need to recognize as well that no single model for ethical review is appropriate for all countries or all research situations globally. And while ethics committees do function differently in different countries and different institutions, they also share an obligation to look beyond their boundaries, learn from one another,

and raise their standards while improving their practices. Just as the science brought to bear on heath issues needs to be challenged, so too do the perspectives we bring to evaluating that science.

This is the approach that FERCAP adopted from the start, and it is the approach FERCAP continues to pursue within its vision of more perfect and more efficient ethical review committees and ethical review systems. The potential societal value, scientific validity, and even the ethical contribution attributed to ethics committees have been legitimately called into question. It is from within this environment of correct and forceful challenges to ethical review practices that FERCAP promotes responsible decision-making within countries and across institutions so that researchers, as well as research participants and their communities, experience genuine value from submitting health research to review by ethics committees.

Against this background and these commitments FERCAP honored Dr. Angela Bowen's vision of human subjects protections in health research and awarded her with the first FERCAP Human Subject Protection Award in 2010 at the 10th FERCAP International Conference in Shanghai, China.

Working together with WHO/TDR and the Strategic Initiative for Developing Capacity in Ethical Review (SIDCER), Dr. Bowen established the WIRB Fellowship Program to better understand ethics in different settings and to enhance the capacity of individuals from different countries to develop and apply ethical principles and practices when reviewing health research. The goal from the start has been to develop an enabling environment that promotes shared values and a common understanding of best practices for protecting research subjects.

The WIRB Fellowship Program, initiated in 2003, has trained 151 scientists. The majority of these scientists came from Asian countries. Most of these WIRB Fellows now play a pivotal role in promoting ethical health research and the establishment of health research systems in their own countries. They are also involved in continually improving the understanding of the role of ethics in health research and improving their practices. The growth of FERCAP continues to be intimately tied with the experiences and expertise of these Fellows.

I met Dr. Bowen for the first time in Brussels in 2001 during a SIDCER meeting that brought various stakeholders together to brainstorm on the implementation of the first SIDCER strategic plan. Many who attended that meeting were skeptical about the chances for SIDCER to succeed, being such an ambitious project with such an enormous vision. During the meeting Dr. Bowen sat quietly in the back, observing. At the end of the meeting, she said to me: "What can I do to help you move this idea forward?" In 2002 Dr. Bowen invited me to visit WIRB and I was impressed with the organization and her leadership. I was invited to her house where I was served my favorite scrambled eggs dinner. That dinner led to two important achievements: the establishment of the WIRB Fellowship Program and our lasting friendship.

To strengthen the fellowship-training program, Dr. Bowen enlisted the Middleton Foundation for Ethical Studies (MFES), which provides support for scientists from developing countries who otherwise would not be able to attend the WIRB Fellowship Program. She continued to dedicate her time, energy, and resources for the

training of WIRB Fellows until 2009 when she stepped down as Chair of WIRB Board of Directors.

However, Dr. Bowen's commitment to promoting ethical research did not end with her retirement from WIRB. She continues to support the establishment of the joint training program of SIDCER and three universities in Thailand (Chulalongkorn University, Manidol University, and Khon Kaen University). The 'MFES Global Fellows Program' was inaugurated in October 2014. Fifteen scientists from Thailand have since undergone training in this exceptional program.

I am grateful for Dr. Bowen's vision, leadership, and engagement in founding the WIRB Fellowship Program and the Middleton Foundation for Ethical Studies. I deeply appreciate her dedicated efforts towards empowering scientists from developing countries alongside her personal and professional commitment to promoting ethical research.

This casebook was written by the recipients of MFES Global Fellows Program as an expression of their appreciation, but even more as an expression of their aspirations. I hope that the Fellows will continue to become more of what Dr. Bowen has shown them they can become.

Juntra Karbwang Laothavorn
SIDCER Coordinator
Professor and Head
Clinical Product Development
Nagasaki University, Japan

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Case Study 1
A Post-marketing Study in COPD

A prospective, multi-center study of the safety and efficacy of a mono-therapy drug (XYZ) compared with long acting bronchodilators for the management of moderate COPD.

The ethics committee was presented with a proposed study of a mono-therapy drug to address moderate chronic obstructive pulmonary disease (COPD). XYZ has recently been approved as a mono-therapy drug for COPD patients with moderate symptoms. XYZ is an inhaler drug commercially packed in a novel-designed device. Alternative treatments for moderate COPD, following GOLD guidelines (2009), include long acting bronchodilators (LABA). There is, however, no information regarding long-term safety, efficacy, tolerability, patient satisfaction, device user-friendliness, or physician satisfaction. This study is planned to be conducted under real world medical practice conditions. The assignment of the patient to the therapy will be decided within the current practice according to the medical indication and will be based solely on the clinical judgment of the physician. The sponsor will not provide the drug. Patients only become eligible for this study after the decision to prescribe the therapy has been made.

The study population will consist of male and female symptomatic patients with moderate COPD (GOLD stage II) determined in accordance with the current diagnosis criteria (2009). Subjects must be 40 years of age or older and they need to agree to complete the COPD questionnaires as well as provide written informed consent. They will be excluded in cases of a previous diagnosis of asthma, having a history of cancer, suffering concomitant pulmonary disease, having prolonged QT syndrome, suffering alpha-1-anti-trypsin deficiency, being pregnant or lactating, having acute exacerbation of COPD or acute cardiovascular events, or having received inhaled corticosteroid within 3 months at the time of study entry. In accordance with the baseline prescription, subjects will be grouped into 2 groups, XYZ mono-therapy and other LABAs, in a 2:1 ratio.

No diagnostic or monitoring procedures additional to standard care and routine practice will be applied to the patients. The observational period for each patient will cover 6 months (+/- 4 weeks). Study visit follow-up intervals will not be fixed per protocol, but will adhere to the common practice in this indication (moderate COPD) and per patient determined.

Patient data originating from assessments and evaluations according to the physician's routine practice as well as data from the patient reported outcome questionnaire will be collected for the purposes of this study.

Challenges Encountered by the Ethics Committee

1. What is the justification for this post-marketing study?
2. Have the researchers raised the appropriate ethical questions in the protocol?
3. Are there any identifiable conflicts of interests?

Perspectives

To understand the background of the protocol presented to the ethics committee, the committee reviewed the US Food and Drug Administration (FDA) requirements for a post-marketing study after granting the approval of certain drugs. From the guidances it is clear that the FDA often requires such studies when it considers that there is a public health concern regarding the risks of a marketed drug. The signals for a safety concern may have arisen from a randomized controlled trial submitted in support of a marketing authorization, a meta-analysis, patient registries, observational studies, or even a case report. The randomized clinical trial is the gold standard for studying drug efficacy before FDA approval, but it provides only a limited assessment of risk associated with a drug or device. Limited sample sizes, limited follow-up times, and the inclusion/exclusion criteria used to select the study population may limit the confidence of the regulatory evaluation. Also, the dynamics of the risk-benefit balance may change over time with the development of alternative treatments, prevention methods, or the evolution of the disease.

Should new safety or efficacy questions arise, a new randomized controlled trial to address these questions may be required to support the continuance of a marketing authorization. The characteristics of a randomized controlled trial should include the precise design used to address the evidence gap; the power of the design, trial procedure, and the analytic plans to answer the questions raised. Additionally, appropriate inclusion and exclusion criteria need to reflect the best available knowledge regarding risks and potential benefits in the population as well as the comprehensive and safety-monitoring plan.

Post-marketing safety studies may identify the infrequent outcomes that occur long after exposure or arise due to the diversity of patients or care settings. However, the observational plan of XYZ drug may likely not provide more information about the efficacy or safety because the study design leaves open selection bias, the data collection has no fixed schedule for outcome measurements and safety monitoring, and the unsound analytical plan. A 2:1 ratio may also threaten to lead to a promotional use of the drug rather than to objective medical-based decision-making. The justification of the 2:1 ratio could be considered acceptable if the targeted drug is seldom used in general practice or the suspected adverse events of the study drug are unusual. In such settings, there may be a need to ensure greater independence of the potential research subjects from the investigator, perhaps excluding the care-providing physician from being the investigator.

The ethical questions the ethics committee expected to see addressed in post-marketing observational studies include the choice of alternative treatment(s), potential undue influence during the consenting process, confidentiality or privacy regarding health information, and no direct benefit to subjects. The discussion of available treatment, the advantages and disadvantages of treatment options, should be clearly made before making the decision. This is particularly important in settings where treatment options are limited, either because of regional/geographical limitations in the availability of marketed medicines or due to financial constraints. The waiver of informed consent did not appear appropriate to the committee in this case because health information is disclosed to the researchers. The process of informed consent should consider the physician-patient relationship. An independent

investigator might provide greater independence in the informed consent process. Subjects should be informed of the confidentiality protection plan and informed that they should expect to receive no direct benefit by enrolling in the study.

The committee considered that conflicts of interest may arise if the investigator is too largely compensated for his/her time and work, which may also impede the trust relationship. This is a concern in settings where physicians generally earn less than their counterparts in more affluent settings. Due to the potential influence of payments to the investigator, the committee thought it best that subjects are informed of these payments from the sponsor.

Case Study 2
A Commercial Sex Worker Interview Study

A social study of health-related quality of life issues among female commercial sex workers in AA province.

The ethics committee was presented with a proposal for a social science study that would interview female sex workers. Commercial sex trade by female sex workers is considered a social problem in many countries around the world. According to a survey by the Ministry of Public Health (2013), the number of female sex workers was found to be highest in AA province. However, their real numbers are probably underdetermined because female sex workers often conceal their status due to their unaccepted status in society. These negative impacts not only cost these women the opportunity to obtain social equality and life security, but also access to health services. These women are at risk for sexually transmitted diseases, such as HIV. The application presented to the ethics committee highlighted the societal interest in researching the quality of life of these women.

The researcher proposing the study anticipates the results from this study will be used as basic information for health planning to improve health-related quality for female sex workers as well as to expand health services to help prevent sexually transmitted diseases (including HIV) for these women.

The proposed study would be conducted through observation and in-depth interview with 30 female sex workers. Researchers would use purposive sampling techniques to approach the potential subjects. Inclusion criteria is set for female sex workers aged 18 years or older with experience in sex working for at least one year and a willingness to participate in this study.

The researcher proposes to approach the potential subjects through officers at the Department of Disease Control of the Provincial Health Office. These officers have relevant information regarding female sex workers. If the female sex workers agree to meet with the researcher, then a meeting for the consent and interview would be arranged. The researcher would provide potential subjects with information regarding the study (objectives, procedures, expected outcomes, confidentiality protection, and other aspects of the study) during the consent process. The researcher has no plan to use the participants' real names and study-related information will not be disclosed to other parties. The researcher will also respect any decision made by the participants, including their willingness to continue in the study. The researcher requests the waiver of written consent in order to prevent the disclosure of the participants' identities.

Each subject will be paid 5 USD to cover her travel cost. If the interview is conducted in a place not requiring transportation, a gift of 5 USD will be provided. To avoid any discomfort and embarrassment, the researcher will ask for permission from the subjects prior to taking any photos or making any tape recordings. All of the data will be kept on a computer secured with passwords.

Challenges Encountered by the Ethics Committee

1. Are the potential subjects' privacy and confidentiality sufficiently guarded for in the study?
2. Should the committee accept the waiver of written informed consent?
3. Are the vulnerabilities of the potential research subjects significantly addressed?

Perspectives

The ethics committee contained members that understood the conditions in which the potential subjects work and understand that the protection of their identity is of high importance, especially regarding their communities of origin and families. Thus the committee considered that there was a high priority to ensure the privacy and confidentiality of the research subjects in this study. This should be extended to include the privacy and confidentiality of the local community in which the female sex workers practice their trade.

In Asia, as in most places in the world, the role as sex workers is not well accepted by society. The sex workers are highly sensitive to the risk of information provided to researchers being leaked to outside entities and leading to personal or community stigma and other consequences. The ethics committee suggested that the consent process should ensure a private study site location for demonstrating the researcher's commitment to protecting confidentiality and privacy.

It was also the ethics committee's view that the waiving of written informed consent would contribute to further the protection of the privacy and confidentiality of the potential research participants as well as providing a more comfortable environment for the potential subjects. At the same time, the ethics committee insisted that a full informed consent process should take place and be documented, although with no identifying information and no participants' signatures being required.

The ethics committee did not see this study bringing a direct benefit to the subjects. Their voluntary participation should be fully respected. The ethics committee also advised the researcher that insensitive survey questions could bring about psychological harm to the subjects. The researcher should ensure that all questions are needed for reaching the study's objectives while maintaining the highest respect for the participants and sensitivity for their situations and concerns.

Case Study 3
An Emergency Medicine Trial

A randomized, double-blind, placebo controlled trial of drug X for patients with traumatic brain injury.

The ethics committee was presented with a proposed study for the investigation of progressive intracranial hemorrhage continuing after Traumatic Brain Injury (TBI). This condition is not uncommon after brain trauma. Among patients with moderate or severe TBI who are found to have intracranial bleeding on a CT scan taken soon after hospital admission, intracranial bleeding progresses in 84% of the patients.

Drug A has been demonstrated to reduce bleeding in elective surgery. There is evidence that it can reduce re-bleeding in the case of a spontaneous aneurysmal intracranial hemorrhage. If the drug is started within 8 hours after extra-cranial trauma, it is more effective in reducing mortality and morbidity. However, drug A can cause cerebral ischemia.

The proposed study would recruit 240 subjects older than 16 years of age having suffered TBI within 8 hours of injury, and demonstrating moderate to severe intracranial hemorrhage on CT brain scan or Glasgow Coma Score 4-12. Those who had significant extra-cranial hemorrhage or an indication requiring surgery, are pregnant, demonstrated evidence of coagulopathy, or for whom the taking of medication affects hemostasis, or have renal insufficiency are to be excluded. Subjects will be randomized to receive Drug A or placebo after written informed consent is obtained from a legally acceptable representative of the comatose patient. The subjects will then be observed for neurological signs routinely until their condition is considered stable. A second CT scan will be repeated 24 hours after TBI. The primary outcome measurement is with regards to progressive intracranial hemorrhage.

Challenges Encountered by the Ethics Committee

1. What justification did the applicant provide for the research in the current local setting?
2. Has the vulnerability of the potential research subjects been sufficiently addressed in the protocol and informed consent procedure?
3. Can the researchers demonstrate an adequate ability to obtain informed consent in an emergency situation within the context of the proposed research?

Perspectives

The ethics committee considered that the subjects to be included in this treatment study are clearly vulnerable, especially given the inclusion of minors and comatose patients. Traumatic brain injury affects a person's understanding and decision-making process, which in turn affect one's ability to knowingly and freely consent. The approval of efficacy of drug A for the treatment of TBI requires the inclusion of particularly vulnerable subjects. The ethics committee thought that patients with TBI

may receive benefits from the trial, but they also take substantial risks to participate in this study (i.e., cerebral ischemia). So, while their participation appeared justified according to the ethics committee, specific measures need to be taken to ensure an appropriate consent process.

The ethics committee insisted that the researcher (Principle Investigator) demonstrate the possibility to receive written informed consent from the legally authorized representatives (LARs) before starting randomization as well as prior to starting the intervention. In this setting patients are generally sent to the emergency room unaccompanied by relatives. Thus, the investigator's ability to obtain informed consent is specifically challenging in this study.

In order to better understand the possibilities, the ethics committee reviewed US 21 CFR 50.24 which discusses the waiver of the applicability of the regulatory requirement for obtaining and documenting informed consent for research that may be carried out in human subjects who are in need of emergency therapy and for whom, because of the subjects' medical condition and the unavailability of legally authorized representatives of the subjects, no legally effective informed consent can be obtained. The committee asked if the investigator might waive the entire consent process or waive only the written consent? The committee thought that waiving the entire consent process may be appropriated if specific criteria are fulfilled.

The ethics committee considered the following possible criteria: The first criteria would be that the subjects are in a life-threatening condition. A further criteria would require that available treatments are unproven or unsatisfactory. In addition, the trial would need to collect valid scientific evidence (e.g., from a randomized placebo-controlled trial) that is necessary to determine, and capable of determining, the safety and effectiveness of the proposed intervention. Further, the consent appears not to be feasibly obtained because the subjects will not be able to consent by themselves and there is a short therapeutic window for the investigator to seek the LARs' consent before starting the intervention, and there is no way to identify the individuals to become eligible for participation before the clinical investigation.

It is also necessary, the ethics committee considered in its discussions, that the participant in the research stands to benefit directly from that participation. It appeared that the research could only be carried out feasibly if informed consent was waived. Additionally, the proposed research plan defines the length of the therapeutic window based on scientific evidence, and the investigator's commitment to attempting to contact the LARs for each subject within a specified time period.

Finally, the ethics committee decided that additional procedures to protect the rights and welfare of the subjects should be considered by the investigator (such as community consultation, public disclosure, and the establishment of an independent data monitoring committee).

As the regulation mentions about the attempt of investigators to contact LARs or family members, the investigator consulted the committee on the most appropriate ways to attempt contact with LARs and demonstrate those attempts. The committee suggested that the investigator consider recording for each subject in the case history the effort that was made to contact the subject's LAR or family member. Those

efforts should include date, time, name of individual to be contacted, the manner of the attempted contact (either in person, or phone, or other acceptable communicable method), the success or failure of the effort, and the name of the staff member who attempted the contact.

The ethics committee proposed that the initial contact not only aim to ask the permission for subject to be enrolled in the study, but that it also be used to provide the opportunity for LARs or family members to object to the subject's participation. If the LARs or family members agree to allow the subject to participate in the study, the intervention can start. If the intervention was administrated before the consent of LARS or family members, the investigator may use various methods that demonstrate verification or confirmation (e.g., a register, email with "read receipts") to ensure that each subject's family is promptly informed about the subject's participation in the study. Referring to the US FDA regulations, the ethics committee found that written informed consent is not required to include a subject's participation once the subject is enrolled. However, the ethics committee thought it best that there be actual documentation for continuing the participation of the subjects that demonstrated the attempts to achieve LAR consent.

Case Study 4
A Randomized Controlled Trial

A Randomized, Multicenter, Open-Label, Phase 3 Study of Enzyme XXX Inhibitor Drug A versus Drug B in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukemia.

The ethics committee was presented with an application for a randomized controlled trial of a drug to address chronic lymphocytic leukemia (CLL), which is an indolent leukemia in adults and is incurable. Some countries presently lack access to effective treatment to address the condition. Chronic lymphocytic leukemia is characterized by an accumulation of monoclonal mature B cells in the blood, bone marrow, and secondary lymph organs. The generation and maintenance of normal and malignant B-cells is controlled by biochemical signals transmitted by the B cell receptor (BCR) signaling. Enzyme XXX is an enzyme required for BCR signaling. Inhibition of enzyme XXX blocks downstream BCR signaling pathways and thus prevents B-cell proliferation. Drug A, currently under development for the treatment of B-cell malignancies, is a first-in-class, potent, orally administered, covalent inhibitor of enzyme XXX. Phase 1 and Phase 2 studies of drug A in B-cell malignancies demonstrate modest toxicity and significant single-agent activity in a variety of B-cell malignancies, including CLL.

Drug B is a high-affinity monoclonal antibody, currently used for the treatment of Non-Hodgkin Lymphoma, CLL, and autoimmune disorders. Drug B in combination with cytotoxic drugs has demonstrated significantly improved outcomes for patients with CLL, with an improvement in overall survival. Unfortunately, this combination treatment frequently induces neutropenia and other toxicities, and is therefore unsuitable for elderly patients or those with significant co-morbidities. However, single-agent drug B has been shown to be efficacious, even in patients with treatment-refractory or poor-prognosis CLL, and makes it an alternative treatment option in patients unable to undergo treatment with cytotoxic chemotherapy. The US Food and Drug Administration (FDA) and the EU European Medicines Agency (EMA) have both approved its use in combination with other cytotoxic agents for the treatment of CLL. However, the Food and Drug Administration in our Asian country has not approved drug B for the treatment for CLL.

The study proposed is a randomized, multicenter, open-label, Phase 3 study designed to evaluate the efficacy and safety of drug A versus drug B in subjects with relapsed/refractory CLL or SLL with active disease requiring treatment who have failed at least 1 prior line of therapy and are not considered appropriate candidates for treatment or retreatment with purine analog-based therapy or combination chemoimmunotherapy.

The study proposes to recruit one hundred and fifty eligible subjects to be randomized into 2 treatment arms to receive either drug B or drug A (in a 1:2 ratio). Subjects randomized to drug B will receive treatment for up to 6 cycles (a total of 8 doses), or until disease progression or unacceptable toxicity, whichever occurs first. Subjects randomized to drug A will receive drug A daily until disease progression or unacceptable toxicity. All subjects will follow the same visit schedule until

discontinuation of study participation. In the Post-disease Progression Phase, subsequent anticancer therapy and survival status will be recorded until death, lost to follow-up, consent withdrawal, or study closure, whichever happens first.

Challenges Encountered by the Ethics Committee

1. Is the comparator drug in this study appropriate to the population being studied?
2. Is there an appropriate level of monitoring?
3. Does the informed consent process reflect adequately the design and risks of the study?

Perspectives

The discussion in the ethics committee focused around the comparator drug in the proposed study. According to the Declaration of Helsinki (2013), the benefits, risks, and effectiveness of new interventions must be tested against those of the best-proven interventions. The use of an active comparator is encouraged, especially in a double-blind controlled trial. However, the choice of the comparator drug or intervention may also itself raise ethical concerns if there is a variety of standard of care treatments or the standard treatment is not available in the location or country.

The ethics committee expressed concern regarding the use of an active comparator in this study. The comparator, Drug B, had been approved in the sponsor country for treating this condition, but it had not been approved in the local country. The ethics committee determined that both drugs should be viewed as investigational drugs. It may be considered ethical to have the same standard treatment in the sponsor country and local country unless there is evidence that the standard treatment in the local country may not be acceptable or cause harm to local people. The latter may occur if there are some drug-related toxicities that are linked to ethnicity or genetic prevalence's or life-styles.

The ethics committee also inquired further into the monitoring of the proposed trial. In this case there appeared to be an incomplete safety profile for the target population. The committee suggested that the monitoring of adverse events should be more frequent. The committee also suggested to address this issue as well in the informed consent process, including the clinical evidence to support the comparator selection as presenting other treatment options.

Case Study 5
Research Involving a Product to Be Used Off-label

The efficacy and safety of X injection under laryngeal electromyography-guided in patients with unilateral vocal fold paralysis.

The ethics committee was presented with a proposed innovative off-label use of a product for addressing unilateral vocal cord paralysis (UVFP). UVFP is a clinical condition that at times presents following certain events, e.g., nerve injury during thyroidectomy or after stroke. When a patient suffers UVFP, the patient is susceptible to choking during swallowing, or hoarseness during phonating. The patient's quality of life is seriously affected and the patient is at risk for aspiration pneumonia. Such complications could be mild or severe, temporary or permanent. Normally the contralateral vocal cord increases in size and moves closer to the paralyzed cord to close the gap. In general practice patients are usually advised to wait for 6 months before opting for a surgical intervention. Such interventional approaches include medialization thyroplasty, arytenoid adduction, and laryngeal reinnervation. Usually these types of surgical correction are performed under general anesthesia. Prior to surgery, the UVFP patients often examined with the assistance of videostroboscopy and/or laryngeal electromyography (LEMG, EMG).

Another approach to augment the patient's paralyzed vocal fold is by injecting certain substance (fillers) into it. The fillers used include paraffin, gelfoam, and autologous fat. The criteria used to identify the ideal filler include its biocompatibility, biomechanical similarity to vocal tissue, injectability, resistance to absorption and migration, and removability during later revision surgery. The injection of such fillers requires direct visualization of the vocal cord, which also requires some level of anesthesia. Paraffin injection has the advantage of resistance to absorption. But the disadvantages are not easily migrated: difficult to inject and painful procedure. The paraffin injection usually require general anesthesia. Leakage of paraffin into the vocal mucosa will cause foreign body granuloma and result in poor voice quality. Gelfoam and autologous fat are easily absorbed so the effects are temporary. The reaction granuloma is seldom seen. It can be injected via videoscopy under local anesthesia.

Medical device 'X' has been legally marketed for use as a filling medium only in the subcutaneous tissues of the human body (e.g., for facial wrinkles and fold, lip augmentation, facial volume loss). There are several particle sizes (small, medium, and large) of X. Small particle X is commonly used. However, it dissolves after 3 months of injection, thus requiring repeated injections. The medium or large particles are used in to address some conditions. The large particle behaves like paraffin.

The study is intended to investigate whether the injection of the X into a paralyzed vocal fold in patients with UVFP is an effective treatment (temporarily or long term). The study also investigates whether laryngeal EMG is a feasible diagnostic tool and potentially a useful guide to injecting a substance into vocal folds in patients with UVFP. Finally, the study proposes to apply LEMG to guide the injection of the X into

the vocal fold in patients with UVFP. The overall study objectives are focused on the feasibility, safety and effectiveness of laryngeal EMG-guided injecting the X into the paralyzed focal fold in patients suffering from UVFP.

The researchers plan to recruit 12 patients with UVFP. Adolescent subjects may also be included. No limits are placed regarding the onset and the degree of UVFP. No exclusion criteria are proposed if the subjects can consent for themselves. Subjects will be enrolled consecutively when they appear in the out-patient department of the hospital. No randomization or control group is included in the study design. The subjects will be followed up according to different timelines that include short-term and long-term outcome evaluation. When submitting this protocol, the Principle Investigator (PI) requested an "exemption from review." The investigator stated that the protocol is not clinical research in his view, but rather an examination of clinical practice. According to the PI: "There is no need for ethical review".

The PI argues that the injection of the X in patients with UVFP is a treatment option in the first place and not simply being used for research purposes. If the proposed study is not accepted by the ethics committee, the PI states that he will administer the treatment in his clinical setting as an available treatment option.

Challenges Encountered by the Ethics Committee

1. Should the proposed intervention be treated as a medical device or as a drug?
2. Does the proposed research present well defined risks that are significant and significantly understood? And is there available compensation for research-related injury?
3. Is an "exemption from ethical review" appropriate in this case?

Perspectives

The ethics committee considered that the main intended effect of this chemical compound is to address health complaints related to vocal cord morbidity and augment the paralyzed vocal fold. The effective action of the testing article, X, was not via a pharmacological mechanism or via the metabolism of the substance, but rather through a 'mechanical' or 'device' effect. Therefore, the ethics committee decided that the study of X should best be viewed as a medical device study.

In the view of the ethics committee, since the PI claimed that he intended to see whether LEMG-guided injection of X into the paralyzed vocal fold in patients with UVFP would be effective and safe, X should be considered an investigational medical device and the LEMG should be considered a new medical technique for this clinical use.

While the local laws and regulations regarding research on medical devices were largely adapted from US regulations (i.e., 21 CFR 812), the ethics committee found that local regulations did not cover the significant risk (SR), nonsignificant risk (NSR) determination issues. From the perspective of the ethics committee, the proposed research on X should be classified in the SR category because the injection of X into laryngeal tissues would result in it acting as an implant device and, thus, falls into the category of SR.

While X has been legally marketed locally and elsewhere, the indication for the use of this device is only as a filling effect in subcutaneous tissues in the body (e.g., facial wrinkles or fold, lips). It is specifically stated that X should not be used for any other purposes in other tissues than subcutaneous tissue. Apparently, for the ethics committee it was clear that the PI was particularly interested in researching the safety and effectiveness of X injected into body tissues that were not approved by the US FDA. The intended use of X in the proposed research protocol involved was, in the committee's view, clearly an off-labeled use.

Additionally, because it is a PI-initiated and self-sponsored study and no industry sponsors are involved, the ethics committees expressed concerns regarding compensation to research-related injury. They inquired as to whether the PI or the institute had insurance that would sufficiently cover the risks involved in this clinical trial. Furthermore, if the manufacturer of product is not a sponsor of the trial, would the manufacturer still provide all the safety and efficacy information regarding the product as well as its composition to the PI?

The ethics committee decided to address this protocol as medical device that is being proposed for off-label used. It is to be tested for a new indication, new treatment, so the committee decided that this study is best reviewed, in a 'full board' ethics committee meeting because it involves more than minimal risk. If the PI decides to use the product off-label and not in the context of a research protocol, then the ethics committee considered that this off-label use would no longer fall within its purview. The committee recommended to the PI that this should be considered a research project and ethical review was both necessary and would perhaps help guide the research in important areas.

Case Study 6
An Innovative Medical Device Research Proposal

The insertion of an innovative self-inflating ambu bag for the control of ventilation following intubation during surgery

The ethics committee was presented with a proposal for research on an innovative ambu bag. The use of a self-inflating resuscitation bag or ambu bag is common in medical practice in order to resuscitate or provide an emergency air supply to patients. A team of researchers consisting of emergency medical personnel developed an in-house ambu bag with a non-rebreathing valve to provide positive pressure for manual ventilation to be used in patients during resuscitation. This in-house invented ambu bag mainly consists of a reservoir bag made from a 1.5 liter plastic bottle, tubing, and two one-way valves. The bottles collected are reused plastic beverage containers. The ambu bag in this study is designed to function similarly to conventional ambu bags, which are otherwise made from plastic or silicone and commercially available. The main reason for the use of a recycled plastic bottle is to reduce cost, making the innovative device approximately ten-times cheaper than conventional ambu bags. In this way, the inventor expects to save cost for hospitals and medical service providers.

The research team that invent the proposed device plans to conduct a clinical trial to compare the use of the newly invented ambu bag with a conventional ambu bag to control ventilation in patients who require intubation during surgery. The measured parameters include average and peak airway pressure during the control of ventilation, and physicians' satisfaction responses. Patients who require surgery age between 18 and 50 years and presenting without a history of respiratory complications will be included in the study and divided into two groups (n = 15 for each group). Informed consent will be sought one day prior to the scheduled surgery. Following the obtaining of informed consent, these two groups will be randomly assigned to receive either the invented ambu bag or the conventional ambu bag. Measurements will be conducted by the research team during the surgery.

Points Raised by the Ethics Committee for Discussion

1. Is sufficient justification provided for the innovative design of this medical device?
2. What are the potential risks to the subjects regarding the chemical composition of the innovative device?
3. What are the potential risks and benefits of the innovative device for patients undergoing surgery?

Perspectives

The ethics committee focused its discussion on the needs of the local community, such as insufficiently available ambu bags in some hospital settings and the expense of the available devices. The committee insisted that the use of proposed ambu bags only for the sake of saving cost should be carefully considered and justified in relation to any potential risks.

A self-inflating resuscitation bag or ambu bag is considered a significant risk (SR) medical device involving the use in patients under anesthesia during the surgery. The committee thought that the proposal to use a recycled plastic bottle instead of standard silicone required more information regarding the safety of the use of a recyled plastic bottle regarding both the material's response after being repeatedly squeezed and the efficiency of the value in this container.

For this device, researchers aim to apply used commercial beverage bottles that are made of polyethelene terephthalate (PET or PETE) as an air reservoir. Generally, PET is semiporous and absorbs molecules of the beverages it contains, which are difficult to clean or remove completely. Even though this kind of material is acceptable for recycling, it is designed for one-time use. Reuse of PET bottles should be avoided since materials such as di(2-ethyl-hexyl) phthalate (DEHP) used in producing plastics might be leached. Researchers should be concerned about the safe use of reused plastic containers regarding their potential to release fine particles as well as their potential contamination from previous uses. Furthermore, the committee thought the researchers should also consider the cleaning/disinfecting procedure used in recycling the plastic bottles as well as the physical and functional stability of reused plastic bottles following the cleaning/disinfection process.

The committee identified several risks that can possibly be caused by an insufficient functioning of the in-house ambu bag. In this case, subjects are under anesthesia during surgery. They are vulnerable and special protection should be considered. The test on sufficient air supply generated from the use of this innovative device should be obtained by other means prior to the clinical test to ensure that any problem during the use on intubated patients will be effectively avoided or mitigated. Information on performance tests of the material's reflecting mechanism is required. The committee suggested that perhaps a performance test in a simulation model prior to clinical testing in humans might be useful to mitigate risk during the clinical trial phase.

From the committee's perspective, it was not clear if the anticipated benefits from the in-house ambu bag made from a plastic bottle would outweigh the potential risks. In addition, the inventor also serves as the principle investigator of the medical device trial. This potential conflict of interest should be properly managed to avoid any biased outcomes.

Case Study 7
A Proposal for Research Regarding Stored Bio-specimens

Expression of antigen A in clinical stage of Pulmonary Tuberculosis

The ethics committee was presented with a proposed study aimed at finding protein antigen used in the diagnosis of the inactive phase of pulmonary tuberculosis. The study will use blood sample remaining from a previous study stored in laboratories. All samples have been categorized according to the status of disease and labeled as healthy (no disease), dormant (inactive disease), and active disease. Several new antigens will be used to test the thousands of blood samples of patients in their various stages of disease. The study aims to define the performance of these new antigens in samples from patients diagnosed with inactive stage of disease. All subjects whose samples are to be used have given written informed consent for the original research in which they participated. However, the previous consent did not specify its use for future research.

Challenges Encountered by the Ethics Committee

1. Is a new consent needed for this research project?
2. If a new consent is needed are their limitations on the effort needed to be put into the new consent?

Perspectives

The ethics committee first reviewed the risks of the proposed study to the previous research participants and the level of risk that may arise from this new study on the samples. This laboratory study threatens no physical risk to the patients from whom the samples were obtained, but the study may have potential psychological and/or social risks if the new study threatens privacy and/or confidentiality (e.g., the study reveals the research participants' HIV status or genetic predispositions).

The ethics committee felt that consent from the owners of the kept blood samples should be required for all studies not relevant to the original study. For the proposed study, the kept samples would be used to find a new protein antigen for the diagnosis of different stages of pulmonary tuberculosis. In our country investigators are required to receive ethics committee approval for the repeated use of these blood samples before initiating the study. All data need to be kept confidentiality and recorded anonymously. The ethics committee may ask the researcher to seek signed consent for subjects on a case by case basis.

The ethics committee also considered that for minimal risk research the seeking of consent must not result in too high a burden on the prospective subjects (e.g., requiring subjects to come to the hospital only for giving consent or the learning the biological or genetic results that show the presence of, or potential for, an incurable disease that may cause anxiety to patients while offering no direct benefit).

Case Study 8
A Proposal for Research in an Intensive Care Unit

The effect of XXL equipment on sputum clearance in intubated patients.

The ethics committee was presented with a proposal for researching an innovative device to reduce sputum production to be trialed in an intensive care unit (ICU). Patients requiring endotracheal intubation (using an ET tube) with respirator-assisted ventilation experience an increased production of sputum due to stimulation caused by the procedure. Physical therapy (such as chest percussion, vibration, or positioning) can be used to promote the sputum's clearance. However, the pulmonary infection rate of these patients remains high.

XXL equipment has been developed by the investigator and demonstrated reduced sputum production when investigated in patients without an ET tube. The proposed study wishes to apply XXL with physical therapy to explore the sputum's clearance ability in intubated patients.

Thirty (30) stable hemodynamic intubated patients with the sputum volume greater than 1 ml per hour will be recruited. Patients with massive hemoptysis, pneumothorax, high intracranial pressure, acute myocardial infarction, and/or major arrhythmia will be excluded.

The investigator is a physiotherapist. The investigator will go to the hospital's intensive care unit (ICU) and check the medical records in order to identify eligible subjects. Informed consent will be sought from either the potential research subject or the legally authorized representative.

Challenges Encountered by the Ethics Committee

1. What risks does this medical device have in the proposed uses?
2. Is the proposed research risk-benefit ratio favorable?

Perspectives

The ethics committee considered XXL to be a medical device following the US FDA guidance. XXL functions by creating resistance in the patient's airway and the stimulation of the cilia's function along the patient's airway. The ethics committee raised some safety concerns here. The potential subjects will be patients who require an ET-tube with respirator assisted ventilation. This group of patients are known not to be able to breath on their own without support. If pressure in their airway is increased by the mechanism of the XXL, the patient might risk respiratory problems or require a higher ventilator setting.

The reduction of sputum production appeared to the committee to be a reasonable potential benefit. If the potential risks identified can be reduced, the risk-benefit ratio may be judged positively. If the mechanism of XXL increases the airway's pressure

so subjects with an ET tube can breathe by themselves as a part of the respirator's weaning process, the risk to the subject can be minimized. Additional close monitoring by the caring physician regarding the ventilator support during the time of using the device was recommended by the committee.

Case Study 9
A Proposal for Research Involving Institutionalized Children

Immune response to XXX vaccine among HIV-infected children.

The ethics committee was presented with a proposal for a study to analyze the immune response to XXX vaccine in a pediatric population selected from institutionalized children. XXX vaccine for influenza virus is widely recommended in a high-risk population. In HIV-infected patients, influenza virus will often cause more severe manifestation of the disease, including prolonged duration and higher mortality when compare to immunocompetent persons. Although antibody response to the xxx vaccine in HIV-infected adults is less than in normal subjects, it is sufficient to protect them from the influenza virus infection.

Previous studies of the vaccine have been conducted in pediatric populations. However, the immune response and CD4 level had never been analyzed in HIV-positive subjects. This study is aimed to study immune response to XXX vaccine in HIV-infected children to evaluate the safety of XXX vaccine and its impact on HIV viral load, and to evaluate efficacy of XXX vaccine in terms of the prevention of respiratory tract infection in HIV-infected children.

The PI proposes to recruit HIV-infected children age between 6 months to 18 years old who are treated in X hospital and compare them with healthy children. Both sets of children live in an orphanage. The potential subjects had never received XXX vaccine. 100-200 HIV-infected children and 20 normal children were recruited.

Both groups are to receive 2 doses of XXX vaccine. The participants will have their blood tested three-times to check for the presence of XXX antibody, to measure their CD4+ count, and to measure their HIV viral load. They will then be followed up for 1 year.

The participants will receive XXX vaccine, which has been demonstrated to both prevent and control the spreading of infection. The study outcomes may contribute to knowledge regarding the immune response to XXX vaccine in HIV-infected children. This knowledge may prove useful in adapting national immunization guidelines for children.

Potential risks include pain from 2 vaccine injections and 3 blood draws. According to the HIV-treatment guideline for children, they should have a blood test every 6 months. Investigators will recruit children with a view toward their regularly scheduled blood tests. HIV-infected children will thus require only 1 extra blood draw.

Vaccine adverse reactions that may be expected include pain, fever, local swelling, warmth, and redness. The participants' personal data and blood samples will be anonymized and coded. Documents will be kept in a secure cabinet with a lock. The study report will not include personal data. After vaccination, HIV viral load may be transiently increased in some participants. Most participants are expected to remain

asymptomatic. Viral load is expected to decrease to baseline in 2 weeks. The investigators are knowledgeable regarding HIV infection in children, and they will monitor viral load throughout the study. If the viral load increases from baseline in some children, the investigators will retest the viral load in those children after 1 month. However, the investigators are also aware that viral load may increase due to factors not related to the protocol itself (e.g., resistance to concomitant antiretroviral drugs).

Challenges Encountered by the Ethics Committee

1. What are the specific vulnerabilities of the potential research subjects in the research and in their environment?
2. Do the researchers have sufficient justification to recruit from this population?
3. Are additional protections required to safeguard the children in this research proposal?

Perspectives

The ethics committee was principally concerned with the vulnerabilities of the prospective research population. Vulnerable groups and individuals are often described as those who 'may have an increased likelihood of being wronged or of incurring additional harm' (Helsinki 2013, CIOMS 2016). The ethics committee identified three vulnerability issues. 1. Participants are children aged between 6 months to 18 years old, representing various stages of decision-making ability and varying consent requirements. 2. The children to be recruited are from an orphanage (institutional vulnerability), in which they hold a clear subordinate position with respect to those in authority. 3. The greater number of prospective participants have chronic disease (HIV infection), which might include an existing deferential vulnerability caused by their doctor-patient relationship and their dependence on that relationship.

However, regarding points 1 and 2 above, in keeping with the CIOMS guidelines, the ethics committee also considered that the research could not be carried out in other populations, because it seeks to address vaccination in just this group of patients. This infection can cause severe manifestation and increase mortality in HIV-infected subject, including children. There is evidence that influenza vaccine is beneficial in HIV-infected adults, but the vaccine has yet to be studied for immune response in HIV-infected children. From this perspective, it is reasonable to conduct the study in HIV infected children.

Studying the vaccine in an orphanage setting could also benefit the study, the study population, and potentially future children in similar situations. Influenza infection often has an outbreak in this population and it is difficult to manage in the setting of an orphanage.

To maximize the potential benefit of the study**,** the ethics committee suggested that the protocol should also provide for other methods of influenza virus prevention and/or treatment if antibody after vaccination is found to be lower than the protective level. The protocol should also consider post-trial access to the xxx vaccine if it is demonstrated to be beneficial to this population.

To minimize risk, the ethics committee proposed that the study protocol should exclude HIV-children with very low CD4 counts who may not benefit from xxx vaccine. It should also exclude HIV-infected children with a very high viral load or uncontrolled disease. Periodic blood sampling for viral load, as stated in the protocol, is appropriate. Furthermore, investigators should provide management/treatment if the viral load is persistently high after vaccination. They should also be prepared to provide treatment for potentially foreseeable adverse events.

From the local ethics committee perspective, this trial may have the potential benefit to the participants in terms of influenza infection prevention. On the other hand, literature reveals viral load may be transiently increased. However, this transient increase should be controllable and not represent a significant risk of harm to the participants.

The committee also insisted that investigators indicate who will be approached to consent for the children generally and individually. When possible, the committee thought that the child's parents should be involved in the consent procedure and their decision should be final. The legal guardians or other appropriate representatives for children and the orphanage should also be approached according to local guidelines and regulations.

Case Study 10
A Proposal for a Social Behavioral Study

Knowledge, Attitudes, and Practice of Young Males about HIV/AIDS Acquired through MSM (males having sex with males) Activities

The ethics committee of KKK city was presented with a proposal for research related to HIV infection involving males having sex with males (MSM). KKK city registered an increase incidence of HIV/AIDS cases in the first quarter of 2014. The city is known to have an active nightlife. Young males who have sex with males (MSM) are at high risk of acquiring HIV/AIDS though MSM activities. The proposed study was aimed to explore and reveal the knowledge, views, and opinions of young males on HIV/AIDS acquired through MSM activities. The researchers planned to recruit young males within the age bracket of 15-24 years old who may or may not have any experiences in MSM.

The participants will be divided into 3 groups according to their age brackets (15-17, 18-20, and 21-14 years old). The researcher will interview 3 participants for each group. For the focused group discussion, the researcher will identify 9 respondents, chosen purposively, which will be divided into 3 groups according to their age ranges (again 15-17, 18-20, and 21-24 years old).

The study proposes to collect information that includes responses to the following questions: What knowledge do young males possess regarding how HIV/AIDS is acquired through MSM activities? How did they receive the knowledge they have? What are the views and opinions of young males on HIV/AIDS acquired through MSM activities? What sorts of risky sexual behavior do people living with HIV/AIDS (PLWHAs) engage in, particularly in the context of MSM activities? and How do the participants regard PLWHAs due to MSM activities?

Prior to the commencement of the research, if approved, the researchers will send letters to the prospective participants' schools or workplace to ask permission to conduct an interview with their student or employee. Once the letter is approved, the researchers will provide the participants with the informed consent form (ICF) and ask to schedule an interview.

The participants in the age bracket of 15-17 will be recruited from a public school, while the participants in the age bracket of 18-20 will be recruited from a private school. The participants in the age bracket of 21-24 will be recruited from call center companies.

The researchers will conduct their interview one-by-one using the prepared questions. With the permission of the respondents, a tape recorder will be used to document the entire conversation. One of the researchers will transcribe the details of the interview. In the same manner, the researchers will assure the respondents that fairness will be observed throughout the conduct of the interview and their identities will remain anonymous and safeguarded.

Challenges Encountered by the Ethics Committee

1. What are the risks and potential benefits to the research participants?
2. Are the recruitment methods appropriate?
3. What are the safeguards for the privacy and confidentiality of the research participants?

Perspectives

The ethics committee discussed the proposed study's us use of a qualitative methodology and its potential contribution to knowledge in terms of the insights gained from the interviews. The ethics committee believed that the methodology used would not be not capable of yielding generalizable conclusions about the topic of the study.

The ethics committee saw the main weakness of the study lying in its recruitment procedures where informants will be recruited from the schools or offices whose heads have granted approval. It appeared doubtful to the committee if the researcher will be able to recruit the target population through the use of official mainstream channels. The committee suggested that the researchers use NGOs that work with PLWHAs to recruit persons. These organizations are more readily in touch with those who have exposure to MSM activities and will likely create a better environment for potential subjects to narrate their first-hand experience.

Another important issue the committee addressed is whether parent consent for the minors should be required. There are privacy issues related to the behavior of minors involved in MSM activities. Do parents know about the MSM activities of their minor children? For those without MSM experience, will parents allow their minor children to participate in an MSM study? Will parents give consent for their children to be interviewed? The ethics committee felt it was necessary to also consult the current law, regulations, and guidelines related to research about risky behavior among children in KKK country. Can such types of study be considered minimal risk? The ethics committee considered the potential and implications of waiving parental consent and simply requiring consent from the minors themselves, like the informed consent given by those who are 18 and above.

One could expect that ethics committees in different countries will review this protocol with a view towards their own specific situation and make recommendations based on their own social and cultural environments and their own appreciation of the levels of risks related to study participation.

Editors

Juntra Karbwang Laothavorn & Francis P. Crawley

Contributing Authors

Bailu Wang, M.D., Ph.D.
Deputy Director, Clinical Trial Center
Qilu Hospital of Shandong University, China

Cristina E. Torres, Ph.D.
FERCAP Coordinator, Adjunct Professor of the Philippine National Institutes of Health, and Ethics System Consultant of the Philippine Department of Health, The Philippines.

Hsiang-Ning Luk, M.D. M.S. Ph.D. CIP
Department of Anesthesia, Hualien Tzu-Chi Hospital, Hualien, Taiwan

Jeffrey Roy Johns, Ph.D.
Faculty of Pharmaceutical Science, Khon KaenUniversity, Thailand

Kwanchanok Yimtae, M.D.
Associate Professor, Department of Otorhinolaryngology,
Director, Academic Clinical Research Office, Faculty of Medicine,
Khon Kaen University, Thailand

Nutjaree Pratheepawanit Johns, PharmD, Ph.D.
Associate Professor, Department of Clinical Pharmacy,
Faculty of Pharmaceutical Science, Khon Kaen University, Thailand

Phantipha Wongwai, M.D. Ph.D.
Department of Ophthalmology,
Faculty of Medicine,
Head, Office of Research Ethics, Khon Kaen University, Thailand

Sahaphol Anannamcharoen, M.D. M.S.
Associate Professor, Department of Surgery,
Phramongkutklao College of Medicines, Thailand

Supatra Porasuphatana, Ph.D.
Assistant Professor, Department of Pharmacognosy and Toxicology,
Faculty of Pharmaceutical Sciences, Khon Kaen University, Thailand

Thipaporn Tharavanij, M.D.
Associate Professor, Department of Internal Medicine, Faculty of Medicine,
Thammasat University, Thailand.

Perspectives on Ethical Review

A Casebook for Reflecting on Challenges and Aspirations for Improving the Role and Function of Ethics Committees and Ethical Review Systems

'Juntra and I built the MFES Fellowship Program from the ground up with our minds, our hearts, and our souls. And yes, at times by the sweat of our brow. This engagement and its results reflect the culmination of a life spent in the appreciation of ethics as it applies to medicine and research. I see it flourishing far far into the future. Now, I can say that, even more than the Program itself, our fellows are that bright future.'

Dr. Angela J Bowen

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