Perspectives on Ethical Review III

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

Perspectives on Ethical Review III

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

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

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

First Edition
1,000 books.

The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER)
Bangkok, Thailand.

ISBN: 978-616-93471-0-1

Price 150 THB

Published by:
The SIDCER-FERCAP Foundation.
74/2 Moo 7 Paholyothin Road
Klong Nueng, KlongLuang, Pathumthani 12121, Thailand.
Telephone: (+66) 25644440 ext 1800
Telefax: (+66) 25644398 Email: atoynavarro@yahoo.com; cristina.torres@yahoo.com;
Website: http://www.fercap-sidcer.org

Printed by:
Klungnana Vitthaya Press,
232/199, Soi Srichan 39, T. Nai-Muang, A. Muang,
Khon Kaen 40000 Thailand.
Telephone: (+66) 43466444.

Introduction

This is the third casebook of perspectives on ethical review which has the same objectives as that of the first casebook in 2016. The success of the first two casebooks led to the decision of the Forum for Ethical Review Committees in Asia and the Western Pacific (FERCAP) to endorse the production of a casebook annually. As part of the Middleton Foundation for Ethical Studies Global Fellowship (MFES GF) training program, the MFES GF fellows were each required to submit a case study of their interest to this casebook, with additional contributions from the members of ethics committee who are involved with the MFES GF training program. During the process of writing this casebook, MFES GF fellows and the training staff had opportunities to exchange ideas and experiences which has broadened our minds to accept various perspectives. It has inspired us to further promote ethical research in our own research fields. The most important product of this process is not the publication of this casebook but the close and wonderful friendships formed that will continue for many years to come.

The casebook presents relevant recent examples of studies that have aspired to improve healthcare in Asia while at the same time challenged 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 aim of the casebook is 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 the health issues that the protocols intended to address. They have also 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 subject protections in health research underlies the objectives and work of FERCAP. Over the course of the past eighteen 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.

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. Research is needed to prevent or alleviate suffering brought about by disease. Obstacles to much needed research should be recognized and removed. This is an ethical requirement.

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 evaluate 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 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 for review by ethics committees.

This casebook was written as an expression of the MFES GF fellows' aspirations to promote ethical research. I hope that the fellows will continue to practice what they have learned throughout the training course and be an example for the new generations in ethical health-related research.

Juntra Karbwang Laothavorn MD, PhD
President, SIDCER-FERCAP Foundation and
SIDCER coordinator

Table of Contents

Case Study 1: Medical Device: Antimicrobial Dental Prosthesis

Clinical trial of silver nanoparticle in acrylic dentures in preventing the recurrence of Candida-related denture stomatitis in elderly patients

Poly (methyl methacrylate), PMMA, based resins are widely used in dentistry for acrylic dentures. Patients with poor oral hygiene or systemic factors contribute to the adherence of *Candida albicans* to host cells or denture acrylic resin. The treatment of oral candidiasis includes denture repair or replacement and the prescription of antifungal drugs. However, difficulty in rendering appropriate application for elderly patients has stimulated the development of incorporating antimicrobials into denture base materials. Silver nanoparticles (AgNPs) have been used for their antimicrobial effect in different biomedical applications. A previous study showed that the addition of AgNPs to a PMMA formulation reduced the adherence of *Candida albicans* and was not cytotoxic or genotoxic. However, the acrylic denture containing AgNPs used in the clinical situation has not been studied so far. The aim of this study is to evaluate the effects of incorporating AgNPs into a denture base acrylic resin on the recurrence of *Candida*-related denture stomatitis in elderly patients.

The ethics committee was presented with an investigator-initiated proposal for a clinical trial to compare the newly developed antimicrobial denture with a conventional denture on the recurrence of *Candida*-related denture stomatitis in elderly patients. The clinical parameters include tissue condition scores, mycological evaluation and patient satisfaction responses. Sixty patients with *Candida*-related denture stomatitis who require dentures and are over 60 years old without a history of abnormal tongue, xerostomia, excessive salivation, allergy to nystatin or silver, TMJ disorder, psychological disorder, physical impairment, diabetes, kidney issues, oral cancer, immuno-compromised and radiotherapy will be included in the study. All patients will be treated with nystatin for one month. After successful treatment, 48 patients will be recruited and divided into two groups (n = 24 for each group). Informed consent will be sought one day prior to the scheduled treatment. Following the obtainment of informed consent, both groups will be randomly assigned to receive either the antimicrobial denture or the conventional denture. Measurements will be conducted by the research team at baseline, 1st, 3rd and 12th month.

Challenges encountered by the ethics committee

1. What are the potential risks to the subjects regarding the use of the innovative device?
2. Are there any identifiable conflicts of interests?
3. Has the vulnerability of the potential research subjects been sufficiently justified and addressed in the protocol and informed consent procedure?

Perspectives

This innovative medical device is classified as Class IIa which must be controlled according to the EU Medical Device Regulation. Conformity tests[1] should be performed before clinical investigational plan. This innovative device is a set of individually customized dentures. While there is no registration needed for the device, the material used in this device must be registered. There can be unique properties associated with submicron or nanotechnology components such as aggregation, agglomeration, immunogenicity, or toxicity. Medical devices with submicron components may require specialized manufacturing techniques if characterization and biocompatibility testing is needed[2]. There may be limitations in the analysis of biocompatibility of submicron components when using chemical leachates-based ISO 10993-12 test conditions. The EC recommends that the investigator consult relevant literature and standards during the development of test protocols for device-specific submicron or nanotechnology component biocompatibility assessments.

The EC also requests the data on the biological evaluation of medical devices which is required prior to the First in Human study[3]. Since this device is categorized as a surface device used for less than 24 hours, the biocompatibility evaluation requires the tests for *in vitro* cytotoxicity, sensitization and irritation or intracutaneous reactivity.

The potential risk of this study rests in the material used in the denture, thus, it is essential that these information are submitted for EC review.

Any conflict of interests between the inventor of the device and the investigator is requested to be identified and disclosed to the EC. The EC will review and evaluate the impact of the COI on the scientific integrity of the study.

The EC has determined that it is justified to recruit elderly participants although some of them may be vulnerable subjects. The patients with *Candida*-related denture stomatitis would receive direct benefits from the trial and the research cannot be carried out in a non-vulnerable group[4]. For a potential research participant who is incapable of giving informed consent, the research team must seek written informed consent from the legally authorized

---

[1] ISO 14155-2011 Clinical Investigation of Medical Devices for Human Subjects-Good Clinical Practices.

[2] ASTM F1903 “Standard Practice for Testing For Biological Responses to Particles *In Vitro*,” or ASTM F1904 “Standard Practice for Testing the Biological Responses to Particles in vivo.”

[3] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Devices and Radiological Health. Guidance for Industry and Food and Drug Administration Staff. Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process". June 16, 2016.

[4] WMA Declaration of Helsinki 2013.

representative (LAR) prior to randomization and intervention[5] as well as the assent of the potential research participant, if applicable.

The informed consent process should take into consideration the dentist-patient relationship. It may be more beneficial for the study team to obtain informed consent instead of the dentist. The informed consent should include the disclosure of COI, if any.

[5] CIOMS Guideline 16.

Case Study 2: Pharmacology Study in Pregnant Women

Pharmacokinetics and pharmacodynamics study of fixed dose combination antiretroviral drug in pregnant women with stable virologically suppressed HIV-1.

The ethics committee (EC) was presented with a proposal to evaluate the steady state pharmacokinetics (PK) of a drug when given as a fixed dose combination with two other non-nucleoside reverse transcriptase inhibitors (NNRTI): Drug B and Drug C. The study also wants to confirm the dose of this fixed dose combination (Drug A/B/C) in the second and third trimesters of pregnancy. Drug A is a potent inhibitor of HIV-1 integrase. Antiviral testing has shown that Drug A is active against a broad panel of HIV-1 viral lab strains and clinical isolates. It is fully active *in vitro* against a panel of mutant viruses with resistance to nucleoside reverse transcriptase inhibitors (NRTI), NNRTI, and protease inhibitors (PI). The US FDA approved Drug A/B/C as a once daily dose for the treatment of adults with HIV-1 infection. This drug combination has also been recommended in the treatment guidelines. However, PK and safety data in pregnant women of Drug A/B/C remains limited.

This study is sponsored by the pharmaceutical company and will be conducted in 20 sites worldwide. This study will include HIV-1 infected singleton pregnant female participants of ages 18-40 years old who have been stable and virologically suppressed for over 6 months prior to screening and are at least at 12-week gestation but less than 31-week gestation at the time of the screening visit. All enrolled participants have to discontinue the previous antiretroviral therapy and use Drug A/B/C during the study period. Participants may switch back to the previous therapy after the study. Consent will be obtained from the pregnant women.

All investigators of this project at this research site are paediatricians who specialized in infectious diseases (ID). All processes from participants' enrolment to laboratory testing and follow-up visits will be carried out at the Department of Paediatrics. Routine antenatal care will be done separately by obstetricians who are not involved with this project. It is noted that Drug A/B/C has drug interactions with several medications, including calcium and iron supplements.

Challenges encountered by the ethics committee

1. Vulnerability of participants and special protection
2. Is spouse's consent needed in this study?
3. Potential risks and benefits of this study
4. The qualification of investigators – are obstetricians required for the research conducted in pregnant women?

Perspectives

In this study, there is a potential risk that the Drug A/B/C may be harmful to the fetus. Under this circumstance, participants in this study can be considered as vulnerable and require special protection[1]. In this case, the EC members must carefully review the preclinical data in pregnant animal models and the labelling of the Drug A/B/C, particularly the side-effects, precaution, and contraindication sections. The pregnant women must be adequately informed about the possible risk(s) to the participant as well as the fetus or newborn[2]. Although the study may be harmful to the fetus/newborn, the decision to participate in the study remains solely with the pregnant women. In this case, she may consult with the father of the fetus if she wishes [3].

Drug A/B/C is an effective antiretroviral drug with a once-daily drug administration. This drug combination is currently being recommended for the treatment of adults with HIV-1 infection. The PK/PD study of Drug A/B/C in pregnant women is necessary due to their altered physiological changes during pregnancy which could change the PK/PD of Drug A/B/C from that of men and non-pregnant women. Furthermore, information about teratology and toxicity is often difficult to interpret from preclinical data or studies in non-pregnant human subjects. The changes in PK/PD could have a significant role in dose adjustment in the future for pregnant women with HIV-1 infection. However, the risk created by switching from effective treatment to Drug A/B/C during the study period raises ethical concerns. The Drug A/B/C level could be suboptimal which would not control the replication of the HIV-I virus. The patients could be at risk for other co-infections and newborns could be at increased risk of HIV-1 infection, specifically during delivery. The EC recommends that the risk be minimized by limiting the PK/PD study period to the shortest length needed to collect sufficient blood specimens to achieve the study objective. The recruitment of patients with lesser than 31- week gestation is appropriate as this would allow sufficient time for ART to suppress the viral replication and stabilize viral load at the time of delivery, thus, decrease the risk of vertical transmission. Visits to follow-up on the health and welfare of newborns should be conducted in order to minimize risks.

Another important issue is the qualification of the investigators. All investigators are experts in the field of infectious diseases which is appropriate for the care of HIV infection. However, as this study will be conducted in pregnant women, it is necessary to have an obstetrician as one of the investigators. The role of an obstetrician in the research team is critical for antenatal care to ensure the good status of both mother and her fetus. The obstetrician will also be able to provide advice regarding the use of other medications that are commonly prescribed for pregnant women, such as

[1] CIOMS 2016 Guidelines 15
[2] CIOMS 2016 Guidelines 19
[3] CIOMS 2016 Guidelines 19

calcium and iron supplements which are known to have a drug interaction with Drug A/B/C. Prompt management can also be done if obstetrical complications occurred.

In this study, the research cannot be conducted in non-pregnant women. There is a potential direct benefit to the participants, an increased risk above minimal risk can be acceptable, provided that the identified risks are minimized[4] as discussed above.

[4] CIOMS 2016 guidelines 19

Case Study 3: Herbal Product as Adjunctive Therapy

Drug interaction, safety and efficacy of 'Pikga mushroom' in HIV

Pikga mushroom has been widely used among HIV patients in Thailand but its efficacy is not assure. The mushroom contains an active compound, which has been claimed to be toxic to cancerous cells. Its activity against influenza, and HIV was also shown *in vitro*. However, there is no proof of its safety and efficacy in human. *In vitro* metabolizing enzyme assays revealed an enzyme-inducing property of Pikga mushroom with no significant interaction with anti-HIV drugs.

The EC was presented with a clinical trial of Pikga mushroom extract as an adjunct therapy in patients with HIV. The objectives of the study are 1) to evaluate the effect of Pikga mushroom on drug concentration of antiviral drugs; 2) to evaluate the safety of Pikga mushroom in HIV patients; and 3) to study the antiviral effect of Pikga mushroom against HIV infection. The investigator aims to enrol 20 participants in this study. Inclusion criteria include males or females aged older than 18 years who were diagnosed with HIV infection and are being treated with standard antiviral regimen consisting of once daily dosing of tenofovir, emtricitabine, and efavirenz for over 3 months. Participants who had a history of liver or renal dysfunction will be excluded from this study. In this study, Pikga mushroom extract will be prepared in capsule form. The proposed dosage regimen is 1 capsule orally twice a day. Five ml of blood will be collected at each interval (7 samples during the first day, once a day from day 2 to day 6, and 7 samples on day 7) for analysis of anti-HIV drugs' concentration and HIV viral load. The viral load will be measured on day 7.

Challenges encountered by the ethics committee

1. How do ethics committee promote and optimize the development of herbal products?
2. What are other special ethical issues involved in the clinical investigation of herbal products for human subjects?

Perspectives

Pikga mushroom in conventional preparation has a long history of use in humans but there is no proof of its safety and efficacy against cancer or viral infections. The researcher would like to determine the anti-HIV drug interaction, safety and antiviral properties of the mushroom extract as an adjunct therapy in patients with HIV using scientific approaches. However, the capsule formulation of Pikga mushroom extract in the study could result in substances that differ from those obtained using conventional preparation. Therefore, certain non-clinical information, including efficacy and toxicity, are required prior to the

conduct of a clinical investigation[1]. Additional herbal product information are required including amount of active pharmaceutical ingredients, sizable percentage of total ingredients, chemical fingerprint of major ingredients, level of contaminating pesticides, herbicides, heavy metals, synthetic drug adulterants, microbials, toxins, storage conditions and stability over the length of the trial[2].

Scientific issue: 1) Insufficient information to support the initiation of human study; 2) Inadequate information on herbal products; 3) The viral load at day 7 might not be scientifically sufficient for the proper evaluation of antiviral properties of Pikga mushroom since HIV viral load might be unchanged within this short duration of treatment, leaving the third objective unanswered (however, the viral load during this period may explain the drug-drug interaction due to the metabolizing enzyme induction of Pikga mushroom); and 4) the multiple blood draws for analysis of antiviral drugs' level should be re-adjusted given the long half-life of a daily dosing antiviral regimen.

Ethical concerns: 1) The justification for adding Pikga mushroom extract as an adjunct therapy in HIV patients whose viral load with standard antiretroviral drugs are well-controlled – is there a need to add herbal product to the patient's treatment?; 2) Risk and benefit assessment – the risk of herbal products could be overlooked as Pikga mushroom has a long history of use and may be perceived as safe but the cultural familiarity of the herbal products could result in underestimation of risks and overestimation of benefits of herbal products; 3) HIV patients generally present with various clinical severities ranging from asymptomatic infection to acquired immunodeficiency syndromes (AIDS), investigators should consider enrolling only asymptomatic participants with low HIV viral load in order to minimize the risks to participants; 4) One of the well-known adverse effects of anti-HIV drugs is dizziness therefore, in medical practice, the drugs are taken at bedtime. In this study, since the drug schedule is changed to the morning, all participants should be informed about this symptom that they might experience during participation in the study; 5) The facility to observe and monitor participants during frequent blood sampling on Day 1 and Day 7 should be properly chosen to maximize the comfort and safety of the participants who will have blood drawn 7 times throughout the day; and 6) As study populations are vulnerable subjects due to their chronic incurable disease, therapeutic misconception must be avoid.

[1] Guidelines for the regulation of herbal medicines in the South-East Asia region, 2003
[2] WHO/TDR Operational guidance: Information needed to support clinical trials of herbal products. TDR/GEN/Guidance/05.1. World Health Organization on behalf of the Special Programme for Research and Training in Tropical Diseases, 2005

Case Study 4: Bench to Bedside Research: CAR-T Cells

Clinical study of Chimeric Antigen Receptor (CAR)-T cells in patients with B-cell malignancies

The ethics committee of one medical school was presented with a proposed study of using autologous CD19 Chimeric Antigen Receptor (CAR)-T cells to treat patients with B-cell malignancies. The investigator team have extensive experience in generating CD19 CAR-T cells. The study aims to evaluate the safety and efficacy of autologous CD19 CAR-T cells as a treatment approach in B-cell malignancy patients. The investigators plan to do a pilot study using autologous CD19 CAR-T cells in patients with B-cell malignancy in their hospital. B-cell malignancy patients who relapse after allo-HSCT and no other treatment options (n=20) will be enrolled into the study after written informed consent has been obtained by their physician. CD19 CAR will be generated following a protocol from published journals. 100 ml of peripheral blood will be obtained by venous puncture and transferred to the research laboratory facility for cell processing. After obtaining peripheral blood mononuclear cells (PBMCs), CD19 CAR will be delivered to PBMCs using lentivirus transfection. After expansion of the CD19 CAR-T cells in the research laboratory facility for 10 days, CD19 CAR-T cells will be collected and transported for re-infusion into the patients. Quality control assays according to the standard protocol, including cell viability, endotoxin level, mycoplasma, bacterial and fungal test, will be done in the research laboratory facility before CD19 CAR-T cells are harvested. Patients will receive pre-treatment drug before CD19 CAR-T cell infusion. CD19 CAR-T cells will be intravenously infused with recommended dose, 0.1-1×107 cells/kg, at 1 drop/sec. After infusion, side effects including cytokine release syndrome, CAR-T cell-associated encephalopathy syndrome, hypogammaglobulinemia and macrophage activation syndrome will be closely monitored by the research team. The additional safeguards are justified.

Challenges encountered by the ethics committee

1. What concern(s) should be raised about this new therapeutic approach?
2. What are the ethical issues of this study and how should the issues be addressed?
3. What are the potential risk and how can the investigators provide adequate participant protection?

Perspectives

CAR-T cells is a frontier therapeutic approach that holds enormous promise – not just for hematologic malignancies but also for other types of cancer. It may cure incurable cancer, bypass the late effects of conventional chemotherapy, radiotherapy and/or bone marrow transplantation and give hope to many patients who suffer from the diseases. However, the approach has

several limitations. The potential risks of this study are due to the high degree of uncertainty caused by limited safety data. Most articles on this topic only reported the effectiveness of this treatment approach. The number of patients who have been treated with this approach remains relatively small with short follow-up period.

Commercially available CD19 CAR have been approved for its effectiveness in killing B-cell malignancy. In this study, the investigator will generate CD19 CAR using an in-house protocol from published papers. The concern is the effectiveness of the generated CD19 CAR. To address this concern, the EC requests the investigator to submit evidences of the effectiveness of the generated CD19 CAR-T Cells such as an *in vitro* study of tumour killing assays (e.g. B-cell apoptosis after co-culturing with CD19 CAR-T cells) or the production of tumour killing cytokines etc. Additionally, the EC would like to have preclinical data to support the product characterization information, safety and dosing for clinical trial. The EC also requests the investigator to confirm that the laboratory facility for CD19 CAR-T cell preparation is GMP compliant.

Ethical issues: the participants of this study are vulnerable subjects due to the life-threatening nature of the disease with no other treatment option. A therapeutic misconception must be avoided. The informed consent forms must clearly state the limitations of the CD19 CAR-T cells treatment approach, lack of information about long-term late effects, potential risks from the intervention and procedures involved in the study, and the chances of a relapse after CAR-T cells treatment. For the informed consent process, the information about the study should be given by the physicians with expertise in this area who could adequately explain and answer issues about the procedure as well as provide information about the potential risks and benefits to the participants. Due to the vulnerability issue, it is more appropriate for another investigator who is not involved in the patients' medical care be the one8 responsible for approaching the participants for informed consent.

The potential risk of this study includes serious complication such as cytokine release syndrome (CRS) etc. The risks can be minimized by the slow enrolment of participants for intervention i.e. one by one to allow effective observation and prompt action if side effects occur after re-infusion of CD19 CAR-T cells. Close monitoring after re-infusion and timely adverse-event reporting are recommended. An additional observation period for monitoring of acute effects in the first participants may be necessary prior to enrolling the next participant. In addition, the re-infusion of CAR-T cells should only be performed by an experienced investigator who could promptly recognize unanticipated risks and take timely actions for the safety of the participants.

Case Study 5: Adaptive Study Design

Ascending dose of primaquine regimen for the radical cure of vivax malaria in patients with G6PD deficiency

Vivax malaria is characterised by its ability to relapse multiple times due to dormant parasites in the liver called hypnozoites. Primaquine is the only available drug which can prevent relapses. However, primaquine can cause dangerous haemolysis in individuals with G6PD deficiency (prevalence rates range from 3 to 35% in malaria endemic countries). In South East Asia, the recommended dose is 30mg daily for 15 days. This daily dose in G6PD deficient individuals may cause potentially dangerous haemolysis. A weekly dose of 0.75 mg/kg (45 mg in an adult) for 8 weeks is recommended for individuals with G6PD deficiency. Although recommended for all regions, this dose was derived from a study in African American patients with Chesson ("tropical") strain *P. vivax* and the 'mild' G6PD A-variant. Recent modelling has shown that a daily ascending dose of primaquine over the course of 3 weeks would provide a much safer alternative to the 8-week regimen.

The ethics committee was presented with a protocol of a Phase I outcome-adaptive trial aiming to characterise an optimal ascending dose primaquine regimen in healthy G6PD deficient volunteers in Bangkok, Thailand. The primary outcome of the trial is the safety of a 20-day ascending dose daily regimen of primaquine such that the total dose is high enough for vivax radical cure (6-7mg/kg). Unacceptable toxicity leading to the withdrawal of the study individual is defined as: 1) Haemoglobin falling below 8g/dL, OR 2) greater than 40% fractional fall with respect to baseline (day of enrolment).

A total of 20 participants with G6PD deficiency will be enrolled in consecutive cohorts (n=5 per cohort). All participants will be in-patients in a specialised Phase I unit in a Bangkok hospital for the duration of the primaquine administration (days 1-20). The initial primaquine regimen, based on mechanistic modelling of historical data, may not be the optimal ascending dose regimen. Therefore, to maximise participant safety and to maximise learning from the trial, the regimen will be adapted within individuals and across cohorts.

Within individual adaptation

The starting regimen is divided into cycles of 5 days, each with a constant daily dose. Before progressing to the next dose level, the individual must have a Hb>9 and a total fractional fall of less than 30%. If the Hb is between 8-9 and the fractional fall is between 30-40%, the individual must stay in this cycle for as many days as it takes to reach the conditions to proceed to the next dose level. If withdrawal criteria is met, the individual will receive no more primaquine.

Between cohort adaptation

The falls in haemoglobin observed in the previous cohort may not be regular. Haemolysis must be considered both in terms of absolute nadir and in terms of speed of decrease. In order to find a regimen which best approximates a slow and gradual decrease in Hb, we allow for across cohort adaptation which can both increase or decrease the doses given during a cycle, and increase or decrease the length of time of a cycle.

Safety and patient consent

All individuals will have multiple one-on-one sessions in Thai to receive an explanation of the possible risks of trial participation. Only those who fully consent will be enrolled. The hospital blood bank will be informed of their blood-type and corresponding blood will be set aside for the duration of the trial. A 24-hour emergency medical service will be available in the hospital.

Challenges encountered by the ethics committee

1. Should the ethics committee approve a protocol where the dose of the drug is not fixed and much is left to the discretion of the investigators?
2. What safeguards should be put in place to give approval to this protocol?

Perspectives

There should be sufficient justification for the use of adaptive design in clinical trials. It should be based on previous sound scientific modelling to be able to predict and manage conditions encountered in the course of the trial. Possible variations among individual participants as well as possible variations within cohorts should be closely monitored to address the risks of the study and to identify possible courses of action in terms of dose variation and length of time for each stage. To allow the use of adaptive design, the ethics committee should examine the qualifications of the investigators in terms of specialization and experience to ensure adequate safety handling of the trial. They should have relevant clinical experience in malaria and in G6PD deficient patients to anticipate possible adverse events and how to manage such events. The inclusion of G6PD subjects in a malaria study should also be justified in terms of direct benefits to participants and the probable contribution of the study to science.

The protocol identifies some safety nets that have been put in place, like ensuring the full understanding of the potential participants of the risks of the study, adequate blood supply in case of haemolysis and readiness for emergency cases. The consent form should be comprehensive enough to discuss the risks, possible adverse events and corresponding management plans as well as vital clinical monitoring points. Site evaluation is important to ensure adequate facilities in case of emergencies. Needless to say, a comprehensive risk management plan should be incorporated into the protocol.

The roles of the members of the investigator team should also be defined to ensure adequate staff support in the conduct of the study. A Data Safety Monitoring Board may be organized to monitor AEs and SAEs and other safety issues.

Case Study 6: Informed Consent Process in HIV Infected Undisclosed Minors

Immunological efficacy of a new Pneumococcal Conjugate Vaccination in HIV-infected children receiving Highly Active Antiretroviral Therapy (HAART)

Pneumococcal infection is an endemic disease in Asia. Clinical manifestations such as meningitis, septicaemia and pneumonia are the leading causes of the disease's high mortality rate. HIV-infected children/adolescents are more predisposed to pneumococcal infections than the general population. The benefits of pneumococcal vaccination are recognized and the Centre for Disease Control and Prevention (CDC 2018) recommends routine Pneumococcal Conjugate Vaccine for all children younger than 2 years old, those between 2- 64 years old with certain medical conditions (such as HIV infection) and adults 65 years or older. The EC was presented with a protocol of a phase III, open label, single arm study. The objective of the trial is to evaluate the efficacy of a new Pneumococcal Conjugate Vaccine against pneumococcal infections in HIV-infected children/ adolescents on anti-HIV therapy (HAART). 23- valent pneumococcal polysaccharide vaccine (PPSV23), contains 12 of the serotypes included in Pneumococcal Conjugate Vaccine (PCV13), plus 11 additional serotypes were evaluated. The immunization schedule starts with a single PCV13 dose, followed by a dose of PPSV23 at ≥ 8 weeks later. A second PPSV23 dose is recommended 5 years after the first PPSV23 dose. Inclusion criteria are HIV children/adolescents 7-18 years of age without AIDS related illness and on HAART treatment for over one month. The trial will be performed in 20 Asia sites. Recruitment will be conducted at HIV clinics of each hospital by an infectious disease doctor who is the principle investigator. Written informed consent will be obtained from a parent or guardian if the potential participant is under 18 years of age. It is known that some of the children who live with their parent/guardian or close caregiver have not been informed about their HIV status. Thus, the investigators proposed that the HIV status children/adolescents remain undisclosed due to limitation on their cognitive and emotional maturity. Disclosure of HIV status may result in stigma and discrimination (shame, fear, guilt and self-hate).

Challenges encountered by the ethics committee

1. Evaluation of risks and benefits of disclosure of HIV status
2. Appropriate informed consent process in HIV minors

Perspectives

The Ethics Committee (EC) has concerns about the disclosure of HIV status in the children who have not yet been informed of their HIV status. The EC discussed on the risk-benefit ratio of HIV disclosure and various ethical dilemmas. Disclosure decisions are dependent on many factors such as the children's emotional and maturational ability to understand and cope with the nature of the illness, stigma, social support, family relations, etc.[1]. There is evidence of health benefits in disclosing their HIV status to the children/adolescents such as safer sexual behaviour, reduced risk of death, increased adherence to treatment and retention in care. The important factor to consider in deciding whether to disclose the HIV status to a child is the developmental level of the child's cognitive ability to understand what is being told and to cope with the nature of the illness. Partial disclosure (no mention is made about HIV/AIDS) can be started at early age (less than 6 years old) but should be completed by a full disclosure by the age of 6-12 years, as recommended by the WHO[2].

In this study, the children/adolescents are on HAART treatment meaning they are under a HIV health program and are taking medications as scheduled. For this reason, some children/adolescents have a chance to know that they are infected with HIV by themselves or by the counsellor at the HIV clinic. These children should have some type of psychological or emotional support from the HIV clinic where they receive HAART treatment. The children who have not yet been informed about their HIV status may have been evaluated as not ready to cope with the nature of their illness, stigma or discrimination. The EC believes that the role of giving full disclosure of HIV status would be better left to the doctor or counsellor at the HIV clinic rather than the investigator team of this study. The investigator should endorse the important role of counselling in providing psychological support. For this study, partial disclosure may be more appropriate. As a consequence, the title of the study should be changed to "Clinical trial phase III, Immunological efficacy of a new Pneumococcal Conjugate Vaccine in immunocompromised children".

This study involves a vulnerable population (HIV infected children /adolescents). The EC has determined that the level of risk involved is more than minimal risk. The study has potential to directly benefit this group of participants (i.e. to prevent the pneumococcal infection in HIV children who have an increased risk of infection in comparison to the general population). The EC requires a written informed consent and assent with adequate provisions to protect the privacy of participants and maintain the confidentiality of their

[1] WHO 2011: Guideline on HIV disclosure counselling for children up to 12 years of age
[2] WHO 2011: Guideline on HIV disclosure counselling for children up to 12 years of age

identifiable data. To minimize the risk, the informed consent document for the children or teenagers should not contain the word 'HIV' both in the title and in the content. Due to the physician-patient relationship between the principle investigator and the participant which may be a factor of undue influence, the EC suggests that obtainment of informed consent be performed by other research team members.

The assent (agreement) must be obtained from children/adolescents participants in this study, along with informed consent (permission) from the parents or guardians. The children/adolescents must be provided with adequate information about research tailored to the child's or adolescent's level of maturity[3]. The process of obtaining assent must consider not only the age of children, but also their individual circumstances, life experiences, emotional and psychological maturity, intellectual capabilities and the child's or adolescent's family situation. In general, for children 7-12 years of age, a simplified assent form should be used, together with a separate more detailed consent form for the parents or guardians. For participants ≥13 years of age, the use of the same consent form with parents or guardians is acceptable but a simplified assent form for the adolescents and a separate more detailed consent for the parents or guardians can be considered as an option as well. If children participants reach legal age during the study period and is capable of giving independent informed consent, the re-consent to continued his/her participation must be performed. It should be noted that the age at which a child becomes legally capable to give consent differs between the laws and regulations of each country.

[3] CIOMS 2016 Guidelines 17: Research involving children and adolescents

Case Study 7: Cluster Randomized Trials

Community-directed educational intervention for malaria elimination: a quasi-experimental study in malaria endemic areas

The Ethics Committee was presented with a community-based study to test the effectiveness of the community-directed educational intervention on malaria prevention and control in malaria- endemic areas. The study is a quasi-experimental study design with the use of both qualitative and quantitative data collection methods. In-depth interviews and focus group discussions will be carried out in addition to household surveys using a structured questionnaire conducted before and after the intervention.

Intervention: Training of basic health unit staff in malaria prevention, who in turn will train Community Action Groups (CAG) who will develop action plans for implementation of interventions within their communities.

Training topics include: 1). Malaria transmission, care and use of LLINs, proper use of IRS, control of mosquito breeding sites, importance of early diagnosis and treatment; 2). CAG members will conduct monthly cleaning campaigns during which they will also provide educational session on malaria prevention and control; and 3). The CAGs will develop action plans for malaria prevention and control that include conducting educational sessions in their local villages, organizing cleaning campaigns to reduce mosquito breeding sites and monitoring

Expected outcomes: Less malaria incidence in intervention group when compared with the control group

Challenges encountered by the ethics committee

1. Is it justified to do research simultaneously with the roll out of public health programs?
2. What is the benefit to the control group?
3. What types of consent should be required?

Perspectives

It is justified to do research simultaneously with the roll out of a public health program provided that certain conditions are met: 1). There is evidence that the public health program being rolled out is beneficial to the community; 2). Research is being undertaken to provide evidence of the benefits of the program, identify weaknesses during implementation and address these weaknesses for better results; and 3). Contamination is avoided by ensuring that the sites are not contiguous to each other.

Should the research results show better outcomes in the intervention group, the intervention should also be performed in the control group. However, if research results are not better in the intervention group, there is no need to replicate the program in the control group. Weaknesses during the first phase of implementation should be addressed during future program rollouts. Study data will be analysed by group (intervention vs. control group results)

Cluster randomized trials make use of the whole site or community, rather than individuals as intervention or control group. Individuals cannot choose which group to join. The consent form should explain the use of cluster randomization and the research procedures and activities should be explained. Administrative permission should be obtained first, then, individual consent of participants next. There should be community feedback after the research is over.

Case Study 8: Privacy and Confidentiality

A qualitative research of unplanned teenage pregnancy

Unplanned pregnancies are pregnancies that are mistimed, unplanned or unwanted at the time of conception. It is related to numerous maternal and child health problems especially in pregnant teenagers. This situation sometimes forces them to seek abortion which often causes serious complications, particularly in cases of septic abortion.

An experienced social scientist who works at a family planning clinic at a provincial hospital submitted a protocol to the ethics committee (EC) for review and approval. The investigator proposed to investigate the attitudes of unplanned pregnant teenagers regarding induced abortion. Data from at least ten pregnant teenagers aged between 10-19 years old will be collected using focus group discussion. The investigator plans to approach the participants at antenatal clinic before seeing doctors. If the pregnant teenagers agree to participate, a focus group will be conducted for approximately 60 minutes in that afternoon. The questions used in the focus group will include:

1. What do you think about your unplanned pregnancy?
2. Has getting pregnant damaged your lifestyle? How?
3. Have you ever heard about unsafe abortion? If yes, what do you think about this?
4. Have you ever heard about the risk or consequences of unsafe abortion? How?
5. What do you plan to do with your life after this?

During the discussion, the investigator plans to record the conversation by video recorder to ensure the correctness of the data.

Challenges encountered by the ethics committee

1. What should the EC consider on this type of study? Is the data collection method appropriate?
2. Is the principal investigator qualified to conduct this study?
3. Do the participants have direct benefit? What about possible risk?
4. Is informed consent necessary? Why?
5. Should the informed consent from the parents be obtained?

Perspectives

Taking into consideration the scientific soundness, the collection of data using a focus group may be inappropriate for this study. The potential risks in this study are to the invasion of the privacy and breach of the confidentiality of the participants. It is difficult to ensure that every participant will respect the confidentiality of the private sensitive information that will be shared during the focus group discussion. The EC considers an in-depth interview to be more

appropriate as it could provide better privacy and confidentiality protection. The questions used in the in-depth interview should be in a semi-structured pattern which consists of open-ended questions. The questions should not promote the idea of unsafe abortion among the participants and should avoid sensitive wording that could trigger psychological risks. The EC recommends that the investigator consider asking questions such as “How do you feel about your pregnancy?” etc. and the interview should be performed in a private room. During the interview, the investigator must keep confidentiality by using anonymized data or real names must be replaced by codes or aliases. The EC believes that the use of auditory tape recording is more appropriate than video recording in terms of protection of privacy and confidentiality. Additionally, the identifiable data must be destroyed 3 years after publication. The Common rule: 45 CFR 46.111(a)(7) recommends that provisions should be made to ensure respect for the privacy of participants and confidentiality of records in which participants are identified[1].

Although the investigator has extensive experience in conducting in-depth interviews and would probably be able to handle the interview and participants’ reactions during the interview, the EC recommends that the investigator invite obstetrician, and child and adolescent psychologist as co-investigators or consultant to better handle the possible obstetrics and psychological risks.

The EC believes that the investigator’s plan to approach the participants at an antenatal clinic is inappropriate because this would be too invasive to the privacy and confidentiality of the participants. The unplanned pregnant teenager would be faced with social risk as the local society's perception of pregnancy in teenagers is that it is a result of shameful and inappropriate behaviour among students. The EC suggests that the investigator approach an obstetrician to identify the eligible participants and ask for their permission to allow the investigator to approach them about the study. Alternatively, the eligible participants may also be recruited from a specialized clinic for unsafe abortion where all are unplanned pregnancies who seek an abortion.

There is no direct benefit from the study to the participants but the participants might benefit from the knowledge gained during the interview process about the impact of unplanned pregnancy, how to have safe sex, how to avoid unsafe abortion. Additionally, the EC suggests that the investigator provide additional help if participants need help or might be inclined towards the idea of unsafe abortion. The investigator should provide assistance such as providing health education on antenatal care, referring the participant to a One Stop Crisis Centre (OSCC) or shelter, informing the participants of the opportunity to study during their pregnancy and safely induced abortion if needed. Verbal consent should be considered instead of written consent to

[1] Common rule: 45 CFR 46.111(a)(7)

avoid participant identification. Because most of the teenagers do not let their parents know about their pregnancies, obtaining consent from parents would make the conduct of the research impracticable and might cause problems in the family. Therefore, waiver of parental consent should be considered[2].

[2] CIOMS 2016 guideline 17– waiver of parental permission

Case Study 9: Research in Surgical Procedure

A randomized controlled trial of intra-umbilicus and infra-umbilicus post-partum tubal sterilization

The infra-umbilical post-partum tubal sterilization is a simple and common procedure in medical practice. The intra-umbilicus procedure is expected to provide a better aesthetic outcome but it is not a common practice as it is more complicated and requires high surgical skills. However, recent medical technology has made it possible to make an incision inside an umbilicus with a single port surgery under a scope. Such a procedure has been proven to be efficient and safe.

The EC was presented with a randomized clinical trial to compare the outcomes of intra-umbilicus using a single port surgery under a scope versus infra-umbilicus in post-partum tubal sterilization. Eligible participants include postpartum women who have requested and are scheduled for sterilization. All operations in the study will be performed by experienced surgeons. The participants who refuse to participate in the study will be operated by obstetric residents under supervision. The assessment includes aesthetic scores of an incision wound, surgical time and complications of post-partum sterilization. The aesthetic of wound will be evaluated by an independent surgeon and the research participants using the 'Patient and Observer scar assessment score' at one week after surgery. The operative times and wound infections and/or complications will also be evaluated one week after surgery. Informed consent for research participation will be obtained after delivery by the obstetrician who performed the delivery.

Challenges encountered by the ethics committee

1. The vulnerability of the participants
2. The ethical issues associated with this study

Perspectives

The participants in this study can be considered as vulnerable as a newborn may be affected by the research. In this case, the EC recommends that the participants must be adequately informed about the risks of wound infection and/or other complications after surgery. The EC also suggests that the informed consent procedure should be performed by another investigator team member who was not responsible for the delivery to enhance the autonomy of the participants in deciding whether they desire to participate in the study.

The EC also has a concern about the inducement of participants to enrol in the study. The surgery of those who agree to participate in the study will be performed by experienced obstetricians. While those who refuse will be

operated on by a less experienced obstetrician (i.e. the resident). The surgery provided by experienced obstetricians might induce prospective participants to consent to participate in the research against their better judgment[1]. In this situation the inducement can be undue. To address this issue, the EC suggests that during the study period, an investigator team member (i.e. an experienced obstetrician) perform the standard post-partum tubal sterilization for those who refuse to participate in the study.

[1] CIOMS 2016 guidelines 13 – reimbursement and compensation for research participants

Case Study 10: Physical Activity and Health Status Study

Correlation of physical activity and health statuses of hospital personnel: A study using questionnaires and a new activity tracker

The ethics committee was presented with a proposal of a study to evaluate the correlation of physical activity and the health statuses of health personnel in a private hospital, using the International Physical Activity Questionnaire (IPAQ) and a new activity tracker. The objective of this study is to find the correlation of physical activity data (physical examination, BIA, IPAQ plus data from the activity tracker) and the health status, which will be obtained from the annual personnel check-up data, to hypercholesterolemia, diabetes, hypertension, obesity or any chronic disease.

The new activity tracker was developed and verified by a university which received funding from the Health Promotion Foundation. The IPAQ is a short form adaption of a standard questionnaire developed by the World Health Organization. The activity tracker is a device that calculates the calories burnt from movement detected on three-axis by the device's sensors. The device also calculates and uses the Metabolic Equivalent (MET) to classify the level of exercise intensity into 1 of 5 levels (I – Basal, II – Light, III - Moderate1, IV – Moderate2, and V – Vigorous).

The study will involve physical examinations, completion of the IPAQ and the use of an activity tracker during regular office hour (8 hours) for 5 days. The investigator team will monitor and record data at the end of each day. The device will be taken off at the end of each day and kept with the investigator team. The investigator team will remind the participants to perform regular physical activity during the study period.

The principal investigator (PI) is a senior administrative medical doctor who works full time at the research department in this private hospital. The PI is a known colleague of the engineer who is the main inventor of this activity tracker before the PI joined this private hospital 5 years ago.

It is proposed that recruitment of the participants be completed using the employee lists. The PI will use a simple random sampling from the lists to recruit 10 percent of the hospital employees and ask the Heads of each division to supply the invitation document to their own staff. The investigator team would advertise the study to the Heads of each and hand over the Participant Information Sheet (PIS) as well as the Informed Consent Form (ICF) to the Heads of the divisions.

Challenges encountered by the ethics committee

1. Is there any conflict of interest that needs to be declared by the PI?
2. How will the investigators obtain health data information and the list of employees?

3. What are the possible benefits and potential risks from this research?
4. Does this population belong to a vulnerable population?

Perspectives

As the PI is a colleague of the inventor, it is necessary that he declares the COI to make it possible for the ethics committee to review the impact of the COI on the study's integrity as well as to suggest a method to address the COI.

The campaign of this study could be done using some form of public announcement in the hospital e.g. paper advertisement, intranet, invitation letter, social media. The simple random sampling of 10 percent of employees should be done in a way that allows an equitable distribution in various strata.

The access to the employees' hospital database should be performed by an authorized person after the completion of the informed consent process. In addition, access to the routine annual check-up health information should be limited to the specific data required for this study.

The physical risk from attaching the activity tracker is minimal. The concern is the potential employment related risks. The PI is a senior administrator who is in a position to coerce potential participants. The employees may fear that their refusal to join the study will be interpreted as non-cooperation and will result in the lose of their jobs or a bad reputation as the study will be advertised as "the better option to get better health in the workplace environment". Additionally, the results of this study will be used in this private hospital as a strategy to develop the hospital's policy in the future. This power imbalance may very well interfere with a potential subject's capacity to choose or act voluntarily. To address this issue, the PI should not be informed of an employee's decision to participate or not. The PI should only be able to review the aggregate data that has been stripped of identifiers. The PI should also identify the person who will be authorized to access, use or disseminate the results to the participants. The details regarding the personal identifiers should be kept confidential in a safe place.

The informed consent form should clearly state how the data will be kept confidential throughout the study as well as after the study period.

The hospital employees are considered as a vulnerable population but the study is justified as it is responsive to the health needs or priorities of this group and cannot be conducted in another group. There is a potential direct benefit to the participants in terms of knowledge and practices, or interventions that could result from the research. The findings from the research study may be able to make recommendations to improve the physical activities of the employees according to their job strata.

The vulnerable nature of this study arises from the possibility of diminished voluntariness during the consent process as the potential participants have a hierarchical relationship with the senior PI, who is also a

hospital administrator, and may be easily coerced. In order to protect the participants from coercion, the PI should not know the identity of the participants. In addition, the heads of the divisions who may have undue influence on the participants should not be the one to recruit or obtain informed consent from potential participants.

Case Study 11: Big Data and Data Sharing

A genetic research in children with Attention Deficit Hyperactivity Disorder

Attention Deficit Hyperactivity Disorder (ADHD) is a childhood-onset condition with impaired attention, impulsivity, and hyperactivity. Several studies have suggested that there may be an association of certain genetic components to the etiology of ADHD and its comorbidity.

The investigator submitted a proposal of a Multicentre Neuroimaging Data Sharing (NDS) project to an ethics committee (EC) for review and approval. The study team is composed of paediatricians, paediatric geneticists and nurses. The investigators will collect a single blood sample as well as a series of clinical and neuroimaging data of children with ADHD from 20 institutes in 10 Asian countries from 2020 to 2025. The clinical data will be collected until the children reach the age of 20. The data are composed of demographic data (age, sex, socio-economic status, parental stress, family communication, drug and family history), clinical, neuropsychological, emotional and behavioural characteristics of ADHD.

The single blood sample will be anonymized and stored in each institute with a unique code. The data collected from each site will be stored in electronic data format with a single code protection. Each site will then transfer the data to the NDS centre, which will be established in country A, on a weekly basis using single coding during transfer. The code for all data will be stored in the locked cabinets at each institute. The data management and sharing will be managed by a data manager in country A. Principal investigator from each site has authority to access the data.

The required sample size is about 6,000 subjects consisting of approximately 300 subjects from each institute. The aim of this study is to use the clinical and neuroimaging data for future development of potential diagnosis and treatment for ADHD.

Informed consent will be obtained in a private room at an out-patient clinic in each institute. The research nurses from each site will explain to the parents/legal representative/legal guardian about the details of the research, the risks and benefits, and their related biospecimen information such as blood samples, clinical data, neuroimaging data. The research participants from each site will be informed that their blood specimens will be stored at each institute while their clinical and neuroimaging data will be anonymized, transferred and kept at the NDS centre in country A. The investigators will ask permission to use the clinical data, blood sample and related information for future research. In case the participants would like to withdraw their consent from the study, the withdrawal of consent need to be signed and documented.

Challenges encountered by the ethics committee

1. Ethical issues in this type of study?
2. The necessity of governance structure of the institutions?
3. What type of informed consent is appropriate?

Perspectives

This study involves the collection of single blood samples and the use of medical and neuroimaging data from children with ADHD for future research. The investigators proposed that the blood samples be stored at the respective study site and that a data centre be established in country A to share clinical and neuroimaging data among participating institutions. The investigators will analyse the genetic information from the blood samples of ADHD participants and associate the genetic information to the clinical and neuroimaging data. The EC sees that the study will benefit the participants with ADHD as the study can accelerate the development of diagnosis and treatment for ADHD[1]. The potential risks are privacy and confidentiality risks as the results of the analysis may result in stigma and discrimination. The investigators must ensure confidentiality to the extent possible throughout the life of the data. To address this issue the investigators proposed to anonymize the data and use single data coding. However, the EC has a concern about the maintenance of confidentiality as well as the protection of participants' interests. The EC suggests that the investigators set up a governance system to obtain authorization for future use of these data in research as an additional protective measure for the participants. The setup should be at both the study sites that store the blood specimens and the NDS centre where the clinical and neuroimaging data will be kept. Governance structure must regulate at least the following items: to which legal entity the material is entrusted, how authorization from the participant is obtained, how the participant can retract this authorization, circumstances that participants will be re-contacted, a procedure for determining whether unsolicited findings should be disclosed, how the quality of the data or specimen collection is controlled, how confidentiality is maintained, who may have access to the data for future research and appropriate mechanisms for keeping participants informed of research outcomes[2].

The informed consent must clearly state whether return of information derived from data analysis is foreseen at the participants' requests. The information should emphasise that providing individual diagnosis is not the main objective of the study in order to prevent false reassurance. If the participant prefers to receive the result from the analysis, the three principles need to be followed: results must be (1) valid, (2) clinically significant and (3) actionable[3].

[1] WMA declaration of Taipei on ethical considerations regarding health databases and biobanks (2016)
[2] CIOMS 2016 Guideline 11and 12 – complimentary on the Governance
[3] CIOMS 2016 Guideline 11 – complimentary on the return of results

This means information of uncertain scientific validity or clinical significance would not qualify to be return to the participants.

The aim of the study is to share neuroimaging data for the development of potential diagnosis and treatment with no specific objective for the study. As such, broad informed consent is more appropriate. Broad informed consent should specify: (1) the purpose of the biobank/databank, (2) the conditions and duration of storage, (3) the method to access the data, (4) the measure for participant to re-contact the databank manager and (5) the return of the result to participants. The participant or legal representatives should have the ability to withdraw their consent for stored specimen and the use of their data in the databank. The withdrawal should be documented in writing by the participant or the legal representatives. Informed consent must state clearly whether the data will be destroyed, returned to the participant or kept infinitely[4]. When the children reach the age of majority, they should be provided the opportunity to give consent for the continued storage and use of their data or to withdraw consent for future research. An informed opt-out procedure in which participants are alerted to their rights to withdraw could be acceptable[5].

The data sharing in genetic research between institutes or between countries requires a Material Transfer Agreement (MTA) and Data Sharing Agreement (DSA) which is a contract that allows the institution to perform the research using both clinical data and biological materials. The EC suggests that principal investigator submit the study's DSA and MTA for review and approval.

[4] CIOMS 2016 Guideline 11 and 12 – complimentary on broad informed consent
[5] CIOMS 2016 Guidelines 11and 12– complimentary on children and adolescents

Editors

Juntra Karbwang Laothavorn, M.D., PhD. & Junjira Laothavorn, J.D., PhD.

Contributing Authors

1. Chairat Shayakul, M.D.
Department of Medicine, Faculty of Medicine Siriraj Hospital,
Mahidol University, Bangkok, Thailand
2. Cristina Torres, PhD.
FERCAP Coordinator, FERCAP
Bangkok, Thailand
3. Kwanchanok Yimtae, M.D.
Department of Otorhinolaryngology, Faculty of Medicine, Khon Kaen University
Khon Kaen, Thailand
4. Laksamee Chanvej, M.D.
Bangkok Hospital Medical Center – Institutional Review Board, Bangkok Hospital Headquarter
Director of Supportive Care Center, Bangkok Dusit Medical Services,
Bangkok, Thailand
5. Napapa Aimjirakul, D.D.S., Ph.D.
Faculty of Dentistry, Srinakarinwirot University
Bangkok, Thailand
6. Patou Tantbirojn, M.D.
Department of Obstetrics and Gynecology, Faculty of Medicine,
Chulalongkorn University, Bangkok, Thailand
7. Phanthipha Wongwai, M.D.
Department of Ophthalmology, Faculty of Medicine, Khon Kaen University
Khon Kaen, Thailand
8. Phenkhae Lapying, D.D.S., Ph.D.
Dental Health Bureau, Department of Health, Ministry of Public Health
Nonthaburi, Thailand
9. Piya Rujkijyanont, M.D.
Department of Pediatrics, Phramongkutklao Hospital
Bangkok, Thailand
10. Saowalak Hunnangkul, Ph.D.
Faculty of Medicine Siriraj Hospital, Mahidol University
Bangkok, Thailand
11. Sirikul Manochantr, Ph.D.
Division of Cell Biology, Faculty of Medicine, Thammasat University
Pathumthani, Thailand
12. Supatra Porasuphatana, Ph.D.
Faculty of Pharmaceutical Sciences, Khon Kaen University
Khon Kaen, Thailand
13. Tada Sueblingwong, M.D.
Chairperson, Med Chula Institutional Review Board,
Faculty of Medicine, Chulalongkorn University
Bangkok, Thailand
14. Thumwadee Tangsiriwatthana, M.D.
Department of Obstetrics and Gynecology, Khon Kaen Hospital
Khon Kaen, Thailand
15. Ussanee Sangkomkamhang, M.D.
Department of Obstetrics and Gynecology, Khon Kaen Hospital
Khon Kaen, Thailand
16. Watcharin Chirdchim, M.D.
Department of Obstetrics and Gynecology, Prapokklao Hospital
Chanthaburi, Thailand

Perspectives on Ethical Review

'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

October 2016