Perspectives on Ethical Review II

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)

Introduction

This is the second casebook of perspectives on ethical review which has the same objectives as that of the first casebook in 2016. The success of the first casebook led to the decision of FERCAP to endorse the production of this casebook. As part of their training program, the MFES GF trainees 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 written 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 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 subject 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 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. 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.

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.

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Case Study 1: The Use of Placebo

A randomized, double-blind, placebo-controlled trial of the efficacy of oral versus topical LMNvir medication in patients with chronic CMV anterior uveitis

The ethics committee (EC) was presented with a proposal for a randomized double-blinded, placebo-controlled drug trial which aimed to compare the oral and topical form of the antiviral agent, LMNvir to treat chronic Cytomegalovirus Anterior Uveitis (CMV AU) in immunocompetent patients.

The rationale for conducting the study was that oral LMNvir, which is usually prescribed for the treatment of CMV infections, carries several systemic side effects. If topical LMNvir is proven to be comparable in terms of efficacy, it could replace oral therapy as an effective treatment with fewer systemic side effects.

This is an investigator-initiated study. The principal investigator is a senior Ophthalmologist in Europe. The trial will be conducted in 4 sites consisting of 1 site in Europe and 3 sites in Thailand. The required sample size is about 200 subjects and each site will enroll competitively.

Patients who are eligible for screening are immunocompetent patients whose clinical presentation is consistent with chronic CMV AU. Eligible subjects will undergo aspiration of aqueous fluid for PCR detection of CMV. Only those with positive PCR will be included in the study. Those with severe disease, as judged by the attending Ophthalmologist, will be excluded and treated intensively as required. The remaining patients will be randomized into 3 groups: 1) oral LMNvir + placebo eye drops, 2) LMNvir eye drops + oral placebo, and 3) oral placebo + placebo eye drops. Topical LMNvir will be prepared in-house from the antiviral agent ganciclovir at each site by a trained Pharmacist according to standard protocols as it is not commercially available. All patients will also receive topical corticosteroid therapy for sterile inflammation which could occur in patients with chronic CMV AU.

Each group will be treated for 6 weeks and evaluation of outcome will be made at the end of the treatment period which includes another aqueous fluid aspiration for PCR viral load quantification. All patients undergo weekly ophthalmic examinations and visual acuity testing to determine the disease progression. The patients will be withdrawn if there is clinical deterioration during the treatment period and rescue therapy will be given which may include intravenous LMNvir or other systemic antiviral agents. The rescue medication will depend on presenting symptoms and the judgment of the attending ophthalmologist. At the end of the study, if either oral or topical LMNvir is found to be more effective than a placebo, patients in the placebo group will be given the most effective regimen of LMNvir.

The investigator proposed to include a placebo arm in this study as the CMV AU in the immunocompetent host can be a self-limited infection and may spontaneously resolve without any complication. Furthermore, a recent Cochrane review of treatment of chronic CMV AU concluded that at the time this proposal was submitted, there was no standard treatment guideline for this condition.

Challenges encountered by the ethics committee

1. What is the justification for using the placebo in this trial?
2. How should the EC make a decision in this protocol?

Perspectives

This protocol presented a dilemma to the EC on the justification of having a placebo group in patients with proven infection. The use of placebo creates the potential conflict between the validity of science and the requirement to protect the interests of the research participants. The design of the study must provide a valid result without withholding treatment from the patients[1]. Placebo controlled trial design can measure the mediated effects of treatment particularly in the case of self-limiting diseases.

The ethical question is whether withholding treatment from patients in the placebo group would be justifiable. In general practice, chronic CMV AU is often not treated as it could be mild and self-limiting. In addition, PCR detection of the virus is not routinely performed, thus, in practice, it is less likely that a patient with chronic CMV AU would receive antiviral treatment. Another issue of note is that the inflammatory reaction in patients with chronic CMV AU could be due to sterile immune reaction unrelated to the viral-particle itself, thus topical corticosteroid therapy is routinely given. In other words, patients with chronic CMV AU do not usually receive antiviral therapy but topical corticosteroid. Similarly, all patients in this study will receive topical corticosteroid. Against this scenario, withholding antiviral therapy from patients is a common practice and seems to be justifiable.

However, despite CMV AU being potentially self-limiting, once the infection is confirmed by PCR, would it still be justifiable to withhold antiviral therapy? In addition, a recent study from France[2] with a long follow-up of the disease progress, suggested that early antiviral therapy (<700 days) of CMV AU may reduce the severity of glaucoma which is one of the complications of CMV AU.

When making decisions regarding the use of placebo in a clinical trial, the EC should refer to the Declaration of Helsinki 2013 and the CIOMS 2016

[1] CIOMS 2016 Guidelines 5: Choice of control in clinical trial

[2] Sara Touhami et al Cytomegalovirus Anterior Uveitis: Clinical Characteristics and long-term outcome in a French Series. American Journal of Ophthalmology Oct 2018; 194:134-142.

where the use of placebo or no intervention may be acceptable if 1) no proven intervention exists, or 2) use of placebo or no intervention is necessary to determine the efficacy or safety of an intervention and subjects assigned to placebo or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

In this study, including a placebo group will ensure the validity of the study that therapeutic effect is not partly due to spontaneous remission. The addition of a placebo group provides an internal standard that enhances the conclusion of the efficacy of topical and oral LMNvir. The EC discussed the issue of withholding treatment from patients in placebo group and concluded that it is acceptable based on the following reasons: 1) in this setting, the chronic CMV AU patients do not generally receive antiviral treatment, 2) the withholding period is short (6 weeks) which should not result in a higher risk of severe glaucoma as suggested by the French study and 3) the patients will receive topical corticosteroid as routinely given to patients with chronic CMV AU. In addition, when a patient's condition deteriorates the patient will be withdrawn and rescue therapy will be provided. Furthermore, there is a provision for the placebo group to receive the antiviral treatment if it is proven to be effective. The EC determined that the use of placebo is justified and the proposed protocol was therefore approved. However, the EC emphasized that the trial setting be noncoercive and patients are fully informed about available therapies and the chances of being in a placebo arm.

Case Study 2: Medical Device in First in Human

Phase I clinical trial of the left atrial appendage occlusion device in patients with non-valvular atrial fibrillation

Atrial fibrillation-related stroke is associated with a high mortality rate (1-year mortality >30%) and serious consequences for stroke survivors. Oral anticoagulants are the standard first-line therapy but it carries the risk of hemorrhagic complications and is often used at a sub-therapeutic level. Many high-risk patients who are anticoagulants intolerant or with contraindication to the use of anticoagulants. Left atrial appendage (LAA) is the most common source of thrombus formation and plays a role in the initiation and maintenance of atrial fibrillation (AF) and atrial tachycardia (AT). The frequency of successful LAA occlusion was 73% with the use of LAA occlusion device, in contrast to 23% with epicardial LAA ligation through thoracoscopic approach with suture or staple exclusion. The Kingman®, a LAA occlusion device, is the most widely used device and it is the only percutaneous LAA occlusion device that has been approved by the US Food and Drug Administration (US FDA) as an alternative to warfarin for stroke prevention in patients with non-valvular atrial fibrillation (NVAF). However, the device is rather expensive, in addition, the procedure requires adequate medical facilities and a specialized cardiologist. The procedure involves implantation of the device in the heart, thus, only a few specialists can perform this procedure. The successful closure of LAA is defined as no contrast leakage on LAA angiogram and less then 1 mm jet as visualized by color Doppler on transesophageal echocardiography (TEE). Major post-operative complications (e.g. cardiac perforation, pericardial effusion) can occur in < 5% of patients.

The researcher submitted a research proposal to test the safety and performance of a local brand of medically innovative LAA occlusion device, KuKu®, for ethical review. The device is manufactured by the same factory and using the same process as the Kingman® LAA occlusion device, with the exception of its size and profile characteristics. The investigator also submitted an Investigator Brochure which includes information on the KuKu® characteristics, results of animal testing over 18 months, as well as data on the comparison of biological and technical characteristics of the modified KuKu® device with the Kingman® device. The study is a first in human (FIH) study of the KuKu® device. The researcher will recruit NVAF patients with high risk of developing stroke (using validated scores CHA_2DS_2-VASc) and contraindication to the use of oral anticoagulants. The researcher is well trained in the specific procedure. The procedure-related safety events and successful outcome will be followed up by clinical and TEE, mainly pericardial tamponade and procedure-related stroke up to 6 months.

Challenges encountered by the ethics committee

1. How should the EC analyze the risks of an innovative medical device used in a FIH study?
2. What are the special ethical issues involved in the clinical investigation of innovative medical devices for human subjects?

Perspectives

In order to assess the protocol appropriately, the EC should review the US FDA and EU Medical Device Regulation requirements for the use of devices in FIH studies[1-2]. In general, the clinical investigation of medical devices in human subjects must take into account the balance between scientific principles and accepted ethical standards as is done in drug trials[3]. Based on the guidelines the EC assessed the clinical use of the device including the anatomical location, duration of exposure, and the target populations. It was concluded that the KuKu® is classified as a significant device according to US FDA regulation (21 CFR Part 812.3) since it is intended to be implanted. It is also classified as an active implantable medical device, a class III device which must be controlled according to EU Medical Device Regulation.

The guidelines suggest that the biological evaluation of medical devices is required before its used in FIH studies. An assessment of potentially biocompatibility risks should include both chemical toxicity and physical characteristics. The biological evaluation requires the tests for *in vitro* cytoxicity, genotoxicity, carcinogenicity, reproductive toxicity, chemical characteristic of material, local effects after implantation, systemic toxicity, ethylene oxide sterilization residuals, quantification of degradation products from polymeric medical devices, toxicokinetic study design for degradation products and leachables, etc.[4]

The KuKu® was designed by modifying a device already marketed by the same manufacturer. However, the different physical characteristics including surface properties, geometry, or presence of particulates may cause an unwanted tissue response. Based on the review of the Investigator Brochure of

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[1] 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.

[2] EU Medical Device Regulation (EU MDR) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/ EEC (1990) Active Implantable Medical Devices and 93/42/EEC

[3] EN ISO 14155-1:2011 Clinical Investigation of Medical Devices for Human Subjects. Good Clinical Practice

[4] https://library.ul.com/wp-content/uploads/sites/40/2017/09/10484_White-Paper-Web_090517-1-1.pdf

KuKu® and the existing information from the literature reviews of Kingman® LAA excluder, the EC concluded that the differences between the modified KuKu® device and the Kingman® device are unlikely to influence the clinical performance and safety of the device. However, with regard to the user-related risks, an adequate training plan for the investigators should be incorporate into the clinical protocol. Furthermore, the risks associated with devices also include device malfunction, migration, tissue reaction, and an increased chance for reoperation. As adverse effects sometime take several years to occur, long term follow-up for adverse events in patients of this study should be considered.

The is a FIH study that will be conducted in patients with limited choice of preventive measures for AF complications. The patients in this study can be considered as vulnerable subjects. The informed consent process must be in a non-coercive environment. The patients must be fully informed of the nature of the study i.e. this is a FIH study whose objective is to assess the safety of the tested device. Informed consent procedures should be carefully performed to make sure that research participants recognize the potential risks of the innovative medical device, and alternative treatments or standard devices. Sponsors should plan to support the provision of compensation for device failure and provide insurance for research related injuries. Any conflict of interests between an investigator and sponsor, or between an inventor and a treating physician, should be appropriately identified and managed.

Case Study 3: New Medical Procedure Study

A multicenter randomized controlled study of ablation procedure in the management of symptomatic Brugada syndrome

The ethics committee (EC) was presented with a proposal to study the use of innovative radiofrequency ablation (RFA) procedure to prevent life-threatening abnormal heart rhythms in patients with Brugada syndrome. Brugada syndrome is a genetic condition that results in abnormal electrical activities within the heart. This condition leads to an increased risk of serious abnormal heart rhythms and subsequent sudden unexpected death. The current standard of care for patients with Brugada syndrome with life-threatening abnormal heart rhythms or sudden heart arrests (symptomatic Brugada syndrome) is the use of implantable cardiac defibrillator (ICD). The ICD is an implanted device that can detect abnormal heart rhythms and releases an electric shock to correct any life-threatening abnormal heart rhythms. However, several complications related to the ICD have been reported. These include inappropriate shock, device-related infections, and abnormal heart rhythm triggering and patients' anxiety and depression during the unexpected shock from the device.

The principal investigator who works in an urban medical center proposed a new guideline of RFA procedure to ameliorate the complications of the ICD. The RFA is a medical procedure using the heat generated from medium frequency alternating current to ablate the abnormal electrical conduction system of the heart. RFA is a procedure that is performed routinely in patients with multiple episodes of life-threatening abnormal heart rhythms during the course of Brugada syndrome. For the newly proposed guideline, RFA will be performed in patients who are at high risk of developing abnormal heart rhythms (Brugada type I) in the early course of the disease. A publication of a case series of 9 patients with symptomatic Brugada type I undergoing RFA with this type of approach reported that 78% were successfully cured and 22% had a mild and spontaneously-resolved complication. The investigator had applied the same RFA approach in 30 patients with Brugada type I, the results showed a similar success rate and complications as that of the 9 case series report. In addition, a systematic review involving 233 patients demonstrated a success rate of 97% in preventing life-threatening abnormal heart rhythms during the follow-up period of 3-78 months. The anticipated risks of the RFA procedure include site infection, bleeding, inflammation of the heart outer membrane, perforation of the heart chambers, injuries to liver and diaphragm, heart blocks due to ablating the wrong foci which may subsequently require the implantation of an additional heart device (pacemaker). Furthermore, the patients may feel uncomfortable with the long duration of a RFA procedure (8 hours).

This study will include the patients who had at least one episode of cardiac arrest and had ICD implanted to prevent future episodes. The

participants will be randomized to receive either the RFA procedure in addition to ICD or stay on ICD alone (standard of care). The additional RFA procedure aims to eliminate the abnormal conduction foci in the heart to prevent recurrent episodes of abnormal heart rhythms while the ICD shocks the heart when the abnormal heart rhythms occur. The investigator proposed to conduct this research as a multi-center study with the small rural hospitals as well as urban medical centers throughout the country participating in this trial. The study is planned to include 200 patients with Brugada type I (100 in the new RFA approach arm and 100 in the standard of care arm). The sample size calculation was based on the total number of patients with symptomatic Brugada syndrome presented to all study sites during the past 5 years.

The investigators will be responsible for medical care and expenses associated with research-related adverse events. This research proposal was submitted to the ethics committee of each study site by the local investigator. This study requires an expert to perform the RFA procedure. The principal investigator works at a leading urban medical center and is well-known to have experience in performing the RFA procedure.

Challenges encountered by the ethics committee

1. What are the potential risks and benefits of this study?
2. What concern(s) should be raised with regard to the potential risks of the new RFA approach?
3. What measure(s) can be used to provide adequate participant protection?

Perspectives

The EC considered that this study has potential benefit to the patients. The RFA may prevent the recurrent episodes of abnormal heart rhythms as supported by the case series and systematic review report as well as the unpublished data from the principal investigator. The information of anticipated risks of RFA procedure came from the systematic review report which the EC felt was inadequate for their decision-making process as the skills of the one who performs the procedure also plays a significant role in contributing to the risks of the procedure. The EC requested the investigator to analyze the data from his unpublished report on the 30 cases and submit additional data on the risks of the RFA approach to the EC. The EC also suggested that the investigator reconsider the sample size calculation method for the clinical trial as the EC believes that the sample size should be based on the results of previously conducted studies, and not on the total number of patients in the past 5 years.

The other important concern is related to the investigators at each of the study sites. Since the study will be carried out throughout the country, it may not be feasible for the principal investigator, who is the only expert to perform the RFA, to be available at every study site. The EC suggested that the principal

investigator set the plan of training for those co-investigators who are interested in performing RFA procedure to ensure a sufficient number of investigators who can competently perform the RFA procedure. This is a very important issue to be addressed given that the procedure is a more than minimal risk procedure that absolutely requires an experienced person to perform. The training is considered as a scientific and an ethical obligation.

The participants are considered vulnerable subjects given the life-threatening nature of the disease that may limit their decision-making process. Additional protection measures for the participants should include the following:

1. The investigators who obtain the informed consent should not be the patients' caring physicians.
2. The study information sheet should clearly state the details about the procedure's efficacy and complications.
3. There should always be a cardiothoracic surgeon on standby during the procedure to manage serious complications such as perforation of the heart chambers and bleeding.
4. Only competent investigators should perform the RFA procedure. The qualification criteria should be established and provided to the EC e.g. completion of required training, number of procedures performed under the supervision of the principal investigator, number of successfully performed procedures, etc.

Case Study 4: A Research involving Human Bio-specimens

A randomized controlled, open-label, phase III trial of an immunotherapy drug in advanced testicular germ cell tumor

The ethics committee was presented with a randomized controlled, open-label, phase III study on the efficacy and safety of an immunotherapy drug in advanced testicular germ cell tumor. The eligibility criteria are patients with advanced testicular germ cell tumor and ages ranging between 15-40 years. The patients will be randomized to receive either an immunotherapy drug plus standard chemotherapy or only standard chemotherapy. Both groups will receive standard chemotherapy up to 6 cycles and the investigational arm will receive an immunotherapy drug treatment until disease progression or unacceptable toxicity. The primary outcome is the overall survival rate. The secondary outcome is safety. The follow-up period is 10 years.

Recent data from other types of cancer studies suggest that the predictive factor of survival benefit from the immunotherapy drug was related to a mismatch repair (MMR) gene mutation. Therefore, the researcher proposed to explore the correlation between a MMR gene mutation and survival outcome. In addition, the investigator proposed to perform DNA extraction from the blood samples collected and store them in another country for future analysis in other genetic studies when relevant data are available. For these purposes, an additional blood sample of 10 ml will be collected.

This study proposed to use only one informed consent form (ICF) for both the participation in the randomized drug study and the collection of blood samples which will be used for both MMR gene mutation analysis and future research. The ICF states clearly that the collection of blood specimens will be used for MMR gene mutation analysis and that DNA extracted from the remaining specimen will be stored for future analysis.

Challenges encountered by the ethics committee

1. The inclusion of adolescent in this study
2. Appropriate informed consent process for the genetic study
3. The requirements for the transfer process of human bio-specimens
4. The informed consent process for storage of DNA extract for future research

Perspectives

Adolescents must be included in this study as testicular germ cell tumors are most common in adolescents and young adult. Since the study has the potential to benefit adolescents as well as adults, the study can ethically recruit

both adolescents and adults simultaneously i.e. conducting research in adults prior to adolescents is not required[1].

The informed consent process must include the acquirement of adolescent's assent (agreement). As the ages of the adolescents in this study range between 15 to 18 years old, acquirement of the parents' consent should also be considered *i.e.* the parent and adolescents can sign on the same ICF. Furthermore, re-consent of adolescents is required once they become 18 years old[2].

With regard to genetic research in this study, the transfer of biological materials to another institution or country requires a Material Transfer Agreement (MTA). This is a contract that governs the transfer of tangible research materials between two organizations. The MTA must document the details of blood collection, appropriate infrastructure at the study sites, and the transfer process so that retrieval of the bio-specimens is possible and accurate, thereby ensuring the integrity of the data. The MTA should also include the range and duration of future use as well as the procedures that will be implemented after the specimens have been used. The responsibilities of the parties involved with the activities stated in the MTA should be clearly specified[3].

Although the additional collection of blood specimens may be considered as a minimal risk, storage of extracted DNA for future research requires explicit authorization from the research participants. In this study, since the researcher proposed to explore the correlation between an MMR gene mutation and survival outcome, the collection of blood for the MMR gene mutation analysis could be incorporated into the main study. However, a separate informed consent is more appropriate for the collection and storage of blood specimen in the form of extracted DNA in another country for the future use. Furthermore, since the specific nature of research is unknown at the time of blood collection, the use of broad informed consent is recommended. The researcher needs to provide information on the governance and management of the extracted DNA for EC approval. The broad informed consent must be obtained in the same way as those described in CIOMS 2016 guideline 9[4] – "Researchers have a duty to provide potential research participants with the information and the opportunity to give their free and informed consent to participate in research, or to decline to do so. Informed consent should be understood as a process, and participants have a right to withdraw at any point in the study without retribution". Some additional information that should be included in the informed consent form include descriptions of (1) the withdrawal process for the use of their DNA, (2) the collection process, (3) the storage time, (4) protective measures regarding the participants' privacy and confidentiality (linking of information or

[1] CIOMS 2016 Guideline 17: Research involving children and adolescents
[2] CIOMS 2016 Guideline 17: Research involving children and adolescents
[3] CIOMS 2016 Guideline 11: Collection, storage and use of biological materials and related data
[4] CIOMS 2016 Guideline 9: Individuals capable of giving informed consent

anonymization of data), (5) the destruction process of the remaining specimen, (6) the patent or ownership rights to information, and (7) the procedure for returning the results to the participants[5]. In this study, since the results may benefit the decision making of patients in choosing the second line treatment, the EC suggested disclosing the results to the patients per the desire of the patients.

[5] CIOMS 2016 Guideline 11: Collection, storage and use of biological materials and related data

Case Study 5: Storage of Blood Specimens in Biobank for Future Research

Collection of blood samples from cholangiocarcinoma patients for future research

The ethics committee was presented with a proposal to collect 10-ml of blood samples from cancer patients who are being treated at an oncology clinic for cholangiocarcinoma (CCA) in three Asian countries. A total of 350 patients (approximately 20 patients per site) with different stages of CCA will be recruited in this study. All the samples and associated clinical data will be coded and transported to country XX in Europe. Blood samples will be stored at the biobank at the National Cancer Center in country XX for future research on possible gene mutations to serve either as prognostic or predictive biomarkers. The generated information is expected to be used for patient risk stratification and appropriate therapy of CCA. At the time of submission for ethical clearance, the sponsor in country XX had not yet specifically planned for future research on the stored blood samples.

The researcher at each site will contact their CCA patients and request for a broad informed consent to collect blood samples and to use personal information such as details of the disease and history of treatment. Patients will be informed of the risks involved in drawing blood and the possible benefits to the future development of a treatment for CCA. Neither travel expenses nor compensation for any discomfort during blood drawing will be provided since the blood will be collected during treatment or regular follow-up visit. The researcher will receive USD 300 per case for the management of blood and data collection. The sponsor will be responsible for the expenses of the specimen and data transfer as well as for the management of biobank for future research. Material Transfer Agreement (MTA) will be signed with all institutes regarding the transport of the blood samples.

Challenges encountered by the ethics committee

1. The vulnerability of patients in the proposal
2. Determination of risk and benefit
3. The Justification for the use of broad consent
4. The consent process with regard to sponsorship, ownership and commercialization

Perspectives

The researcher proposed to collect blood samples from the cancer patients who are being treated at the oncology clinic. The Ethics Committee (EC) is concerned about the vulnerability of the patients as it is likely that the patients in this study have a dependent relationship with the researcher (treating

physician) and may have difficulty refusing the blood collection. This could result in invalid consent as it would compromise the voluntariness of the patients in the informed consent process. The EC suggested that recruitment of patients be done by a third party [1].

The EC considered the risks involved in blood collection as no more than minimal risk. However, the storage of blood specimens and the clinical data for future research involves the risks related to the maintenance of privacy and confidentiality. The patients are unlikely to receive any direct benefit from future research. In this proposal, the collection and storage of blood samples will be performed exclusively for future research, which requires explicit authorization from the patients. Since the precise purpose of the research is not known at the time of the blood collection, the EC reached a consensus that the broad informed consent can be considered as an acceptable procedure. However, the EC Chair emphasized that the broad informed consent is not the same as "blanket consent" that would allow unrestricted use of bio-specimens and data. While a broad informed consent allows the use of specimen for a wide range of future researches, there are certain provisions to allow patient/donors to have control over the use of their specimens and health data. These provisions should be defined in the informed consent form to be accepted and signed by the blood donors. It is suggested that sufficient relevant information about the nature of the study be specified to allow for a better decision-making process. The EC suggested that the informed consent form should include the elements recommended by the CIOMS 2016[2]: the purpose of the biobank, the conditions and duration of storage, the rules of access to the biobank, the safeguards to protect confidentiality and their limitations, the ways in which the patients can contact the biobank custodian and remain informed about future use, the rights of patients to decide about future use, refuse storage and to have blood sample destroyed, the foreseeable uses of the blood samples e.g. limited to basic or applied research or also for commercialized purposes, and the possibility of unsolicited findings and how they will be dealt with.

During the board discussion, the issue of sponsorship and fair benefit-sharing was raised. In this study, the researcher will receive USD 300 per case for the management of the blood and data collection, however, there is no payment for the participants. The EC suggested that the informed consent form should include disclosure of sponsorship and also a statement that the patient will not receive any payment. If the study foresees the use of blood samples for a commercialized purpose, the informed consent should include the statement on whether the patients will or will not share in the profit. The patients should be informed to what extent, if any, they can expect to receive compensation from future commercial use.

[1] CIOMS 2016 Guideline 9: Individuals capable of giving informed consent
[2] CIOMS 2016 Guideline 11: Collection, storage and use of biological materials and related data

The broad consent can be ethically acceptable under the following conditions: 1) the broad informed consent form has sufficient information for the decision-making process, 2) there is proper governance of the biobank, and 3) management of the biobank has a process of oversight and approval of future research activities. It is therefore crucial that the information on governance and management of the biobank at the National Cancer Center in country XX be submitted for EC approval[3] [4] .

[3] Grady et al. Broad Consent for research with biological samples: workshop conclusions. Am J bioeth. 2015;15(9):34-42

[4] CIOMS 2016 Guidelines 11: Collection, storage and use of biological materials and related data

Case Study 6: Collection and Use of Data from Routine Clinical Care

The correlation of patient characteristic and the outcome of rare neurological disease: a retrospective and prospective study

A retrospective study on the correlation of patient characteristic and the outcome of rare neurological disease was approved by the ethics committee (EC). A year later, the researcher submitted a protocol amendment to add a collection of prospective data from the medical records consisting of the evaluation of the disability index score, the cognitive impairment score, and outcome of rehabilitation. In the past 2 years, these routine tests have not been performed due to the shortage of personnel. The researcher proposed to collect data from patients' medical records and perform tests which are routine tests for a patient follow-up visit. This study will have no additional intervention, the patients will receive the standard clinical care and the data collected will be coded. The researcher has requested for a waiver of informed consent.

Challenge encountered by the ethics committee

1. Can a waiver of consent be approved, if not, what are the other options?
2. Would a broad consent procedure be a better option for this study?

Perspectives

With regard to the researcher's request for a waiver of informed consent, CIOMS 2016[1] recommended that the EC may approve a waiver of informed consent for a study under the following conditions: 1) the research would not be feasible or practicable to carry out without the waiver or modification; 2) the research has important social value; and 3) the research poses no more than minimal risks to participants.

The EC reviewed this case and recognized the research value of data routinely collected during medical care of rare medical diseases. This study may have important social value and may contribute new knowledge that allows a better understanding of the disease which may eventually lead to the development of a treatment of this rare neurological disease.

The EC determined the risk of this study to be minimal risk based on the following reasons: 1) the confidentiality of the collected data will be protected as identification data will be coded and 2) study will collect data from medical records and will perform the tests which are routinely performed in clinical practice for this disease.

[1] CIOMS 2016 Guidelines 10: Modifications and waivers of informed consent

However, the EC did not approve the waiver of consent as it is obvious to the committee that obtaining an informed consent from the patients in this study is both feasible and practical.

With regard to the study proposal to use the data from routine clinical care, an informed opt-out procedure must be used according to the CIOMS 2016 guideline 12[2]. The informed opt-out procedure honors the ethical principle of the right of the patient to object to the use of their data. The researcher may store and use the data from routine clinical care unless the patients explicitly object. However, the guideline also mentions that explicit informed consent (whether specific or broad informed consent) may be required under any of the following conditions: 1) the study is more than minimal risk; 2) the study uses controversial techniques; or 3) the study is conducted in contexts of heightened vulnerability. The EC determined that explicit informed consent is not required in this study and that informed opt-out procedure is adequate. This determination was based on the fact that this study involved no more than minimal risk, the tests used are routine medical tests for this disease, and the research is not conducted in the context of heightened vulnerability. The EC recommended that the researcher use informed opt-out procedure for this study, and required the researcher to demonstrate that the informed opt-out procedure that will be used complies with the following conditions: 1) patients must be aware of its existence; 2) sufficient information is provided; 3) patients need to be informed that they can withdraw their data; and 4) a genuine possibility to object has to be offered. The researcher is required to submit the proposed informed opt-out procedure for EC approval.

Broad informed consent is not required in this study as mentioned above. The EC determined that a procedure of informed opt-out is adequate for this study. However, if the data are collected and stored for future research with unspecified purpose at the time of data collection, broad informed consent procedure is recommended. Broad informed consent procedure is an explicit informed consent; therefore, informed consent must be obtained in the same way as described in CIOMS 2016: Guideline 9[3] – "Researchers have a duty to provide potential research participants with the information and the opportunity to give their free and informed consent to participate in research, or to decline to do so. Informed consent should be understood as a process, and participants have a right to withdraw at any point in the study without retribution". Furthermore, the ethical acceptability of broad informed consent relies on proper governance and management of the databank. The governance system to obtain authorization for the future use of data must be established in the institution that collected and stored the data.

[2] CIOMS 2016 Guideline 12: Collection, storage and use of data in health-related research
[3] CIOMS 2016 Guideline 9: Individuals capable of giving informed consent

Case Study 7: Online Questionnaire Survey

The assessment of the learning and working processes and the outcome of a practicum course

The Ethics Committee (EC) is presented with a proposal about a socio-behavioral study that will use an online questionnaire to assess the learning and working processes, and the outcome of a practicum course that the Company and the University plan to use as part of a new graduate business curriculum.

The researcher is an employee of the Company who is currently doing a Ph.D. in the institute and has obtained a list of student names, addresses, telephone numbers and e-mail addresses of those who are training or have been trained in the Company. The research tool is an online questionnaire from the Google Form link. The online questionnaires will be sent to undergraduate students who are current trainees or have been trainees in the Company.

Challenges encountered by the ethics committee

1. Should the protocol be reviewed by the EC or does it meet the exemption criteria?
2. What are the risks of participating in this study and how should these risks be managed?

Perspectives

This protocol is eligible for exemption under Category 1 since it is research conducted in an established or commonly accepted educational setting, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods (45 CFR 46.101).

Information about this study should be emailed along with the Google Form link to the email addresses of the students as a means to contact practicum students who may be interested to participate in the study. Logging in to the Google Form system by email to respond to the questionnaire should be avoided. Responses should be sent directly to the researcher without any identification details. Written consent can be waived as the act of actively responding to the questionnaire through the Google Form can already be considered as the participants giving implied consent.

Participation in this study may pose a risk for current students if they are identified as it may affect their current performance evaluation, thereby possibly impacting their future career. As such, the EC suggested that the researcher reconsider the inclusion criteria to recruit only those who have graduated from the practicum course within an appropriate time frame to ensure valid and reliable recall of their experiences.

Case Study 8: Stress Management among Minors

A randomized controlled study of a stress management program in junior high school student

The study proposal presented to the Ethics Committee (EC) was about the effects of a stress management program on stress levels of junior high school students in School 'A.' It aimed to compare the stress levels of students in an experimental group that undergoes a stress management program with a control group that is made to watch movies to de-stress. The researcher was a guidance teacher at this school.

Stress Scales developed by the Department of Mental Health will be used to evaluate the stress levels of students of School 'A'. The researcher will ask the School Director for permission to collect data and 450 students who are 13 – 15 years old in grades 7 – 9 will be asked to complete the Stress Scales to measure stress levels. The sampling will be done by the researcher by selecting 60 students who have moderate to high levels of stress and randomly assigning 30 of the selected students to the control group and 30 to the experimental group. This sample size determination was made in accordance with previous studies. The researcher will get consent from parents or guardians to allow the students to participate in the study. Students will be excluded if they have high levels of stress together with physical illness or medical history of mental illness.

In the research arm, the researcher will provide to the group a stress management program developed by the researcher based on literature review and comprising of guided imagery to enhance self-confidence, peer sharing, and art activities. In this program, group activities are arranged after school once a week for six weeks. In the control arm, six movies will be provided to the group to watch—one movie per week. After completing the program, the post-experiment evaluation of the student stress will be done by the researcher in week 10.

Challenges encountered by the ethics committee

1. Is it necessary to conduct the research in a group of junior high school students?
2. Do these participants belong to a vulnerable group? If yes, how does the researcher protect the participants?
3. What possible risks may emanate from this research? How does the researcher deal with these risks?
4. How should the informed consent process be conducted?

Perspectives

According to CIOMS 2016[1], it is necessary for this research to be conducted with junior high school students as the research question is a specific and essential problem among this group of students. This research may directly benefit the student participants if the interventions prove to be effective. It will generate useful knowledge and help to develop appropriate stress management programs for various grade levels of students.

There may be social risks involved as conducting activities among students identified to have moderate to high levels of stress may affect the reputation of the research participants. The EC suggested that the researcher adjust the methodology of data collection by conducting a stress survey among all the students of one grade. Randomization should be done at the class level and each class may be randomized to the intervention or control arm. After the survey, the stress level should be evaluated by the researcher to identify students who have moderate to high levels of stress, according to the prescribed criteria. Interventions will be conducted separately for each class and analyzed at the end of the six weeks. Assigning the intervention at the class level will reduce the risk of social stigma. In addition, the researcher needs to address how to protect the confidentiality of the research data.

Prolonged intervention may cause tiredness among students in the stress management program since this group needs to participate in six sessions after school hours. Therefore, the researcher should conduct and finish activities on time as well as provide a break time with snacks for participants since the activities are conducted in the evening. The EC requested that the researcher be properly trained and equipped with skills to ensure proper implementation of the program. Resource persons may be invited to assist during the conduct of the intervention. For the control arm, the 6 movies should be selected properly to ensure that they help the students relax and reduce stress. During an academic presentation or publication of results, the researcher should anonymize the school's name

The sample is comprised of students in grades 7 – 9 and aged less than 18 years, making them a vulnerable group. Although the respondents can make decisions for themselves to participate or refuse to participate, as minors, they are under the custody of their parents. Furthermore, they may not be able to refuse to participate since the researcher is a guidance teacher in the school where they study. The students may be coerced into participating in the study by their guidance teacher, parent, or guardian who may see some benefit in the students' participation in the study. The EC suggested that the research information may be given by the researcher, but obtaining actual informed consent should be conducted by a person who cannot coerce nor influence free decision making among the students. Consent should be obtained from the

[1] CIOMS 2016 Guideline 17: Research involving children and adolescents

parent/ guardian and assent from the student. Both consent and assent forms should be written in understandable language. The informed consent should not include phrases indicating that research participants have a moderate or high level of stress in the information sheet. It should be presented as research intended to develop a program to manage and reduce stress among students. Students with high stress levels should be referred to appropriate care.

Case Study 9: Alcohol Dependence and Domestic Violence

Correlation between alcohol dependence and violence within the family

Patients diagnosed with alcohol dependence who attended the Alcohol Treatment Center will be invited to participate in the study. The main objective is to identify the correlation between alcohol dependence and violence within the family. The patient and family members who are older than 12 years old will be interviewed. There are 74 questions consisting of general information about household members, acute health problems from alcohol, direct and indirect accidents caused by alcohol, injury, death, violent behavior, physical harm, family violence and crime, financial problems, the impact on others, and economic losses. The investigator is a social worker and will recruit subjects from the Center. The investigator will visit the houses of subjects and interview every family member. The duration of the interview is 60 minutes. The participants may withdraw at any time during the research procedure. The PI has applied for a waiver of consent document.

Challenges encountered by the ethics committee

1. What are the challenges and possible risks of this study?
2. How should risks be minimized?

Perspectives

This is an important study that deals with an important social problem. It will use the interview process to collect data focusing on the impact of alcoholism on domestic violence that may involve abusive behavior, physical and emotional abuse, as well as neglect of family members or intimate partners. Valid and reliable data could only be obtained if the interviewer is able to cover relevant information about alcoholism and its effect on domestic violence within the family.

The EC discussed the feasibility of visiting the houses of participants and interviewing family members. The psychological risks related to violation of privacy of participants and their family members are possible since breaches of confidentiality may cause embarrassment and result in social stigmatization. Some interview questions will make participants and their family members recall their domestic violence experiences that can trigger anxiety and depression.

The EC suggested that the study should only enroll alcoholic patients who are willing to undergo therapy and are therefore willing to answer the questions during the interview. Since information regarding family members' experience of domestic violence stemming from alcoholism is important to answer the research question, consent of family members should also be obtained prior to interviewing them. The informed consent form should state that research participants may refuse to answer questions that cause discomfort and that they

can withdraw or discontinue from the study anytime. While oral consent may be allowed for this study, the text of the consent form should still be reviewed by the EC. The confidentiality and privacy of the participants should be managed through a waiver of signature in the consent document[1], anonymized forms, coded records, and arrangement of a private interview location. The EC requested that a qualified person be available to provide psycho-social support to participants during the course of the study.

[1] CIOMS 2016 Guidelines 10: Modifications and waivers of informed consent

Case Study 10: Domestic Violence among Pregnant Women

A Qualitative Study of domestic violence among pregnant women: an in-depth interview

Domestic abuse is a critical problem affecting both the physical and mental health of pregnant women and children. Domestic violence is an issue that is not openly discussed because it sounds shameful and the pregnant women may be abused by a partner if she talks about it. This qualitative research aimed to explore abuse among pregnant women and how to deal with it.

The researcher is a social worker. Data will be collected through in-depth interview of at least eight pregnant women who are being treated at an antenatal clinic. The woman will be invited by the researcher for a 45 to 60-minute interview which will be conducted while she is waiting to see a doctor. There are four questions for in-depth interview which have been validated by specialists in qualitative research: 1) Have you heard about domestic abuse? How? 2) Have you ever experienced domestic abuse? How? 3) How does domestic abuse affect you and your child? 4) How would you deal with this problem if it happened to you?

Challenges encountered by the ethics committee

1. Should this research be approved?
2. What are the risks and benefits of research participation?
3. Is informed consent necessary? Should the husband's consent be required? How should informed consent be obtained?

Perspectives

The EC reviewed the rationale of this research and considered whether it is necessary to study pregnant women or whether the research questions can be satisfactorily answered by another group of women who are also victims of domestic violence. The EC agreed with the researcher that this research should be conducted in pregnant women as the context of the issues is quite different from other victims. However, the researcher should clearly define the research problem and knowledge gaps in this area.

The EC recommended that risks related to research participation should be assessed carefully and the following issues should be considered and addressed:

1. Further physical and mental abuse may result if the husbands of the participants get to know about the participation of their wives/ partners

2. Social risks and confidentiality breach may result from the informed consent process being done by the researcher at an antenatal clinic with other

pregnant women waiting to see a doctor. How does the researcher know which women are abused? Because abuse is perceived as a shameful issue, collecting data through interviews at a medical diagnostics unit may let other pregnant women know about the research topic that could potentially identify those who are victims of abuse

3. There may be emotional risks involved due to the sensitive questions and the researcher's lack of experience in conducting in qualitative research. How would the researcher handle the situation when a participant breaks down?

4. If a woman participating in the research has been abused, how will the researcher deal with that?

The EC emphasized that the informed consent process should be conducted in order to protect the participants from physical, mental, and social risks. It was suggested that researcher should ask for assistance from the health care workers in the antenatal clinic to help him identify potential participants who may be willing to join the study and that interviews should be conducted in a private room. Tape recordings must be kept confidential and names of participants must not be identified. Codes or 'aliases' must be used instead of real names for tape transcription, and original recordings must be anonymized or transcribed in case the respondents want them destroyed.

The EC required that the researcher have experience in conducting qualitative research, including having an advisor proficient in qualitative research, in case the researcher is a student. Moreover, the researcher should provide psycho-social support in case some participants break down. The participants should be given information about support mechanisms and rescue centers that are available in case they need some help.

In terms of benefits of research for participants and society as a whole, this research does not directly benefit the participants, but the research results can benefit this group of women and generate useful knowledge.

Oral consent may be more appropriate as written consent can identify research participants. In case written consent is required, the documents should be kept under lock and key. For this study, the husband's consent should not be required.

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