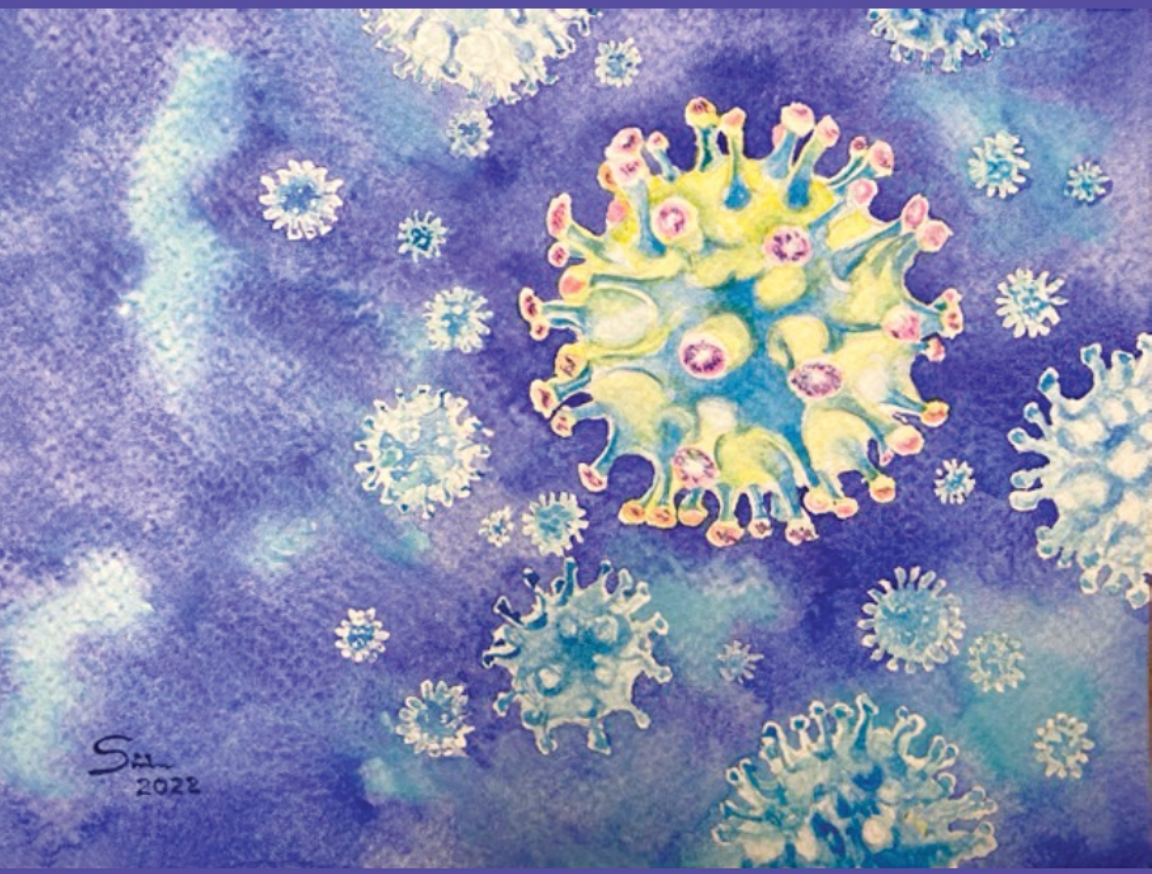
Perspectives on Ethical Review IV



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 IV:
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 fourth 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. COVID-19 epidemic has interrupted the production of the casebook series for 2 years. The situation is back to normal and the International FERCAP Conference is now back to being held face-to-face again, thus, the FERCAP re-initiated the production of a casebook for distribution to the Conference attendees. COVID-19 also interrupted the MFES GF training (now re-named as SIDCER FERCAP Global Fellowship - SFGF), thus, the MFES GF alumni together with the FERCAP secretariat have written this version of the casebook this year. The SFGF activity on casebook production as part of their training will resume next year in the fifth casebook.

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 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 by 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 the friendship we achieve when we collectively reflect on ethics.

Promoting human subject protection in health research underlies the objectives and work of FERCAP. Over the course of the past 22 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 diseases. 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 health 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's 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

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Case Study 1: A Double-blinded Randomized Controlled Trial in Neonates

Postnatal corticosteroid for bronchopulmonary dysplasia prevention in preterm infants

Background

Bronchopulmonary dysplasia (BPD) is one of the leading causes of death and morbidities accompanied by poor neurodevelopmental outcomes. Antenatal and postnatal inflammation plays a role in BPD development. The inflammation usually leads to abnormal pulmonary development presented by fibrosis and alveolar simplification. Based on this pathogenesis, postnatal corticosteroid (PNS) is used to prevent and manage BPD. Even though the anti-inflammatory properties were recognised to decrease the morbidity of BPD [1,2], a significant challenge in adrenal insufficiency and premature deaths is of concern.

The ethics committee (EC) was presented with a randomised, double-blind, placebo-controlled trial to determine the efficacy of early inhaled corticosteroid on the incidence and severity of BPD in very low birth weight (VLBW) neonates. The investigator aims to enrol 140 participants in this study. Inclusion criteria include preterm infants with gestational age less than 32 weeks and birth weight less than 1500 grams who need assisting invasive mechanical ventilation within 24 hours of life and require non-invasive ventilation when they are extubated.

A blocked randomised placebo-controlled trial at the ratio of 1:1 will be used. Seventy preterm infants will receive inhaled methylprednisolone at a dose of 250 micrograms per day, while the other 70 will receive a placebo. The allocated treatment will start immediately after birth and continue until these infants are either off the oxygen supplementation or reach 36 weeks of postmenstrual age. Primary outcomes include mortality, BPD and long-term neurodevelopmental outcome (blindness, deafness, cerebral palsy and significant neurosensory disability). Secondary outcomes are failure extubating, late rescue with a corticosteroid, need for home oxygen therapy and complications during primary hospitalisation (infection, hyperglycemia, hypertension, pulmonary air leak, patent ductus arteriosus, severe intraventricular haemorrhage, periventricular leukomalacia, necrotising enterocolitis, gastrointestinal bleeding, intestinal perforation and severe retinopathy of prematurity).

Points for Discussion

1. The scientific validity of the study
2. Ethical issues associated with this study
3. The informed consent process

Perspectives

According to a previous study [3], early postnatal corticosteroid administration demonstrated the benefit of BPD prevention and a decrease in mortality. However, adverse outcomes (e.g. hypertension and hyperglycemia) need to be closely monitored during admission.

The EC has concerns about the beneficence of early inhaled corticosteroids in VLBW infants due to the inconclusive evidence on the type and administration route of corticosteroids. The EC has concerns about the risks in these high mortality and morbidity participants. Risks associated with the study have to be appropriately minimised. The participants are a vulnerable group, and specific protections are needed.

Scientific validity

The EC evaluated that the double-blinded randomised placebo control study design is appropriate and that the use of a placebo is justified. However, there are several issues on scientific validity that require changes. The study proposed to start intervention immediately after birth. However, the death rates among preterm VLBW infants are potentially high during the first 24 hours of life, and it will be challenging to determine whether the cause of death is from corticosteroids or prematurity itself. The EC thus recommended that the intervention should start after the period of the first 24 hours of birth. Another concern about the study's validity is the evaluation of the long-term effects on the neurodevelopment at 34 weeks. The EC evaluated this period as too short and suggested that the evaluation of these long-term effects be extended to 18 months. Furthermore, the EC had concerns about the quality of the placebo and requested the investigator to submit the supporting documents for EC review.

Ethical validity

The EC found some ethical issues associated with the study that needed to be addressed. This study involves a vulnerable population and the EC determined that the study is greater than minimal risk. Specific protection must be provided to this group of participants. The potential risks must be minimised to the acceptable risk/benefit ratio, and the informed consent process must be appropriate.

In terms of risk, the EC suggested that the investigators enrol only preterm infants with a gestational age between 28-34 weeks to decrease the risk of death, morbidity and infections. Preterm infants with gestational age less than 28 weeks should receive the standard management for BPD prevention until clinical equipoise of corticosteroids prevention is established. Preterm infants being administered with NSAIDs should be excluded due to an increased risk of intestinal perforation.

Risk monitoring must be implemented and include, but not be limited to, the monitoring for PNS infections, hypothalamus-pituitary-adrenal (HPA) axis suppression as well as the risk of adrenal insufficiency when corticosteroid is rapidly stopped. Additionally, the provision of interim analysis should be considered as the study involves potentially high mortality and morbidity participants.

Informed consent process

As this study will be conducted in an urgent and critical situation, the EC had concerns about the undue influence or coercion of pregnant women or mothers of preterm infants to enrol their offspring in the study. The informed consent should be taken by a research team member who is a paediatrician with no dependent relationship with the parent of the neonates. The informed consent process could be conducted during the antenatal visit of mothers with a high risk of having a preterm infant. If informed consent was not obtained during an antenatal visit, the father may be in a better position than the mother to give the informed consent as the mother would be under stress and worried about the infants. Alternatively, both the mother and father can discuss and make decisions together.

The consent form should be comprehensive enough to explain the risks, possible adverse events, potential benefits, the possibility of being in the placebo group, corresponding management and a vital clinical monitoring plan, including an extended follow-up period and alternative preventions of BPD if the guardian decides not to enrol their infant in the study.

Reference

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2. Filippone M, Nardo D, Bonadies L, Salvadori S, Baraldi E. Update on Postnatal Corticosteroids to Prevent or Treat Bronchopulmonary Dysplasia. Am J Perinatol. 2019 Jul;36(S 02):S58-S62.
3. Doyle LW, Cheong JL, Hay S, Manley BJ, Halliday HL. Early (< 8 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants. Cochrane Database Syst Rev. 2021 Oct 21;10(10):CD001146.

Case Study 2: Social and Behavioural Research

Livelihood strategies of elderly gay men amid the COVID-19 pandemic

Background

Elderly gay men (EGM) in the Northeast are among those who face internalised homophobia and ageism. Most of the people in this group are single (not married or have no partner) with unstable careers, such as small business owners or wage-earners, and receive a small amount of elderly pension from the government. Although many of these gay men suffer from physical and mental health problems, they accept their destiny and can manage their daily lives and bear the economic difficulties and health constraints. However, the spread of COVID-19 for over two years has aggravated their fate. For this reason, the researcher aimed to study the epidemic's effects on the EGM in an urban area and their survival strategies to cope with the situation. This research uses a phenomenological qualitative research methodology. The data-collection techniques include in-depth interviews as well as observations of the daily life of research participants and non-participants aged 60 and over. Key informants are openly and undisclosed EGM who live in a city or the suburbs. The informants will be purposively selected, and some will be derived from the snowball sampling technique.

Points for Discussion

1. Vulnerability of research participants
2. Recruitment of research participants
3. Risks and potential harms
4. Privacy and confidentiality
5. Informed consent process

Perspectives

The study design is appropriate for the proposed research topic. However, the potential participants are vulnerable [1] due to multiple factors: age group, health, gender, and economic status. This group of people could be easily influenced or induced to participate in the research. This means they “may have an increased likelihood of being wronged or of incurring additional harm” [2] and may be more susceptible to deception or confidentiality breaches. Thus, specific protection is needed [1].

Recruitment of research participants

The researcher should have appropriate means of contacting the prospective participants to avoid or minimise the invasion of their privacy. In using a snowball sampling technique, there must be a gatekeeper to contact the target group. The researcher can approach the participants and provide details

of the research only when the potential participants agree to meet the researcher.

Risks and potential harms

The ethics committee identified depression, breach of confidentiality, physical harm from the length of an in-depth interview and economic risk as potential risks of this study.

To minimise the risk of depression, the researcher must be a qualified in-depth interviewer, and the evidence of such qualification must be submitted to the ethics committee for review. The researcher must be aware of questions that may make informants, who are affected by the COVID-19 pandemic situation and restrictions imposed by the state, uncomfortable or depressed. In addition, the researcher must make provisions for additional help from a psychologist to support the participants if necessary.

To address the issues of breaches of confidentiality, pseudonyms or codes should be used to substitute the real names of research participants. However, using a pseudonym or code for the research participants who already disclosed their gender identity could make them feel more mistreated or marginalised. The researcher can identify the real names of study participants only if they have provided complete details of their real names and provided their consent. Careful measures for privacy must be implemented during the interview and observation for research participants who have not yet disclosed their sexual orientation. The researchers must ensure the security of confidentiality measures in all cases. For example, keeping both paper and digital data in a safe place, restricting who has access to research data and encrypting data files stored in a server or space provided by a third party.

To address the issue of physical harm, since this study has no direct benefit to participants, the researcher should exclude potential participants with limited capacity to answer questions, such as persons with dementia or other sicknesses that would make participants uncomfortable during the in-depth interview. The researchers may set inclusion criteria to healthy EGM or exclusion criteria for those who will be at higher risk from the length of the in-depth interview. In addition, the in-depth interview time should be designed to suit the elderly. There should be breaks at intervals to ensure the participants' comfort throughout the interview.

To address the economic risk, the researcher must select an appropriate time for the observation that will not interfere with the EGM's work, leisure, or activities unless permitted by the participants.

Informed consent process

Regarding the informed consent process, the ethics committee may waive written consent to minimise the risks that may arise from a breach of

confidentiality [3]. The target research participants can provide their verbal consent to participate in the study and the place of consent must be private. The date, time, and place of verbal consent need to be recorded in a document, paper or electronic format, which will be stored in a safe place.

References

1. CIOMS 2016 guidelines 14
2. Declaration of Helsinki 2013
3. 45 CFR § 46.117 (c) (1) (i)

Case Study 3: Anthropological Research

Wounded history of an internally displaced ethnic group

Background

This research aims to study (1) the history of the forceful eviction of an ethnic group from their homeland and (2) the group's negotiations with the state for a return to their motherland where they were born, raised and have lived for generations. A researcher, who is a government official and graduate student, plans to stay immersed in the research area for a long time. The researcher plans to use an ethnographic qualitative research methodology which will involve the collection of data through participant observation and in-depth interviews of key informants. The target research participants are members of an ethnic group that used to inhabit one of the country's fertile forests. They were recently forced by the state to leave the area as their home was designated as a national park. Some of these people have no citizenship because they have not been surveyed and registered by the relevant authorities. Although most of them speak Thai, only a small number of the group can read and write Thai.

Points for Discussion

1. Sensitivity of research issue and vulnerability of research participants
2. Recruitment of research participants
3. Risks and potential harms
4. Privacy and confidentiality
5. Informed consent process

Perspectives

This research is scientifically sound, and it is essential that the researcher lives in the research area long enough to gain insights and trust from the native people. However, some ethical considerations involving the research methodology need to be addressed. First and foremost, this research examines a very sensitive issue, namely, the conflict between ethnic groups and the state over a natural resource. There are also several interest groups involved, both government officials and NGOs. Secondly, the target group of this research is considered a vulnerable group as they are in a difficult situation. They were forced to leave their homeland where they were born and grew up. Most of them cannot read or write Thai and some do not have Thai citizenship.

Recruitment of research participants

Before recruiting research participants, the researcher must determine the level of trust at intervals to ensure adequate relationships and trust. Nevertheless, the researcher must be aware that the trust may lead to the hope that participating in the research may help the ethnic group in getting the land

back. The researcher must clearly emphasise the study's objective during the informed consent process to prevent such hope.

Risks and potential harms

The ethics committee identified individual depression, invasion of privacy, and breach of confidentiality as potential risks of this study.

During the in-depth interviews, some of the questions could stimulate the recall of painful experiences from being forced to leave their homeland and having difficult experiences in adapting to the new designated residential area. It is required that the researcher has extensive experience in in-depth interviews and that the evidence of such expertise must be provided to the ethics committee for review. In addition, the researcher should make provision for additional help from a psychologist to support the participants if necessary.

The state may review the participation of community members. It is essential that the researcher avoid using the real names of participants and use pseudonyms or codes instead. In addition, the ethics committee requests the researcher to avoid taking any photography or video recording as it does not add any value to the data analysis but creates a risk to participants. The state may interpret the participation of individuals as opposing the state forest protection policy and may negatively affect the whole community.

Informed consent process

The research involves sensitive issues and the participants in this research are considered vulnerable as they are in conflict and difficult situations. Consultation with and obtaining the agreement of the local community leader on the proposed research prior to obtaining individual informed consent is a good research practice to ensure the relevance and acceptability of the proposed research to the affected community [1]. Verbal informed consent is appropriate for this research to minimise the risk of breach of confidentiality [2]. The recruited research participants should be asked to express their verbal consent only after they have been given the details of the research, provided an opportunity to ask questions and given enough time to decide to participate in the research. The researchers must document the date, time and place where the recruited participants gave their verbal consent. In addition, an impartial witness is required for participants who cannot read Thai.

References

1. CIOMS 2016
2. 45 CFR 46.117c (1)(i)

Case Study 4: Children with Reading Problems in an Orphanage

A learning program to address reading problems in children with mild intellectual disability in an orphanage

Background

Intellectual disability is defined as neurodevelopmental disorders that begin in childhood and are characterised by intellectual difficulties as well as difficulties in conceptualisation, socialisation and daily life [1]. Intellectual disability results in delayed linguistic ability.

A group of researchers created a computer-based learning program to enhance the reading ability of children with mild intellectual disability presenting with reading problems. The process will begin with a read-along word-by-word on a computer. Then the children will play a game generated by the computer program. They will get a score if they can read the words correctly. The objective of this study was to explore the effectiveness of this program in improving the reading ability of mildly intellectually disabled children with reading problems. The researcher plans to recruit 50 Thai children, aged 8-12 years old, who are mildly intellectually disabled (IQ 50-69) with reading problems, from an orphanage. Reading problems will be diagnosed by standard caregiver-reported questionnaires. The teacher will train the participants to read using the computer program. The teacher will stop or withdraw the participants if child discomfort is observed. The effectiveness of the program will be evaluated by pre and post-intervention questionnaires.

The researcher will contact the head of the orphanage and provide 10,000 Baht for administrative costs. The teacher will screen children's eligibility and obtain assent from the children.

Points for Discussion

1. Justification for conducting the study in institutionalised mildly intellectually disabled children with reading problems
2. Identify risk and benefit
3. What is the proper consent process?

Perspectives

The ethics committee (EC) evaluated the potential participants of this study as very vulnerable and determined that extra protection must be provided. The EC arranged a special meeting with a paediatrician, who has expertise in child development, and a linguistic expert to thoroughly evaluate the intervention program as well as the risks and benefits. An officer working at the orphanage was also consulted to reflect the community's point of view.

The EC decided that it is justified to do the study on children with reading problems as there is a potential direct benefit to this population. The computer program is designed specifically for mentally challenged children with reading difficulty. However, the researcher must exclude children with secondary causes of reading problems, e.g., vision disorder, mental retardation, autism, poor motivation and systemic diseases, as this would confound the interpretation of the results. The EC asked researchers to consider excluding low IQ participants as this would affect the outcomes.

Carrying out the study in orphanages is reasonable as there is a high frequency of reading problems in institutionalised children. Although the computer program has a potential direct benefit to participants, the EC considered this research to be more than minimal risk. The research procedures may pose a risk to the children as they may become frustrated, ashamed or depressed if they cannot read the words from the computer program. To minimise the risk, the duration of the computer program should not be too long with the appropriate frequency of intervention. The teachers must be trained to use this program appropriately and evaluate the children's reactions during the intervention. The teachers should stop promptly or withdraw the participant if a child becomes frustrated and unwilling to participate. It is essential to ensure that the teachers are not influenced by incentives or coerced by the head of the institution to complete this study.

The researchers should obtain consent from the guardian or proxy, e.g. caregiver, followed by assent from the children. However, as most orphans do not have a guardian, a nursemaid may be eligible to consent. In this study, the teacher or the head of the institution may not be appropriate to give consent for the participants as there may be a conflict of interest from receiving 10,000 Baht for research administration. The consent process in the orphanage must be aligned with local regulations and performed before the children are approached.

Along with the consent of adults, the children's willingness is evidenced by assent. The informed assent can be in verbal, picture-based or short VDO format representing the study [2]. Generally, it is acceptable if the child says “yes” or expresses body language.

Note

The Diagnostic and Statistical Manual of Mental Disorders, 5th edition, defines intellectual disabilities (ID) as neurodevelopmental disorders that begin in childhood and are characterised by intellectual difficulties and difficulties in conceptual, social, and practical areas of living. The DSM-5 diagnosis of ID requires the satisfaction of three criteria:

1. Deficits in intellectual functioning—“reasoning, problem-solving, planning, abstract thinking, judgment, academic learning, and learning from

experience”—confirmed by clinical evaluation and individualised standard IQ testing (APA, 2013, p. 33);
2. Deficits in adaptive functioning that significantly hamper conforming to developmental and sociocultural standards for the individual's independence and ability to meet their social responsibility; and
3. The onset of these deficits during childhood.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013 5th edition.
2. Informed Consent Guidelines re Minors (including orphans and vulnerable children (OVC)) and Parental Substitutes. (Accessed 30 December, 2021, at http://www.hsrc.ac.za/uploads/pageContent/5498/Guidelines%20for%20research%20with%20minors%202012.pdf.)

Case Study 5: Advanced Ovarian Cancer

Phase II study of two targeted as neoadjuvant therapy in advanced-stage ovarian cancer patients

Background

The ethics committee received an application from an oncologist who is well-known in the field of chemotherapy for ovarian cancer. The primary standard treatment of ovarian cancer is surgery which may be followed by chemotherapy (CMT) depending on the stages of the cancer. When the tumour mass is inoperable, the treatment of choice is neoadjuvant chemotherapy before delayed surgery and followed by CMT. Standard CMT is a platinum drug, which can be used as a single or combined regimen.

The investigator proposed a phase II study of two targeted agents (A and B) as neoadjuvant therapy in advanced-stage ovarian cancer patients whose tumour masses were inoperable. Both targeted agents were effective in the previous phase II trials as a single agent in recurrent ovarian cancer patients who failed from platinum-based chemotherapy (P-CMT). The investigator proposed to use either of the two agents for three cycles, followed by surgery and further P-CMT. If there is no response or surgery is still not optimal after three cycles, the patients will receive only P-CMT.

The study's primary objective was to compare response rates from the targeted agents. Overall survival (OS) of patients from the two groups, measured from the date of enrolment before targeted agent treatment, will be assessed as a secondary objective. The study will involve procedures normally performed in clinical practice for advanced-stage ovarian cancer. However, there will be more frequent safety laboratory monitoring.

The principal investigator (PI) declared a conflict of interest that he is a shareholder of one of the investigated agents – Agent A. He thus proposed that his junior colleagues, who are the primary physicians and have no dependent relationship with the PI (and not study team members), provide counselling and obtain informed consent from every advanced ovarian cancer patient for the study. The pharmaceutical company will provide the investigated agents at no cost to all research participants.

However, the expenses for surgery, any treatment thereafter, and any cost incurred from the side effects of treatment will be reimbursed from the patients' health coverage. No compensation will be provided because the research funding was limited.

Points of discussion

1. Appropriateness of the study design
2. Outcome measurement

3. Vulnerability of the participants
4. Cost and compensation coverage
5. Conflict of interest of PI

Perspectives

The efficacy data of the two targeted agents in a recurrent setting cannot justify the use of these agents as a single agent in the neoadjuvant setting. Even with the standard P-CMT being planned as an adjuvant treatment after surgery or as salvage therapy when there are no responses from the neoadjuvant treatment, the chance of cure is expected to be lower than standard therapy [1]. To address the issue, the investigational targeted agents should be given together with P-CMT in the primary neoadjuvant setting. It is recommended that the study design for primary neoadjuvant treatment be a randomised controlled trial of three arms, consisting of targeted agent A plus P-CMT, targeted agent B plus P-CMT, and P-CMT alone as a control.

Regarding the outcome measure, as approximately 30-40% of advanced ovarian cancer fail to react to primary treatment and will either progress or reoccur [2], second or further-line chemotherapy would commonly be given. The overall survival (as proposed) is not a reliable measure of the efficacy of investigational drugs (targeted agents) as there would be variable effects from the second or further-line chemotherapy and other factors. It is recommended that, aside from the response rate, progression-free survival is used as an outcome measure by measuring from the starting date of the targeted agent to the date when diseases progress.

The participants for this study are considered vulnerable due to the nature of their illnesses (inoperable advanced cancer). The patients are in an uncertain situation and may welcome any option that is offered. However, it is justified to include this type of patient in this study as there is a potential direct benefit and the study cannot be done on a less vulnerable subject. Nevertheless, specific protection must be provided. In this case, the participants must be free from coercion or undue influence. The primary physicians with no dependent relationship with the PI or the study team can provide counselling on the natural course of the disease and possible treatment options. It is recommended that the members of the study team (not the PI), who are experts in the field and have no dependent relationship with the patients, provide research information and obtain informed consent from the potential participants. The process of obtaining informed consent must be carefully performed, and the investigators responsible for obtaining informed consent must spend sufficient time discussing the information with the potential participants to ensure their comprehension. An ample amount of time should be given for the participants to make a decision. The informed consent must include the disclosure of the PI's COI, the statement that the cost of surgery and any standard treatments will

be reimbursed from the patient's health coverage and the alternative treatment if the patient chooses not to participate in this study.

The ethics committee also recommended that the PI be responsible for compensating for adverse events from the investigational agents.

To address the issue of conflict of interest of the PI, it is recommended that the PI limits his involvement to the study coordinator role and not be directly involved with the conduct of the study, including the randomisation, recruitment, assessment of the patients and data analysis.

Reference

1. Bookman MA. Optimal primary therapy of ovarian cancer. Ann Oncol 2016; 27 (Suppl 1): i.58-i62.
2. Coleman R, Monk B, Sood A, et al. Latest research and treatment of advanced-stage epithelial ovarian cancer. Nat Rev Clin Oncol 2013;10: 211–24.

Case Study 6: Parenting Styles and Protective Factors for Self-Harm Behaviours Among Young Persons Involved with Cyberbullying During the COVID-19 Pandemic

A mental health study on parenting styles and protective factors for self-harm behaviours among young persons involved with cyberbullying during the COVID-19 pandemic

Background

While numerous studies have been conducted on risk factors for self-harm behaviours, fewer research concerns protective factors. As such, a research group of online guidance counsellors proposed to carry out a study on parenting styles and protective factors against self-harm behaviours among youths aged 18-24 years old, during the COVID-19 pandemic. Although cyberbullying associated with self-harm behaviours during the COVID-19 pandemic is prevalent among those aged 15-24 years old, this research will exclude young persons aged 15-17 years old so as not to involve their parents, which can only complicate this study given the topic of parenting styles.

To gather data for this study, the online guidance counsellors will conduct online interviews with cameras on their patients who have experienced cyberbullying during the COVID-19 pandemic. The research group will ask the participants questions about their: 1) views on and experiences with cyberbullying; 2) thoughts of and/or experiences with self-harm; and 3) ideas on and experiences with authoritarian, authoritative, permissive or uninvolved parenting style. The questions were mainly adapted from an anonymised self-administered questionnaire in google form previously developed by the same research group.

The online guidance counsellors will obtain informed consent from their patients after their regular consultations. The participants will be notified that refusal to take part in this study will not affect their online guidance counsellor's service to them. Informed consent will be obtained remotely, and the participants will use electronic signatures.

The results of this research will serve as a springboard for developing an online parental engagement program that hopes to enhance protective factors against self-harm behaviours for the participants, in particular, and among other youths, in general.

Points for Discussion

1. Scientific validity
2. Ethical validity
3. Informed consent process

Perspectives

Scientific validity

It is not enough to say that the involvement of parents will complicate this study. A good scientific reason [1] should be provided to justify the exclusion of young persons aged 15-17 years old, who require parental permission. Since youths aged 15-24 years old are susceptible to cyberbullying related to self-harm behaviours during the COVID-19 pandemic, those aged 15-17 years old should be included in this research.

The preference for an online interview instead of the previously developed anonymised self-administered questionnaire in google form should also be explained and rationalised since both research methods will likely provide similar information. The questionnaire in google form can simply be revised to meet the needs of this study.

Ethical validity

All the patients are vulnerable because of their hierarchical relationship [2] with their online guidance counsellors. While young persons aged 15-17 years old have a second layer of vulnerability because of their age—being minors under the age of majority, they face higher risks than those aged 18-24 years old—the prospects for potential individual and societal benefits [3] are generally the same for the entire age group of 15-24 years old.

Regardless of whether an online interview or a questionnaire in google form is used, there are psychological risks linked to sensitive questions that may trigger anxiety and other strong emotional reactions. There should be an explicit trigger warning. Emergency medical and psycho-social support should also be on standby to address such reactions. The risk of breach of confidentiality is higher with an online interview than with a Google form questionnaire since the latter is anonymised. There are social risks associated with breaches of confidentiality. Specifically, social stigma is related to cyberbullying and self-harm behaviours in youths [4].

Informed consent process

Those aged 15-17 years old should give assent. Parental permission may be waived since parental knowledge of parenting styles may place the vulnerable participants at risk of questioning, intimidation or even physical harm by their parents. In this case, special protections for vulnerable participants should include the involvement of independent adolescent advocates aside from the previously mentioned emergency medical and psycho-social support [5].

Online guidance counsellors should not be directly involved in recruiting their patients and obtaining their informed consent to avoid possible coercion, intimidation, or undue influence or inducement. If the questionnaire in google

form is employed, all these will be avoided, especially if consent or assent by action is utilised.

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Case Study 7: Quality of Hospital Services During the COVID-19 Pandemic

A qualitative health social science study on the effectiveness, safety and patient-centeredness of hospital services during a public health emergency

Background

An experienced public health researcher proposed to conduct a study on the quality of healthcare services provided by a government provincial hospital during the COVID-19 pandemic. The researcher will employ a healthcare quality framework that focuses on the effectiveness, safety and patient-centeredness of hospital services during the COVID-19 pandemic. For this study, the researcher will use qualitative research methods such as focus group discussion (FGD) and questionnaire survey.

The researcher plans to conduct FGDs with selected healthcare providers working at the hospital. Each group will be diverse with at least two administrators, two doctors and two nurses as participants. The researcher will ask for the assistance of the Hospital Director in identifying the potential administrators who can join the FGDs. For the doctors and nurses, the researcher will seek the help of the doctors' association and nurses' union in naming the potential participants.

With the help of the nurses, the researcher will identify the COVID-19 patients who are about to be discharged from the hospital. Once identified, the researcher will approach these patients and ask them if they are willing to answer an anonymised questionnaire survey about the quality of hospital services.

The researcher will obtain informed consent from all the participants—administrators, doctors, nurses and patients. Informed consent will be obtained on the hospital premises during the researcher's hospital visits.

The study results will be submitted to the Ministry of Health and shared with the public to help shape policies and programs on health care services during public health emergencies.

Points for Discussion

1. Scientific validity
2. Ethical validity
3. Informed consent process

Perspectives

Scientific validity

While FGD is an effective research method for generating diverse ideas and multiple perspectives in the context of group interaction, it is not recommended for tackling sensitive topics because of its susceptibility to bias [1] that may lead participants to be influenced and/or intimidated by the other participants. In FGDs, there is always the danger of groupthink which discourages individual creativity and responsibility. Some participants may also become timid due to the presence of other participants who are in a higher position of power. In this case, the nurses and even the doctors may be unable to freely share their views out of fear of retaliation from the administrators. In this context, using key informant in-depth interviews may be a better option than FGD, as the obtained information is likely to be more reliable.

Ethical validity

For FGDs, there is the risk of breach of confidentiality [2] since the participants could share the responses with others who are not part of the FGD. Asking the participants to sign a confidentiality agreement is an option to minimise this risk, but, as discussed earlier, a change of qualitative research method from FGD to key informant interview is a desirable option not only for scientific reasons but also for ethical reasons. There are social risks associated with a breach of confidentiality. FGD participants' career advancement or employment may be jeopardised due to possible retaliation by the hospital for their negative responses. For the questionnaire survey, since it is anonymised, there is less risk of a breach of confidentiality. However, all personal identifiers should be removed as per national laws. On the other hand, questionnaire survey participants may be denied future healthcare services because of their negative responses. All these social risks can be avoided by ensuring that confidentiality is protected in the conduct of the appropriate qualitative research method.

The potential improvement of healthcare services during public health emergencies is the primary benefit of this study. To maximise favourable outcomes, training can be provided to administrators, doctors and nurses on how to provide effective, safe and patient-centred hospital services based on the results of this study.

Administrators, doctors, nurses and patients — as dependent participants — are vulnerable because their willingness to volunteer in this study may be unduly influenced by the expectation of a retaliatory response from the authorities in case of refusal to participate.

Informed consent process

Measures should be in place to prevent possible coercion, intimidation, or undue influence or inducement by the Hospital Director, doctors' association, nurses' union and patient's nurse due to their hierarchical relationship[3]. One strategy to minimise potential coercion, intimidation, or undue influence or inducement is through the use of advertisements or general announcements. The Hospital Director, doctors' association, nurses' union and patient's nurse can help disseminate the advertisements or general announcements, but they should not be directly involved in recruiting the participants. In this setup, the researcher will only be approached by those who have preliminarily agreed to participate.

Appropriate informed consent that includes items on voluntariness should be properly obtained. In line with privacy and confidentiality protection, the researcher should only approach patients who have preliminarily agreed to answer the anonymised questionnaire survey about the quality of hospital services. The privacy of the hospital premises where informed consent will be taken should be ensured. Informed consent should be obtained at a time that is convenient for the participants. This is particularly important to consider for COVID-19 patients who are about to be discharged from the hospital.

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Case Study 8: Conducting Research on Stimulant-using MSM

A qualitative and longitudinal research

Background

HIV transmission is escalating among men having sex with men (MSM) who use amphetamine-type stimulants (ATS) in the sexual context. Since the 1980s, the country has engaged in the so-called "war on drugs" that has resulted in harsh punishment for the possession of small amounts of drugs. ATS has become one of the most popular drugs used by MSM to enhance sexual pleasure. Facilitated by socio-sexual networking apps, ATS has been increasingly normalised and widespread among MSM. Conducting research in this population is challenging because of the double stigma and criminalisation of homosexuality and drug use.

Social science researchers propose to conduct a qualitative and longitudinal research with this hidden population affiliated with the Embrace Us, an NGO support group for MSM. They propose to use third-party apps to maintain anonymity when communicating with the target population. However, initial feedback from research participants revealed suspicions that the study could be an entrapment by law enforcers as MSM and drug use are culturally unaccepted.

Points for Discussion

1. Recruitment of participants
2. Can the cognitive ability of drug user participants be determined during an online informed consent process?
3. Should participants remain anonymous to the researcher?
4. What are the possible benefits of this study to the participants?

Perspectives

Maintaining anonymity is very important for participants to join this study. The assistance of the MSM NGO is essential for the researchers to ensure that recruitment is being done with the target population. Recruitment can be done by the NGO who can invite participants that meet the study inclusion criteria. The social science investigator does not need to personally see and identify the participants provided the NGO guarantees the adherence to the inclusion/ exclusion criteria. It is also the responsibility of the NGO to check that the participants are lucid during the informed consent process and interview. The interview may also be done by a member of the NGO whom the researcher has trained to guarantee anonymity. What is important is to be able to gather valid and reliable data from the target population that comprises a vulnerable group.

The minimum benefit of this study is a referral to care if the NGO is not yet doing that. The social scientist can also provide counselling or other behaviourally-based interventions to address drug addiction cases.

Case Study 9: Covid Vaccine among Participants with Co-morbidities

A global multicenter, randomised, double-blind, placebo-controlled, parallel-group phase III clinical study

Background

The investigator proposed to do a global multicenter, randomised, double-blind, placebo-controlled, parallel-group phase III clinical study. Subjects aged 18 years and older will be enrolled in this study to evaluate the efficacy, safety and immunogenicity of recombinant protein vaccine.

After determining eligibility (adult in stable medical condition) to be in the study, the subject will be assigned to receive either the study vaccine or a placebo. The subjects will need to come to the site for screening and the first dose of the vaccine, if eligible, the second dose of the vaccine, and 12 months after receiving the second dose. There will be a subgroup whose blood will be analysed to detect serum SARS-CoV-2 RBD protein-binding antibody levels and live virus-neutralizing antibody levels, which will require three additional visits to the site for blood sample collection. Subjects will receive US$50 per visit for travel costs to the site and food.

Note: This study will be implemented at a time when this vaccine has been granted Emergency Use Authorization (EUA) by the regulatory authorities.

Points for Discussion

1. Is it justified to do this clinical trial when EUA has been granted to the study vaccine?
2. Is the use of a placebo justified when a mass vaccination roll-out is already underway?
3. Is the use of a placebo justified on a vulnerable target population with co-morbidities and stable health conditions as determined by the principal investigator?

Perspectives

US FDA defines emergency use authorisation as a ‘mechanism to facilitate the availability and use of medical countermeasures, including vaccines during a public health emergency.’ FDA may allow the use of unapproved medical products when certain statutory criteria have been met, including the lack of available alternatives. Clinical trials may still be done even if EUA has been granted to a medicinal product to finetune efficacy data related to a particular population such as those with co-morbidities.

The use of a placebo needs to be justified considering that one arm in the clinical trial is not receiving the EUA vaccine being rolled out to the general

population. The main ethical issue to be determined is the presence or absence of clinical equipoise related to the efficacy of the vaccine to specific co-morbidities. Clinical equipoise refers to the state of uncertainty on whether a specific intervention (a Covid vaccine) is better than nothing to prevent Covid among groups with different co-morbidities.

This study will also identify the adverse events specific to existing co-morbidities of the participants. A literature review should be done to determine existing literature on whether this type of vaccine is contraindicated to some health conditions to enable an in-depth risk assessment. The exclusion criteria should be examined to include all contraindications of the intervention vaccine. The inclusion criteria should cover co-morbidities related to the absence of evidence on the effect of the vaccine on specific health conditions.

Case Study 10: Association Between Genetic Variants & Risk Factors for Bipolar Disorder: A Nationwide-Population Based Study

A genomic and psychiatric study on the link between single nucleotide polymorphisms and risk factors for bipolar disorder

Background

Several studies have shown that genetic factors account for most of the risk factors for bipolar disorder [1], but particular genetic variants are still generally undiscovered. Recent genome-wide association studies (GWAS) reported the link between single nucleotide polymorphisms (SNPs) and risk factors for bipolar disorder in samples of European descent [2]. However, these studies haven't been replicated in a large nationwide population of Asian lineage. Given this, a research group composed of three geneticists and two psychiatrists proposed to conduct a cohort study on three SNPs (i.e., rs140504, rs131690 and rs131702 in the breakpoint cluster region [BCR] gene) genotyped from 1,000 clinically diagnosed bipolar disorder patients and 1,000 healthy regular check-up patients without any personal or family history of neuropsychiatric condition to investigate the possible association between genetic variants and risk factors for bipolar disorder.

The researcher will collect 5 ml of blood from participants in order to extract genomic DNA. Genotype frequencies and Hardy-Weinberg equilibrium will be calculated by SNPStats. No genomic DNA results will be provided to individual participants. In compliance with international ethical guidelines [3], the research group will publicly release all sequence data to enable immediate international research use of such data.

Informed consent will be obtained from all participants. The participant information sheet (PIS)/informed consent form (ICF) will contain provisions on the possible future use of the collected and stored genomic DNA. A genome centre will be established to manage the collection, storage and future use of the genomic DNA.

Points for Discussion

1. Scientific validity
2. Ethical validity
3. Informed consent process

Perspectives

Scientific validity

In this prospective study, the researcher proposed to do a cohort study but the study design described was that of a case-control study where the two groups of the population are clearly defined at the start as one group with the

presence of bipolar and one without bipolar disorder. The investigator will measure three SNPs and other risk factors that have been reported as associated with bipolar disorder. The presence and absence of three SNPs and the identified risk factors will be compared.

Sample size (1,000 clinically diagnosed bipolar disorder patients and 1,000 healthy regular check-up patients) justification should be provided. The sample size of the cases and the controls should be determined by proper power calculation based on the allele frequency of the minor allele of the genetic variants. For this research, the inclusion criteria in terms of case definition should be more stringent than the clinical case description. It is best to define exclusion criteria as well. The cases and controls will also have to be matched for age, sex, ethnicity and other confounding factors. Access to potential participant information and the recruitment process should also be clearly laid out.

Ethical validity

This research stated that no genomic DNA results would be given to individual participants. This may be justified because the findings of this case-control disease association study will most likely not be useful for individual participants. However, in rare instances, there may be findings that the research group should provide to individual participants for ethical and moral (but not necessarily legal) reasons [4]. There is an evolving consensus that at least some findings must be returned to individual participants if requested. The general guiding principle for providing genomic DNA results to individual participants is that the results must have analytical validity and clinical significance as well as be actionable [5]. This means that genomic information for immediate clinical use and life-saving genomic information related to a significant health problem must be offered for disclosure, whereas genomic information of uncertain analytical validity or clinical significance would not qualify for communication to individual participants [5].

Regarding data sharing with the public release of all sequence data, it is essential to note that unrestricted data sharing has been challenged because of the privacy risks linked to public access to genomic information [6]. The research group must respect the privacy of individual participants. As appropriate, data use agreements must be employed, privacy protections beyond de-identification and data security must be observed, and an independent panel that includes members of the public to review data-sharing requests must be appointed [5].

All clinically diagnosed bipolar disorder patients are vulnerable. There is another layer of vulnerability if the patients are patients of the psychiatrists who are part of the research group. Specific protections must be in place to safeguard these participants' rights, safety, and welfare [7].

Informed consent process

Clinically diagnosed bipolar disorder patients are incapable of giving informed consent because of their neuropsychiatric condition. Hence, it is important to get permission from the participant's legally authorised representative (LAR) who should take into account the participant's previously formed preferences and values (if any). The participant should also give assent to the extent of her/his decisional capacity [8]. Emergency medical and psycho-social support should also be made available to the participants.

Regarding the collection and storage of genomic DNA for future use, a separate specific informed consent for a particular use or broad informed consent for unspecified future use must be obtained from the participants. The ethical acceptability of broad informed consent relies on a proper governance system (that may include a genome centre) that should already be in place once the research has commenced [9].

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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

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