MAHIDOL UNIVERSITY
Wisdom of the Land

Ethical Considerations in *IRB-IEC Review*

Jaranit Kaewkungwal

ORS – FTM-EC

Mahidol University

Types of Review

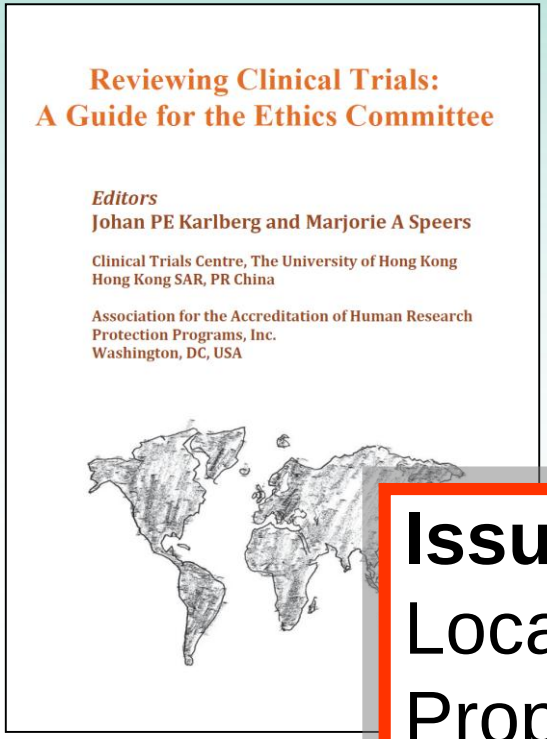
Types of Review

Convened IRB Review (full committee review): Any study involving greater than minimal risk, including studies with vulnerable populations and/or sensitive questions, as well as studies with the possibility of physical risk.

Expedited IRB Review (individual committee member review): Only research involving no more than minimal risk to subjects, including blood sampling in minimal amounts, review of records collected for non-research purposes (such as chart reviews), and survey research.

Exempt from Continuing IRB Review: Research with very minimal risk to human subjects as determined by regulatory guidelines may be exempted from continuing review at the discretion of the IRB. An exemption is granted by the IRB upon review of the application.

Case Scenarios - IRB/IEC Review


Reviewing Clinical Trials:
A Guide for the Ethics Committee

Editors
Johan PE Karlberg and Marjorie A Speers

Clinical Trials Centre, The University of Hong Kong
Hong Kong SAR, PR China

Association for the Accreditation of Human Research Protection Programs, Inc.
Washington, DC, USA

Issues of EC Procedures

Local Laws and Institutional Guidelines

Proportionate EC Review: Expedited/Full

Acceptability of Trial

Continuing Review

Trial Amendments

Full vs. Expedited Review

Dr. Strong is going to conduct a surgical procedure clinical trial. His co-investigator friend mentions that this protocol has been approved by the EC at Academia University. Dr. Strong is led to believe that his own EC will "*rubber stamp*" or expedite the approval of his EC application since it has already been approved by his friend's university. He thus asked for expedited review at his university.

Can the Dr Strong's protocol submission be "expedited"?

Note:** it is important to stress that the local EC should undertake a full review on human interventional studies and accept the decisions of other ECs only when there is a formal written arrangement to do so. **Examples are a centralised EC that serves several institutions or a mutual recognition of the EC decisions made at individual institutions.

Full vs. Expedited Review

Dr. Groth has been informed by the sponsor of a drug trial that it has decided to amend the trial protocol. The amendment means that each trial participant has to visit the hospital 26 times, not 20 times as the original protocol spelled out. Any protocol amendment must be reviewed by the local EC; and the change can be adopted only after the EC provides written approval for the change. This is why Dr. Groth submitted the amended protocol to his EC.

Can the Dr Groth's amendment submission be "expedited"?

Note: This is a very common scenario, i.e., protocol amendment. A full EC review is required if the change may increase the risk of harm for the participants. Informed consent forms often require amendments and must be signed by each trial participant, before amendments can go ahead.

Continuing Review

Two years ago, Dr. Simpson initiated a single-centre, randomised, blinded lung cancer trial to study the effect of the combination of two recently registered anti-cancer drugs. She has worked day and night on this trial. To her satisfaction, she has been able to recruit 76 patients into the trial out of the anticipated 120 with an additional 18 months to go.

One day, Dr. Simpson reading one of the scientific oncology journals she subscribes to. The clinical trial in the article she is reading is seemingly identical to her ongoing trial. However, the investigators have been able to prove the combination therapy to be slightly more effective than the standard treatment, with 55% of patients responding to the combination therapy.

Can the Dr Stella continue her study?

Dr. Simpson notes that the fir one of her previous residential ward a large national cancer centre in Europe.

"What can I do?" she wonders. "And I have to complete my annual EC trial continuing review progress report today. Will the EC stop my current trial if I inform them about the results of the European trial?"

Continuing Review

Dr. Simpson reflects and then reminds herself that the stolen protocol is, in fact, not the final one; she amended genomics and proteomics methodologies into the protocol after that *"bandit"* left.

Note: Emerging knowledge about a test medication can provoke a reassessment of the value of a clinical trial. Newly published results of other similar trials can have both positive and negative effects. The EC continuing review report is one of the regular points for re-assessment.

benefit from being participants in our trial. Moreover, our trial is unique compared to the published trial since we have access to important biomarkers, thus allowing us to identify characteristics of responders and non-responders."

Should EC let Dr Stella continue her study?

Acceptability of Trial - I

Dr. Soares was invited to be an investigator for a major pharmaceutical company and asked to conduct a phase III trial of a new anti-diabetic agent in patients with type-2 (non-insulin dependent) diabetes.

The trial is a phase III, randomised, double-blind trial, comparing a newly registered oral anti-diabetic agent with another currently available treatment on the market. It is a multicentre, global trial, recruiting 100 patients in total, of which she will be required to recruit 10.

More important, she notes that patients who are enrolled into the trial must first undergo a 2-week washout period that consists of a regimen of diet and exercise, after which, they will be randomised to the trial medication or the control medication. Dr. Soares submits her application to the EC of the hospital where she works.

Should EC consider this study methodology acceptable ?

Acceptability of Trial - I

During the EC review meeting, all members expresses concern that patients enrolled into the trial must first undergo a 2-week *"washout period"* that consists of a regimen of diet and exercise, without any diabetic drug treatment. The EC members request an in-depth clarification from the investigators of how the washout period might affect the patients and their diabetes status.

Should EC let Dr Soares conduct her study?

Note: Whenever there is a "washout period" in a clinical trial design, EC members should be alert and consider the associated risks of not providing any treatment to the participants. Certain disease trials that require continuing medication – such as severe asthma – should not use a "washout period" design.

Acceptability of Trial - II

Dr. Hernández plans to the trial that is a randomised controlled trial, comparing a conventional antibiotic for the treatment of pneumonia with the new treatment.

Before the participants are randomised, there would be a short run-in period where the participants would be given no medication for the first two days, so that microbiological tests can be performed in order to establish the diagnosis. After this, each participant would be randomised to either the conventional medication or the new trial medication.

Should EC consider this study methodology acceptable ?

Acceptability of Trial - II

During the EC review meeting, one member notes that there would be a *"run-in period"* for the first two days before the participant is randomised to one of two treatment arms. The same EC member pointed out that local standard medical practice is to initiate pneumonia drug treatment at the time of diagnosis and that it would be seen as unethical to wait for two days in initiating the treatment.

Should EC let Dr Hernández conduct his study?

Acceptability of Trial - III

ACME currently manufactures and markets a drug approved by the regulatory authorities in the US for the treatment of benign prostatic hyper... comm... growt... The p... in th... multi... indication.

Note: An open-label trial is a type of clinical trial in which both the researchers and participants know which treatment is being administered. An open-label trial may be unavoidable under some circumstances, but in most cases, a blinded design can be adopted, as in this scenario and especially in a phase III confirmatory trial.

Dr. Massironi submits an application to the EC at the hospital where she works. The EC review mostly focused on the open label design and it was promptly decided that a better trial design should be adopted, such as a randomised, blinded trial. The EC thus asks for a revised protocol.

Can EC suggest to change study design?

Trial Amendment

Dr. Ben Bolt is the investigator for a phase IV multicentre, randomised, double-blind, placebo control trial of a new beta 2 agonist for the treatment of asthma and chronic bronchitis. A requirement of the trial is that a 24-hour contact name and telephone number of a clinical research coordinator be provided to all participants on the participant informati the participa eone in case t

***Note:** Some trial changes may not be subject to an EC review, but minor changes that alter the content of the informed consent form should always be reported to the EC, so that the EC can review and approve the changed form.*

Halfway Bolt decides t ntact in the event of an emergency has to be changed.

Dr. Bolt asks the trial monitor to makes all the necessary changes to the informed consent form for submission to his EC for review.

Did Dr Bolt have to do this amendment?

Suspension or Termination of a Trial

Dr. Lopez is involved in many ongoing clinical trials and one is a phase II trial of a test article for leukemia. She has been able to recruit 34 patients into this trial and several are getting better, while others are getting worse, and some have even died during the course of the trial.

Dr. Lopez has a strong feeling that the test article is very efficient, although she cannot state this for sure, since she is blinded for the type of treatment given to each patient. Whenever she examines participants who are getting worse, she feels unhappy and dissatisfied with her institution.

Dr. Lopez decides to call the office of the EC chair and he suggested that *"You should contact the sponsor and clarify your gut feeling and then ask for an interim un-blinded data analysis. If they refuse, the EC will arrange a meeting so that we can make a formal request for the analysis*."

Can EC do this role?

Suspension or Termination of a Trial

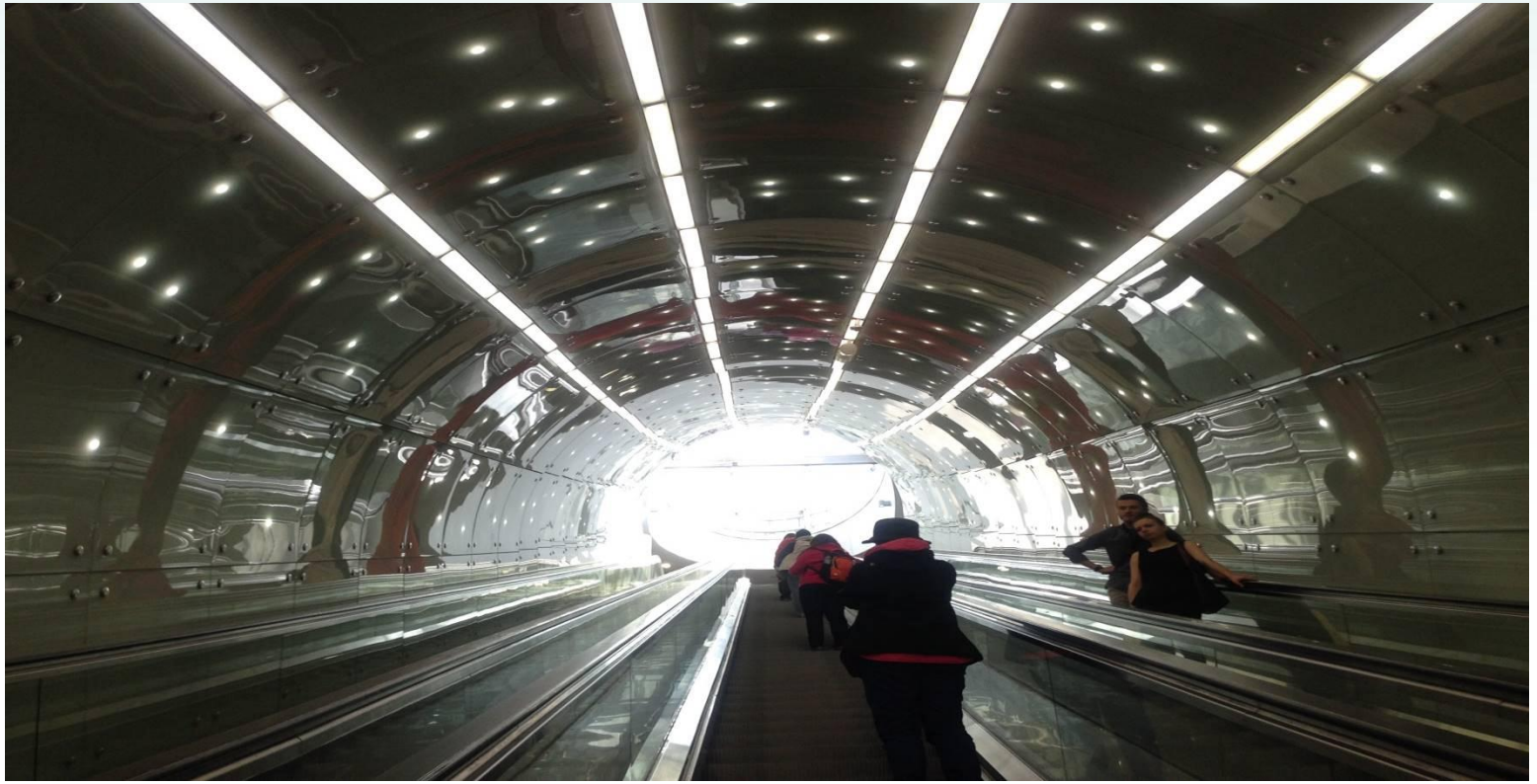
Dr. Lopez feels that it is unethical to continue the trial, since the new drug can save lives. She follows EC chair contacting the sponsor for an interim unblinded statistical analysis.

The sponsor, a German company, responds quickly to the request and pools the data of 78 participants. It is confirmed that the new drug is very efficient, and after contact with the regulatory authority, the trial is terminated. A new protocol is developed so that all participants are provided the new treatment, and the trial is now open labeled without having a control group.

***Note:** There can be good reasons to terminate a trial following an unblinded interim sta… maintain the treatment… may not always be the case that a test article is associated with increased risk of adverse events or, as in this scenario, with increased benefits. The sponsor must always be involved in the decision, and regulatory authorities must be consulted so that all parties reach a consensus prior to the suspension or termination of a trial.*

Why the study get terminated but have another protocol continue?

Ethical Considerations in IRB/IEC Review



Basic Ethical Issues

- Autonomy
- Beneficence
- Nonmaleficence
- Justice

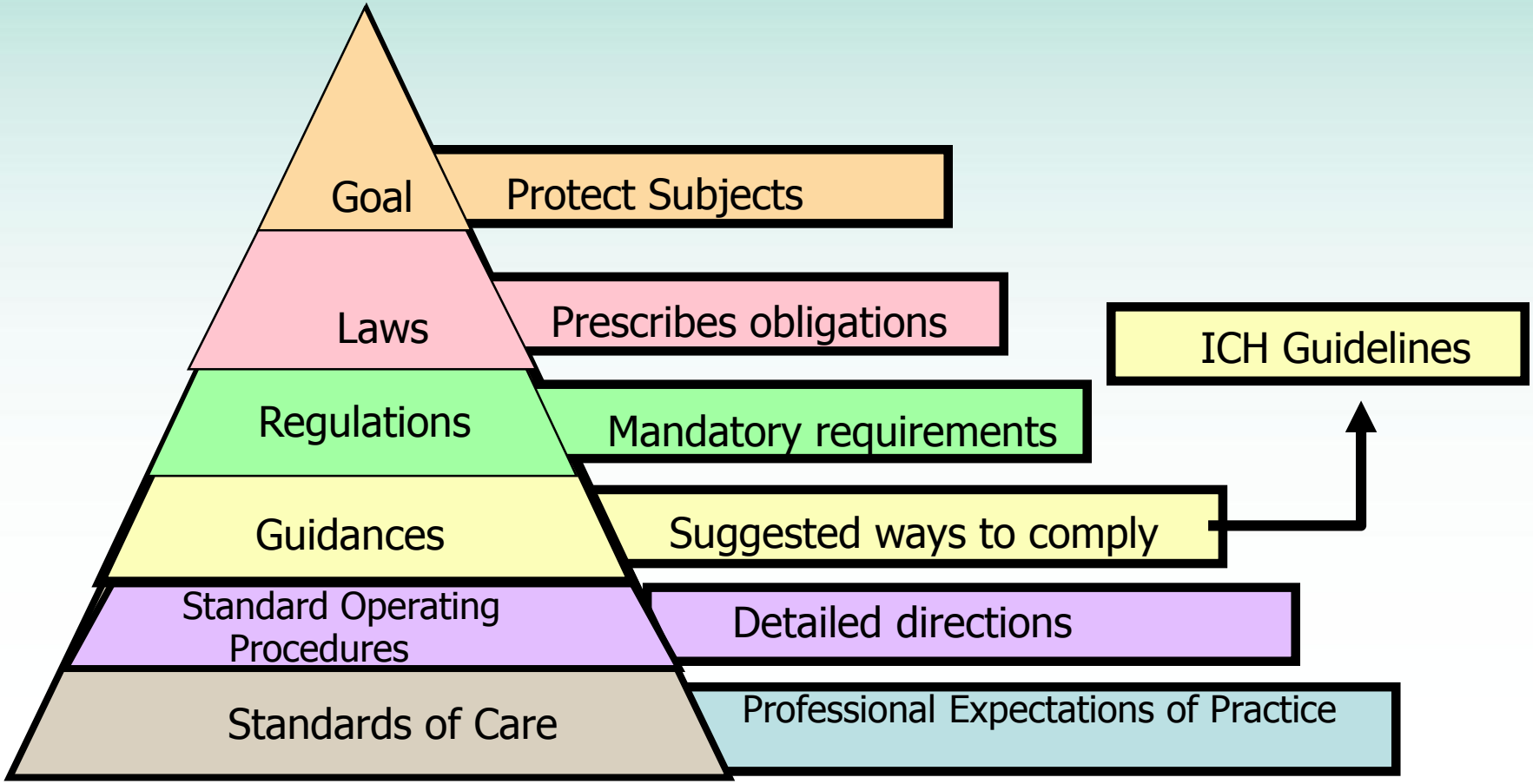
Good Clinical Practice (GCP)

"Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible"

ICH HARMONISED TRIPARTITE GUIDELINE , GUIDELINE FOR GOOD CLINICAL PRACTICE , E6

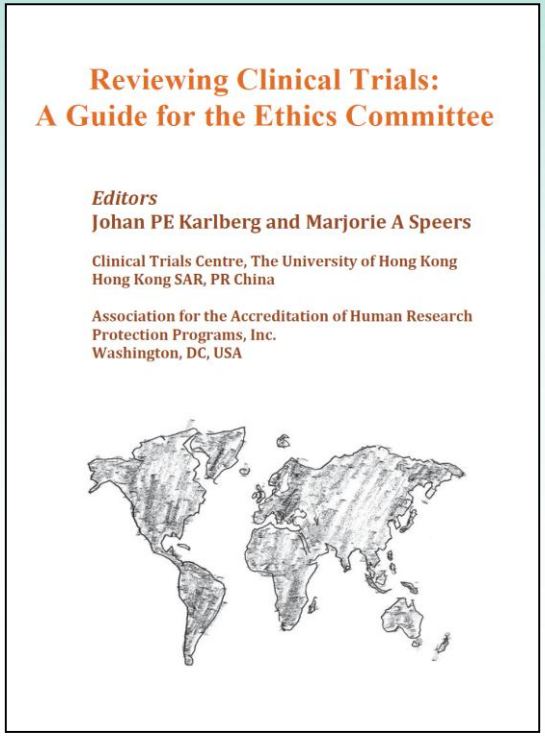
(http://www.ich.org/LOB/media/MEDIA482.pdf)

Good Clinical Practice (GCP)



 Source: Eugene Oddone, Understanding Our HRPP and Your Role in the Accreditation Process

Case Scenarios – Ethical Issues


Reviewing Clinical Trials:
A Guide for the Ethics Committee

Editors
Johan PE Karlberg and Marjorie A Speers

Clinical Trials Centre, The University of Hong Kong
Hong Kong SAR, PR China

Association for the Accreditation of Human Research Protection Programs, Inc.
Washington, DC, USA

Issues of Ethics of Clinical Trials:

- Risk-benefit balance.
- Informed consent process.
- Vulnerable participants.
- Privacy and confidentiality.
- Data safety monitoring.
- Participant recruitment procedures.
- Qualification of investigators.
- Conflict of interest.
- Clinical trial insurance and indemnity.
- Essential clinical trial documents.
- Clinical trial registration.
- Dissemination of trial results.

Risk vs. Benefit

Dr. Haugen - consultant oncologist - has been approached by a CRO to conduct a phase I clinical trial of a novel drug for the treatment of acute small cell carcinoma of the lung for a multinational pharmaceutical company based in the US. The drug under evaluation will be tested in a small group of patients with late stage cancer and requires the investigator to draw regular quantities of blood amounting to no more than 800 ml in total over a two-week period, so that a full range of haematological, biochemical, pharmacokinetic and pharmacodynamic parameters can be assessed. The size of the tumour will also be measured. The new drug being evaluated will be a breakthrough in the treatment of cancer. Dr. Haugen is naturally very keen to be an investigator for the trial and duly submits an application to her hospital's EC for consideration

Should EC approve this protocol?

Risk vs. Benefit

The EC chair was surprised when he read the protocol, i.e., that as much as 800 ml of blood would be drawn from terminally ill cancer patients. Being a specialist in haematology, he knows that a normal blood donation of healthy individuals varies from 200 to 550 ml, depending on the country, and a full blood donation should in principle not be repeated over an eight-week period.

Should EC approve this protocol?

The chair noted that the protocol had listed a well-known medical university in the United Kingdom as a potential trial site, so he simply sent an email to the EC chair at that university and asked for comments on the protocol in question.

Should EC chair call other EC site?

Risk vs. Benefit

It took just a few hours before the email reply: *"No, we did not accept the protocol, since it is harmful and unethical to collect 800 ml in terminally ill patients – no gain, just pain for very sick participants."*

Should EC chair disapprove this protocol?

The EC chair could not disapprove the protocol, since that can only be done by during a full EC review meeting.

Note: **This scenario in fact represents a true case; sponsors may assume that even if one EC does not accept a protocol, maybe another will. Consulting other ECs involved in the review of the same protocol is in fact good practice and should be encouraged.**

Inform Consent Process

Dr. Crown, a residential doctor, to be a coinvestigator in an investigator-initiated trial related to bone marrow harvesting, draft the informed consent form. She writes up the informed consent form, including the following two sentences: ***"I waive any possibility of compensation for injuries that I may receive as a result of participation in this research. By giving consent to participate in this research, I give up any property rights I may have in bodily fluids or tissue samples obtained in the course of the research."***

Is the Informed Consent acceptable ?

Inform Consent Process

It could be better worded as: 'This hospital is not able to offer financial compensation or absorb the costs of medical treatment should you be injured as a result of participating in this research. Tissue obtained from you in this research may be used to establish a cell line that could be patented and licensed by the university.' "

Vulnerable Participants

Dr. Higgins is a consultant psychiatrist who works in a psychiatric unit of a local community hospital. She specialises in the treatment of patients with psychiatric illnesses, particularly those with dementia. The trial she submitted to EC stating: ***Basically, we want to examine the blood of groups of participants – senior citizens with mild senile dementia – taking a small amount of blood from them and then analysing it for genetic markers related to dementia and two treatment regimes.***

Is there a major concern for this protocol?

Vulnerable Participants

The EC quickly identifies the potential vulnerability of the trial population, but it also finds the trial scientifically sound and of low risk. The protocol has addressed the informed consent process for tissue sampling and genetic makers, so these are not issues of concern.

But dementia patient – can they understand this protocol?

Data Safety Monitoring

The EC is to review a 36--participant, single-centre, phase I sepsis trial sponsored by an overseas biotech company. The EC chair, Dr. Ping Wang, is concerned about the safety aspects of this trial, since the mortality rate is normally high in sepsis patients – sometimes as high as 30%.

Dr. Wang calls the investigator of this trial, Dr. Su Liu, and informs him: *"The EC will not be able to review your EC application at this point in time. The EC asks for an independent committee to monitor the trial and for you to provide the committee with safety reporting."*

Is it OK for EC to ask for DMC/DSMB?

Data Safety Monitoring

Dr. Liu fully understands the concerns and is well aware that some of the participants will die during the course of the trial. He subsequently draws up a new protocol for the EC to review. After some discussion, the investigator and sponsor decide to establish a data safety and monitoring committee (DSMC) for this trial – comprising an intensive care clinician independent of the trial conduct, a biostatistician and the director of the clinical trials center at the institution.

The monitoring committee chair can call for a committee meeting at any time. There will be an un-blinded interim safety analysis after 12 participants have been treated, where the committee will inform the sponsor and the EC of its interim analysis interpretations and subsequent recommendations.

Data Safety Monitoring

Note: **An EC should ensure there is a monitoring plan for clinical trials through regular reports and continuing review reports. However, the DSMC offers a better choice of monitoring since it is responsible for overlooking a particular trial and its operational procedures are trial-specific. But establishment of a DSMC should be selective, reserved only for certain types of high-risk multi-centre trials or when design decisions are to be made during the course of a trial.**

Participant Recruitment Procedure

This is a new and promising drug for the treatment of influenza. Dr. Kim, while not concluding that finding suitable cases for the trial will be particularly difficult, she decides that it is perhaps best to draw up some sort of advertisement, to supplement the pool of existing patients already on her lists.. With her assistant's help, Dr. Kim prepares and submits the following advertisement to her EC, along with all other relevant EC application documents:

DO YOU HAVE INFLUENZA?

If your answer is "*YES*" you may be considered an eligible participant for entry into a clinical trial of a promising new drug for the treatment of influenza. By participating in the trial, you will receive the following benefits:

- **Free medication.**
- **Free medical examinations by a qualified physician.**
- **Reimbursement of travel costs to and from the hospital.**

For further information contact: Dr. Kim - telephone 2020 2345

Should EC approve this advertisment?

Participant Recruitment Procedure

After EC meeting, the chair of the EC informs Dr Kim by email that she is not allowed to use a phrase like "*a promising new drug*" in an advertisement for trial participant recruitment. Wording such as "*promising*" or "*new*" is not permitted, since it is a test article. It is not known if the drug will be "*promising,*" and it is not "*new*" until it has been approved by the regulatory authority. The EC chair also writes that he has no further comments about the contents of the advertisement and that he will be happy to expedite the review after Dr. Kim submits an appropriate advertisement.

Note: **This advertisement tries to gain the attention of potential participants by using unsuitable and inaccurate phrasing such as - *"a promising new drug."***

Protocol Amendment

Dr Sam is a distinguish professor in the field of dengue research. She is conducting a proof-of-concept trial challenging 30 healthy volunteers with a certain regimen at dose 60 mg/day. The challenging regimen and dose was the treatment used in the study area several years back, but not now; however, it is still used elsewhere in Africa. The study was approved by her institution review board. After 10 cases enrolled into the study, there were 2 cases reported nausea and 1 vomiting. She thus wrote the amendment to the protocol and submitted the ethics committee. The amendment states that the study will continue recruiting another 20 volunteers to complete the original study but the dose will be changed from 60 mg to 30 mg.

Should EC approve this amendment?

Protocol Amendment

The EC decided not to approve the amendment. The main reason is that the study has now changed the main intervention of the study; it is not the same as original protocol. The title of the study was about 60 mg/day challenge, not 30 mg/day challenge.

The 30 study participants will be under different doses and thus not possible to combine the two exposures in one analysis to conclude about the investigating regimen. The ethics committee recommended her to drop the current study and submit new protocol with the new dose regimen.

Cooperative Research

Dr Sun is conducting a study on certain drug in Thailand. The study was single-site and was approved by his local IRB. However, some of his co-investigators were non-Thai and were required to submit the protocol at their affiliated IRB in the US.

Half way to the study, Dr Sun submitted an amendment asking for major changes in the study conduct to his local IRB. The amendment was also submitted to the IRB in US. The local IRB disapproved the amendment due to the changes would have major impact on study volunteers. Dr Sun argued that the IRB in the US did not reject the amendment and approved it even before local IRB. Why local IRB has to be different?

Is the local EC in-efficient?

Cooperative Research

From: 45 CFR 46: MOST FREQUENTLY ASKED QUESTIONS

Question: Why would a standard cooperative research protocol or a standard informed consent document need review at the local level when it has already been reviewed by another national organization or even by the IRB of another institution with an approved Assurance?

Answer: Cooperative protocol requirements may be standard, but the research setting is not standard across institutions. In addition, one should not assume that because a protocol or informed consent document has been reviewed by another entity, it necessarily conforms to pertinent regulations, local laws, or the local research setting. For example, local laws, institutional policies and constraints, professional and community standards, and population differences are all factors that can influence the research setting. [*See* 45 CFR 46.103(d), 46.107(a), and 46.111(a)(3), noting the relevance of the particular setting in which the research is to take place.]

Cooperative Research

The Office for Human Research Protections (OHRP) of the Department of Health and Human Services (DHHS) states that "Institutions have a profound responsibility to ensure that all IRBs designated under an OPRR-approved Assurance possess sufficient knowledge of the local research context to satisfy these requirements. This responsibility endures regardless of the IRB's geographic location relative to the institution and the research. It is particularly critical where the research involves greater than minimal risk to subjects or vulnerable categories of subjects."

Adverse Event Reporting

Dr. Pourpongporn has seen 15 death cases in 100 liver cancer patients following the new surgical procedure. The 15 deaths have continuously been reported to the EC, and the most recent death was reported last week. The EC chair reviewed this newly reported death and found out the investigator thought the death was most likely related to the surgery, rather than to the disease itself. The patient suffered from extensive post-operative abdominal bleeding because of a long-lasting and difficult surgery. The chair reviewed the other 14 deaths reported to the EC for this trial and found they all happened several months after surgery, owing to tumour recurrence. Since the last reported adverse event was related to the surgery, the chair decides to bring up the case at an upcoming full EC review meeting. He also thinks the review of this scenario would be educational for new/novice EC members.

Should EC recommend to stop the trial?

Adverse Event Reporting

Note: **Extensive surgical procedures always come with high risks, so the riskbenefit balance is very much present. One should thus consider that 5% of the liver cancer patients who undergo established surgery will normally die within 3 months. The observed frequency of death of the liver cancer patients is expected and thus not a concern for the EC.**

Privacy & Confidentiality

Dr. Lucia is a clinical biochemist and is currently planning her first genetic treatment trial.

She plans to take blood samples and perform DNA analysis on 100 elderly females diagnosed with osteoporosis and include it in an industry-sponsored trial to relate the DNA analysis with the treatment response.

In the planning phase of this trial, Dr. Lucia asks one of her colleagues, Dr. Bennato, to act as a potential trial participant in order to identify key points for the informed consent process.

Dr. Lucia asks Dr. Bennato, *"So, you have now heard about the details of the study. Do you have any questions that I can help you clarify?"*

Dr. Bennato declares in his razor-sharp voice, "*Yes, in fact I have six major concerns…*

Privacy & Confidentiality

"How will my confidentiality and privacy be protected?" **Reply:**

"What are my rights to my DNA?" **Reply**

"Can I withdraw my DNA from the study?" **Reply:**

"How long do you plan to keep the DNA?" **Reply:**

Privacy & Confidentiality

"What will I find out about my DNA results?" **Reply A:**

"Will you use my DNA for other purposes?" **Reply:**

Investigator Qualification

Dr. Black is the head of the department of nursing at an Australian medical school. She is a nurse by training and she acquired her PhD degree five years ago in the UK. Dr. Black has been able to secure a research grant from the Health Promotion Research Fund for an interventional *quit smoking* randomised clinical trial.

The trial will have two groups of current smokers; one group will be followed without intervention, and the other will be given educational information by means of lectures, videos and brochures.

Dr. Black is very surprised when she gets letter from EC: *"The ethics committee has after much consideration not approved your application as it stands."*

Why EC not approved this protocol?
Is it because Dr Black is a nurse, not clinician?

Investigator Qualification

Dr. Black's EC application was rejected on the grounds that some of the EC members thought it was unethical to follow smokers without providing any sort of information about the risk of smoking.

With some modifications to the design, the EC approves the revised EC application.

The EC members did not dispute the qualification of Dr. Black as the sole investigator since it is an anti-smoking health promotion interventional trial.

Conflict of Interest

After Dr. Bend devoted 10 years to developing a scoliosis device, he will finally be able to use it in patients. The device is novel because its initial curvature will become more or less straight over a period of a few months once implanted in patients.

The project has sufficient financial support from a government research fund, and the patent of the device is jointly owned by Dr. Bend and his university. The first trial will be conducted on five adolescent patients with scoliosis, and the primary objective is to observe safety.

Dr. Bend will be the principal investigator, and he has completed the protocol himself. Dr. Bend sends the application to his EC along with an investigator's conflict of interest form.

Should EC accept his declare of COI document?

Can he be PI of the project?

Conflict of Interest

By acting as the principal investigator for the first clinical trial of five patients, Dr. Bend can unquestionably come into a difficult conflict-of-interest situation. Dr. Bend has a strong financial interest in the device, and any negative trial results may thus be ignored and not reported.

The EC decides not to allow him to be the principal investigator, rather suggesting a "*neutral*" orthopedic surgeon instead.

Note: **The way to mitigate apparent conflicts of interest is to avoid them entirely when possible.**

Essential Documents

Dr. Kwabean is a junior physician has been approached to be an investigator in a multinational osteoporosis clinical trial. The sponsor, an American company, requests each investigator to sign a conflict-of-interest form because this is a requirement of the US FDA.

Dr. Kwabean asks, *"Why should we sign a COI form? We are not US citizens, and we are conducting the trial outside the US."*

Does Dr Kwabean have to sign COI document?

Essential Documents

Dr. Kwabean is a junior physician has been approached to be an investigator in a multinational osteoporosis clinical trial. The sponsor, an American company, requests each investigator to sign a conflict-of-interest form because this is a requirement of the US FDA.

Dr. Kwabean asks, *"Why should we sign a COI form? We are not US citizens, and we are conducting the trial outside the US."*

One senior investigator interrupts abruptly by saying, *"A COI form is seen as an essential trial document, since we must ensure that we have no conflicts that may distort the data that we will collect. In fact, our institutional EC [illegible] the EC application revie[illegible]*

Does Dr Kwabean have to submit COI document to his institute?

Dr. Kwabean signs the conflict-of-interest form and asks for a copy to bring home so he can submit it to his own EC. Even though he has already submitted the EC application, he will also submit the conflict-of-interest form.

Essential Documents

The Faculty of Medicine Board looks at Dr Kwabean's *EC trial application and said* *"Everything seems to be in order with the application, but why have you included a signed US FDA conflict of interest form? That is not a requirement by our regulatory authority or by our institution. I assume that this is just a simple mistake from your side. If you like, I can return the signed form tomorrow."*

Does EC here know nothing about international trial?

or

Does this mean that there are different requirements in different countries?

Discussion…