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สถาบันวิจัยและประเมินเทคโนโลยีทางการแพทย์ กระทรวงสาธารณสุข จังหวัดนนทบุรี 11000

Abstract : Looking Back and Moving Forward to Human Subject Protection Program at Ministry of Public Health, Thailand

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The Ethical Review Committee (ERC), Ministry of Public Health (MOPH) was established in 1978 with the mission to protect the rights, safety, and welfare of human subjects through advancing knowledge and facilitating the highest quality research while meeting international standards of data integrity and research benefits to the public health. Over the past 39 years, the Ethical Review Committee, Ministry of Public Health (MOPH ERC) has reviewed an average of 100 clinical trial and public health research protocols each year. Principal Investigators of the submitted protocols have opportunities to defend their protocols in person. The MOPH ERC members are representatives from various departments in MOPH and experts working outside the MOPH. The MOPH ERC convenes regular monthly meetings. Nevertheless, the work of MOPH ERC has received some criticism. We systematically described and reviewed the works of the MOPH ERC over the past four decades using literature review and the Strengths-Weaknesses-Opportunities-Threats analytical methods. Although the MOPH ERC was accepted by international organizations and pharmaceutical companies, Bureaucratic Management System and chronic understaffing caused interruptions and delays in reviewing protocols. Most importantly, the MOPH ERC still needs support from its organizational leader, a stronger enforcement of the relevant policies and laws as well as the quality assurance in order to increase the confidence in the protection of the human research subject in Thailand.

Keywords : Human subject protection program, Ethical review committee, Ethics committee

บทคัดย่อ

คณะกรรมการพิจารณาการศึกษาวิจัยในคน กระทรวงสาธารณสุข จัดตั้งขึ้นอย่างเป็นทางการเมื่อปี 2521 โดยมีวัตถุประสงค์เพื่อคุ้มครองสิทธิ ความปลอดภัย และความเป็นอยู่ที่ดีของอาสาสมัคร รวมทั้งเพิ่มพูนความรู้และสนับสนุนให้เกิดการวิจัยที่มีคุณภาพ เพื่อให้การดำเนินการวิจัยเป็นไปตามหลักมาตรฐานสากล และข้อมูลที่ได้มีความสมบูรณ์น่าเชื่อถือ ผลการวิจัยก่อให้เกิดประโยชน์สูงสุดต่อวงการสาธารณสุข ตลอดระยะเวลา 39 ปี คณะกรรมการฯ พิจารณาโครงการวิจัยทางคลินิกและโครงการวิจัยด้านสาธารณสุขโดยเฉลี่ย 100 โครงการต่อปี ผู้วิจัยที่ยื่นเสนอโครงการวิจัยได้มีโอกาสเข้ามาชี้แจงโครงการวิจัยด้วยตนเอง คณะกรรมการฯ ประกอบไปด้วยผู้แทนจากกรม กองในสังกัดกระทรวงสาธารณสุข และผู้ทรงคุณวุฒิจากหน่วยงานภายนอก มีการประชุมเป็นประจำทุกเดือนอย่างน้อยเดือนละ 1 ครั้ง คณะกรรมการฯ ทุกท่านที่เข้าร่วมประชุมต้องลงนามในเอกสารข้อตกลงเรื่องการรักษาความลับและการแจ้งผลประโยชน์ทับซ้อนก่อนเข้าร่วมประชุมทุกครั้ง ผลการพิจารณาตัดสินตามฉันทามติ (Consensus) ในช่วง 4 ทศวรรษที่ผ่านมาการดำเนินงานของคณะกรรมการฯ มีปัญหาและอุปสรรค ผู้ศึกษาได้วิเคราะห์สถานการณ์และทบทวนการดำเนินงานของคณะกรรมการฯ ทั้งด้านเอกสารและการวิเคราะห์สภาพแวดล้อม (SWOT) พบว่าคณะกรรมการฯ จะได้รับการ

ยอมรับจากองค์การและบริษัทยาในระดับนานาชาติ แต่การสนับสนุนด้านงบประมาณและสภาพงานล้นคน (Understaffing) มักทำให้เกิดความล่าช้าในกระบวนการพิจารณาโครงการวิจัยที่สำคัญที่สุดคณะกรรมการฯ ยังคงต้องการการสนับสนุนจากผู้นำองค์กร การบังคับใช้นโยบายและกฎหมายที่เกี่ยวข้อง รวมทั้งการประกันคุณภาพเพื่อเพิ่มพูนความเชื่อมั่นในการคุ้มครองอาสาสมัครวิจัยในประเทศไทย

คำสำคัญ : คณะกรรมการพิจารณาการศึกษาวิจัยในคน คณะกรรมการจริยธรรมวิจัย จริยธรรมการวิจัย

Introduction

The international standards on human research protection and good clinical practices, such as the Helsinki Declaration[1], the International Conference on Harmonization Good Clinical Practice (ICH-GCP)[2], the Nuffield Council on Bioethics[3], and the Belmont Report[4], requested that any clinical trial or public health research performed on the human subjects must protect the rights, safety, and well-being of those study participants. These standards were adopted in Thailand in conjunction with the local tradition, culture, religions, laws, rules, and regulations[5-6].

However, the first Ethics Committee in Thailand was abruptly established after demonstrations against the human subject research in Northern Thailand in 1975[5]. Three years later, the MOPH ERC, the supposed national ethical review committee, was established. Moreover, during the past four decades; the MOPH ERC went through several phases. During these years, many researchers submitted their protocols only to their institutional ethics review committees. They avoided the existence of the MOPH ERC due to reasons ranging from technical difficulties to the issue of time frame, although many felt the need for a national body specifically responsible for ethics of research involving human subjects[6].

Having a systematic recording and reviewing the works of the MOPH ERC is essential in setting a stronger future path for this program as well as the protection of human participants in clinical trials and public health studies conducted in Thailand. This article aims to systematically describe and review the 39 years of the MOPH ERC's work on human subject protection in Thailand.

Methods

We performed a literature and document review regarding the establishment and the workings of the MOPH ERC from published articles, governmental documents, and personal records of the MOPH ERC senior staff members. On 10th March 2017, we invited relevant stake-holders to perform the Strengths-Weaknesses-Opportunities-Threats (SWOT) analysis. We protected the confidentiality of the invited stake-holders. All answers were given without any links to their names or organizations. We used the results of the SWOT analysis to review and determine the factors most affecting the work of the MOPH ERC.

History of the MOPH ERC

In 1975, there was demonstration against human research conducted by foreigners in Northern Thailand causing an awakening to human subject research in Thailand. As a result, the Faculty of Medicine at Bangkok's Ramathibodi Hospital hosted the first conference about research on human subjects. This conference established the National Research Council of Thailand. The council created the "Guidelines for Biomedical Research Involving Human Subjects". However, the conference could not agree on a resolution for a single national ethics review committee. The conference agreed that each institution should establish their own ethics review committee and generate their own reviewing procedures and guidelines. The first research ethics committee in Thailand, the Human Experimentation Committee (HEC) was established in that year by the Medical Department, Chiang Mai University[5].

In 1977, Thailand sent three representatives to attend the International Conference Medical Research (ICMR) in Colombo, Sri Lanka. One of the resolutions from that meeting was to focus on research development in each member country. In 1978, the MOPH established the MOPH Research Committee with the Permanent Secretary, Ministry of Public Health (PSMOPH) assigned as a Chairman of this committee[7]. Since then, the MOPH ERC has evolved as follows:

- In 1978, the MOPH ERC was established to be under the MOPH Research Committee. The MOPH ERC had the same Chairman and members as the MOPH Research Committee.

- In 1980, the MOPH established the Advisory Council on Disease Prevention and Control which was under the Office of the PSMOPH. Subsequently, the MOPH ERC was then moved to be a responsibility of the Office of the PSMOPH directly and then moved to be under the responsibility of the Office of Academic Integration and Human Resources Development, MOPH.
- In 1991, the Public Health Research Policy Committee was appointed for policy formulation; the review and approval of protocols; ongoing monitoring of medical and public health research projects.
- In 1992, duties regarding the medical and public health research were delegated to the following three committees : 1) the Public Health Research Policy Committee, with the PSMOPH as a chairman, was responsible for setting the policy on the medical and public health research ; 2) the Research Management Committee was responsible for setting the guideline on the medical and public health research ; and 3) the Ethical Review Committee for Research in Human Subjects (MOPH ERC), with the Director General of the Department of Medical Services (DMS) as a Chairman, was responsible for establishing criteria and methods for considering the conduct of research on humans.
- In 1999, the MOPH ERC was appointed without supervision by any other committee in order to promote and support the implementation of human research conducted by MOPH entities. At this time, the Director General of the Department of Medical Services was assigned as a Chairman and representatives from the departments within MOPH were the committee members. The MOPH ERC registered with the Office of Human Research Protection, U.S. Department of Health and Service with the currently active IRB Organizations (IORG) number 001220 and Federal wide Assurance (FWA) number 0001653[8].
- In 2000, the Office of Secretary, the MOPH ERC was established by the Department of Medical Services and the MOPH ERC Secretary position was assigned to personnel from the Medical Development Section, the Department of Medical Services. This Office of Secretary reported directly to the Director General of the Department of Medical Services. The responsibilities of the MOPH ERC were revised to give it the responsibility to protect the rights and safety of subjects participating in research and to verify the validity of human research in order to promote and support human research implementation as well as to use human research outcomes for Thailand public health development.
- In 2001, three government officers were assigned to work for the Office of the Secretary of the MOPH ERC. This Office of Secretary was then moved under the Medical Development Section, the Department of Medical Services.
- In 2005, the Office of Secretary of the MOPH ERC was reassigned as an internal unit within the Department of Medical Services. This structure was set up to manage the operation and budget more efficiently. The Office of Secretary was ordered to support the operation of the MOPH ERC and other academic works related to research on humans and to report directly to the Director General of the Department of Medical Services.

The Office of the Secretary of the MOPH ERC has worked under the Department of Medical Service since 2000 (Figure 1). At present budget, staff and resources are supported by Annual Government Statement of Expenditure and subsidy or fringe benefit through Institute of Medical Research and Technology Assessment (IMRTA).

Current Composition of the MOPH ERC

The MOPH ERC is comprised of experts experienced in research ethics from various departments of the MOPH and individuals from outside of the MOPH[9-10]. On 23rd December 2016, MOPH appointed the Director General of the Department of Medical Services as a Chairman MOPH ERC. On 8th February 2017, Chairman MOPH ERC appointed Sub-Ethical Review Committee (Sub-ERC). Sub-ERC composed of multisectorial experts who have

experienced in research ethics[11] and is responsible for reviewing protocol, monitoring research project and reports the final considerations to ERC.

The Office of the Secretary is responsible for supporting the ERC and Sub-ERC operations, for example, arranging the meetings and managing the documents as well as training and educating ERC members and researchers. The organization chart is shown below (Figure 1).

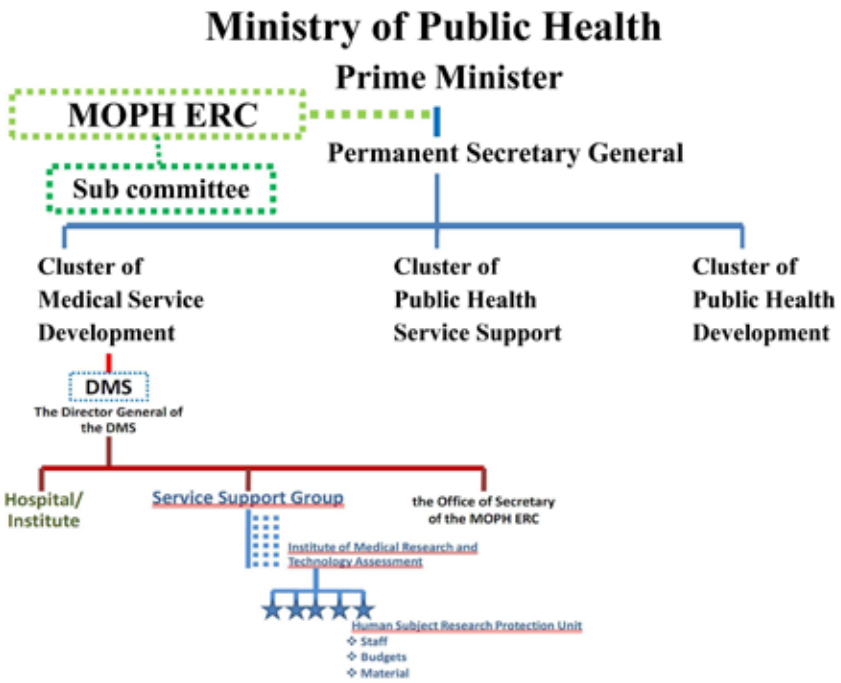

Figure1 MOPH ERC Organization Chart

Current Roles and Responsibilities of the MOPH ERC

The MOPH ERC was responsible for ensuring that approved protocols were conducted in compliance with international research ethic standards ; developing policies related to quality and human ethics research standards ; reviewing and approving study protocols per the MOPH ERC requirements and ethical principles ; suspending or terminating any approved protocols if they were not being conducted in accordance with the MOPH ERC requirements ; annually reviewing the approved protocols for continuation of approvals; engaging in the regional and global ethics committee networks ; developing the Thailand human research database; training researchers, and developing the guidelines for Human Subject Protection Program in Thailand[12- 13]; and performing other tasks related to human research as assigned by the MOPH.

Research Ethics Training and Counseling by the MOPH ERC

To improve the quality of HSRPP, especially in review process, continuation of training and education is essential. The Office of the Secretary, MOPH ERC, supports all MOPH ERC members to continue human research ethics training at least once every two years. The MOPH ERC office arranges research ethics courses for MOPH ERC members, EC members of other ECs, and researchers at least once a year. The Office of the Secretary also provides research ethics counseling on protocol revision and resolution regarding to the MOPH ERC recommendations. To date, more than 300 organizations attended the training and counseling sessions provided by the MOPH ERC.

Management of the Confidentiality and Conflict of Interest of the MOPH ERC members

The MOPH ERC functions are independent and separate from political, institutional, professional and

business interests in order to protect rights, safety and well-being of research participants and/or relevant communities. The MOPH ERC members who present in the convened meeting must disclose any possible conflicts of interest with the reviewed research protocol. The MOPH ERC members must sign the Confidentiality and Conflict of Interest Agreement Form prior to attending the convened ERC meeting. Any MOPH ERC member who has a possible conflict of interest (for example, is the advisor, supervisor, or subordinate of any of the researchers named in the reviewed protocol) must abstain from voting on that particular protocol. However, such the MOPH ERC members may be allowed to provide pertinent details on the submitted research protocol.

Current Reviewing Process of the MOPH ERC

The MOPH ERC members and the External Reviewers review and evaluate the submitted research protocols, information sheets and informed consent forms, as well as other study documents to ensure that scientific and ethic aspects are appropriate and complete. The submitted research protocols must comply with applicable laws, rules and regulations, as well as conform to Thai tradition, values, and culture. The submitted research protocol must include the medical and public health system and community aspects related to the study concepts. The final determination is made after comprehensive discussions and a consensus is reached.

The MOPH ERC convenes a meeting at least once a month. The average number of MOPH ERC members attending the convened meeting is about 11 (range : 10-15 members). Usually, the majority of members were scientific members (85%) and MOPH affiliates (60%). On average, meetings were last 5 to 8 hours. It took about 45-60 minutes to review 1 new protocol and about 30 minutes to review post-approval protocols respectively. 8% of each meeting is new protocols and 92% is post-approval protocols (Figure 2). Among the post-protocol approval submissions, 17% were for protocol amendments; 13% were for revised protocol as recommended by MOPH ERC; 7% were for renewal; 10% were for acknowledgement; 8% were for protocol deviation; 26% were reports of serious adverse events and 19% were for MOPH ERC considerations because researcher disagreement with MOPH ERC resolutions or recommendations. MOPH ERC assigns experts to assist in the careful review of all protocols for any ethical or scientific issues prior to scheduling it on the agenda. Average number of days from submission to approval was 90-100 days. Protocol review timeline was about 30-42 days/protocol and revision or response timeline from researcher to MOPH ERC was about 58-60 days/protocol.

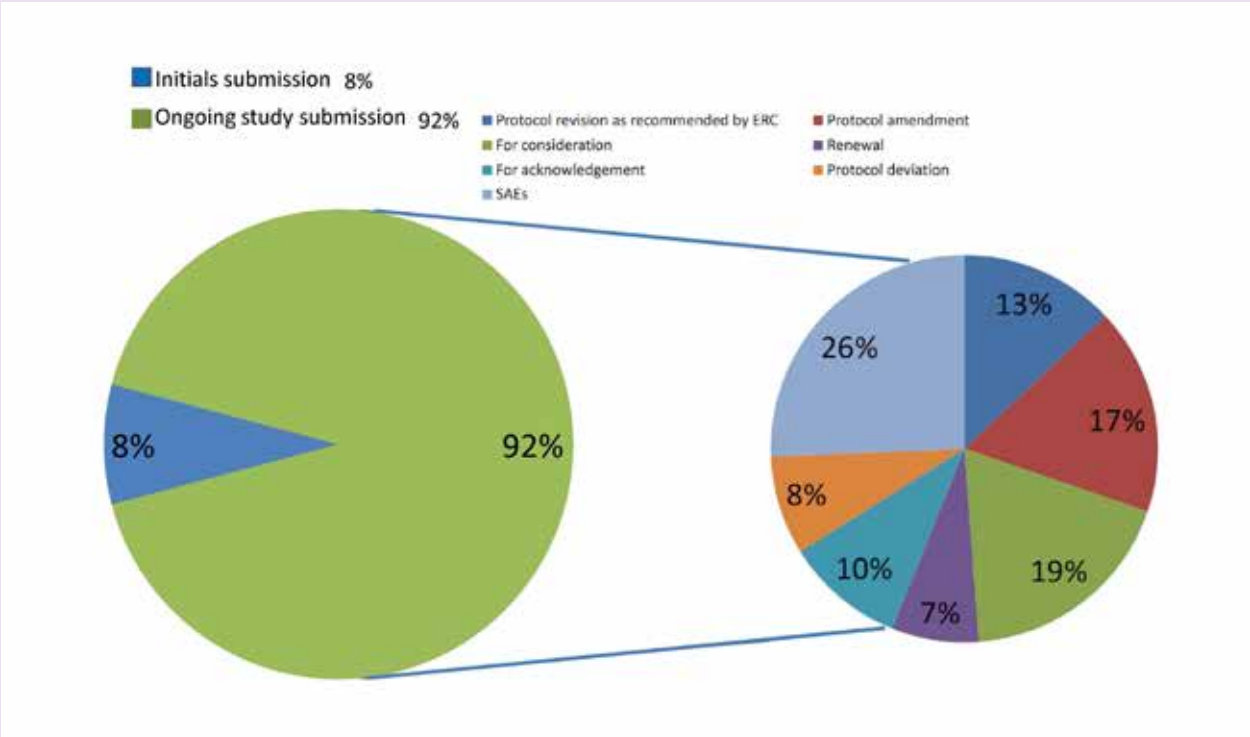

Figure2 Average proportion of reviews in each MOPH ERC convened meeting convened meeting

The most common questions and concerns raised in the convened meetings were about research ethics issues, such as methods for participant recruitment and obtaining informed consent, physical and psychological risk assessments, risk prevention actions and risk management, participant's confidentiality, compensations, post-trail assessments, and level of language that was appropriate to the research participants.

Clinical Trial Oversight after Approval by the MOPH ERC

The MOPH ERC conducts routine site visits to at least one research facility per year to ensure that the approved research protocols are being conducted in accordance with the applicable ethical standards. Selection of site for a visit is based on, but not limited to: having a large number of recruited participants ; involvement in the investigational new drug (IND) protocols; involvement with vulnerable participants (pregnant women, children, and/or incarcerated prisoners) ; or having frequent reports of serious adverse events, protocol deviations, complaints and/or concerns by participants, family members of the participant, or the research team.

Situations of the MOPH ERC in the Past Decade (1997 - 2016)

During 1999 – 2009, the MOPH ERC routinely reviewed more than 100 new protocols per year (Figure 3). Since 2009, the Drug Control Division of the Food and Drug Administration (Thai FDA) approved 10 other certified ECs to review the research protocols requesting drug import permits. We suspected this to be the main reason for the substantial decrease in the number of new protocols submitted to the MOPH ERC.

Strengths, Weaknesses, Opportunities, and Threats of the MOPH ERC

On 10 March 2017, the MOPH ERC invited 26 persons from relevant stakeholders/organizations to perform the SWOT analysis. Among the 15 (58%) who provided their opinions, 12 (80%) were female, 9 (60%) were under 40 years of age, 12 (80%) were from either the clinical research organization or a pharmaceutical company.

They agreed that the MOPH ERC has STRENGTH in research ethics and methods as the MOPH ERC had long experience in protocol reviewing, qualified personnel, great structure of the organization, creditability and reliability, and was accepted by national and international FDA and relevant organizations. Moreover, the MOPH, the umbrella of the MOPH ERC, had its own research teams and sites, both hospital-based and community-based, that covers the majority of Thai citizens. The WEAKNESSES of the MOPH ERC were listed as over-burdened and inadequate number of staff; strict rules and regulations on budget expenditures; inadequate modern equipment (telephone conference system); and having an overly bureaucratic management system causing delays in the reviewing process. The participants viewed the OPPORTUNITIES for the MOPH ERC as having support from the government and high-level management that could be the key to improving the research in Thailand to meet the international levels and could be the national trainers on the ethics of research, and could be transferred to be an independent organization. Moreover, the new Thai FDA guidelines for submission of the drug import permits allowed the parallel submission of the protocol to the MOPH ERC. This could shorten the time needed for the whole reviewing process. They also agreed that the newly formed ASEAN Economic Community (AEC) could allow more experiences and knowledge sharing. However, the MOPH ERC was viewed as having the

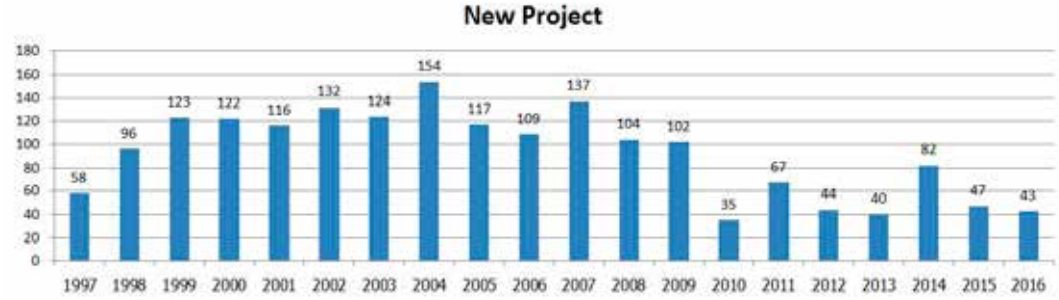

Figure 3 Number of new protocols submitted to the MOPH ERC during 1997 – 2016

following as THREATS : inadequate fluidity in the budget management could result in inadequate reviewing of the submitted protocols as well as in providing training; having other ECs for competitors ; strict rules on reviewing only the Thai-translated protocols causing inability to make changes in the master protocol ; and the committee could be not fully independent as they were mostly government officials who were assigned which could cause the conflicts in the interests, work schedules, and work load.

From the SWOT analysis, a majority of factors affecting the work of MOPH ERC were EXTERNAL THREATS. The MOPH ERC members themselves were independent of politics, institution, academic, and business interests. They could fully protect the rights, well-being and safety of potential study participants, including the communities relating to the submitted research protocols. These were ensured by employing the principles of respect for person, risk-benefits evaluation, and risks management in human participants as well as ensuring that research participants receive appropriate medical care according to the regulations of the applicable regulating organizations and relevant laws.

The law and system on human research ethics review might not be adequate. To ensure the quality of the ethics review, building trust in the ethics review process such as the transparency of the MOPH ERC reports and findings, having clear understanding and accuracy in the regulations, having the system to monitor the committee, having specific and essential qualifications of the members, reporting important research progress and findings, credible sponsors, having appropriate amenities for the committee, and having intellectual property protection laws, these must be documented. Moreover, creating the database for the approved research protocols could be one of the important elements in monitoring the research. Ultimately, certification by third parties should be in place at MOPH ERC.

Future Direction of the MOPH ERC

At present, the Ministry of Public Health requested its affiliated agencies to establish ECs, both at the provincial level and the hospital level. This might be reduced the workload of the MOPH ERC. Moreover, the MOPH ERC had a conceptual idea to establisha regional ethics committee network or the MOPH central institutional review board (IRB) in order to reduce the workload of the researchers. However, each institutional review board should participant in the decision making process, such as joint consideration of the research protocols via teleconference. Furthermore, each IRB should have ability to freely repeat the reviewing process as the IRB must be independent and is directly responsible for the research participants.

As the current research protocols are more complex and with mixed methods and sequences, for example, the monotherapy cancer treatment or the investigation of medical devices, reviewing the research protocols in order to protect the rights, safety, and well-being of the study participants needs the collaboration of stake-holders [13] and can be achieved via:

1. The public sector and community : By promoting knowledge and understanding of the research to the people or community to create an additional public monitoring system.
2. The researchers: By promoting training and educating the researchers to motivate them to conduct standardized research with good informed consent and standardized and accurate data collection processes.
3. Having a strong research ethics network
4. Laws, rules, regulations, society, customs and traditions.

Conclusions

For the past four decades, the works of the MOPH ERC was never interrupted and was accepted by several international organizations, such as National Institute of Health, World Health Organization, US Centers of Disease Control and Prevention, The Armed Forces Research Institute of Medical Sciences, and others. The leader of the MOPH ERC should continue to advocate for the efficient and standardized work by having a commitment to quality assurance in research ethics and accreditation program. This will increase the confidence of the stake-holders, such as research sponsors, researchers, participants, and ethics committee members, in the ethics review process and warrant the future of the human research subject protection in Thailand.

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