*Special Article*

# Factors Affecting Protocol Review Process in Standard Operating Procedures of The Human Ethics Committee of Thammasat University No. 1 (Faculty of Medicine)

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In 2002, the Faculty of Medicine's Human Ethics Committee of Thammasat University No. 1 (TU-EC1) was established, creating standard operating procedures (SOP). Our previous study revealed there was a notable delay in the protocol review process. The authors identified factors that would improve the process for principal investigators (PIs); this would help advance research commencement. A survey was performed using questionnaires. Descriptive data were analyzed by STATA version 9.0. Time used from protocol submission to returning the initial review results to PIs in 2015 to 2018 were collected from protocol review records and analyzed by mean and interquartile range (IQR), 25% and 75%. Problems with literature review, research methodology i.e. limited details, and research design, were the most prevalent delay factors noted by reviewers. Other issues were inadequately written information sheets/informed consent: unnecessary information, inappropriate language choices, and overly complex design. These findings provide important clues to improve the TU-EC1 review process. PIs would likely benefit from more protocol training. In addition, identifying pitfalls, learning the ethics for human studies, and coaching/mentorship programs for new researchers and reviewers would help support the quality and efficiency of the process.

***Keywords:*** Human ethics committee of Thammasat University No. 1 (Faculty of Medicine), Efficiency, Protocol review process, Ethical approval

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There has been great concern about research ethics in human studies due to allegations and reports of misconduct. National and international guidelines have been widely distributed for research participants' protection[(1)]. In Thailand, The Guidelines for Biomedical Research Involving Human Subjects was published in 1975 after intensive discussion. Later in 2007, the National Health Act was given regulatory responsibility for all human research. At least 69 ECs have been established in Thailand at medical schools, public and private hospitals, and other institutes[(2,3)].

As a direct consequence, research ethics committees (ECs) have been formed to protect participants from risks or harms, which could take place during and/or after research; these ECs can, in theory, ensure participant, investigator, and societal rights and wellbeing. Therefore, the ECs role is to ensure proposed research will be conducted in line with appropriate research rationales/plans, scientifically sound. Possible harms, risks, and benefits are vigorously examined. In addition, the participants must be recruited with fair selection criteria and given an opportunity for consent in an appropriate location.

In 2002, The Human Ethics Committee of Thammasat University No. 1 (Faculty of Medicine) (TU-EC1) was established. Total of nine hundred and thirty-three initial review protocols including full board, expedited and exempted review protocols were submitted during 2015 to 2019. Member of human ethics reviewers expert in different medical fields (n = 76) and lay persons (n = 2). One expert and lay person are appointed to review full board protocol type while two experts and one lay person are responsible for expedited review protocol.

There is no appropriate typical single procedure for ethical review for all countries and all research settings. Therefore, we developed our own standard operation procedures (SOPs) firstly in the year of 2006 according to standard international guideline for SOPs. The SOPs provided for all committees, reviewers and researchers to ensure our standards and practices in ethical medical research protocol review are being followed correctly and comprehensively. The revisions are made in every two years or any minor changes of correction is needed. All SOPs include version 1-5 and current SOP version 5.2. The standardized SOP is one of the factors to enhance efficiency of TU-EC1 performance such as speeding up the review process for researchers to conduct efficiently and ensure the procedure performed according to SOPs. Thus, it is necesscary to improve our pratices regarding to the SOPs for efficient evaluation of

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research protocol review. Appointed reviewers must understand their roles according to the SOPs and guideline of human ethical research review for effective protocol review. In addition, reminders of reviewed protocols return from reviwers should be alert in advance to ensure the punctual returning protocols within timeline of ethical approval. The expected outcome of the appropriate SOPs is to facilitate researchers to get their researches started faster and procedure performed according to SOPs. Therefore, the protocol review guideline in the SOPs should be strictly followed to overcome the delay of protocol review process.

Our previous retrospective review was analyzed from research protocol reviews and approvals to explore factors associated with efficient performance in process protocol review and approvals between 2011 to 2014, after the implementation of SOPs version 2.0 and 3.0.

The results revealed a significant delay in the time used in the protocol review process with the rate of achieving KPI goal 39% in expedited review and 16% in full board review. This obviously included the sending of protocols to reviewers all the way to receipt of initial comments for the principal investigators (PIs). The critical problem to be clear where the bottleneck took place was obviously from the reviewers' response Table 1.

Full board protocol review was markedly failed at 83.5%. In addition, randomised research was the most potential factor that caused the delay of response from reviewers. Those of some delay were affected by the year of protocol review in 2013 was 22% delay in sending initial protocol to assigned reviewer and 85 to 89% delay in sending report of reviewer's comments to PI due to the randomized, descriptive, and experimental research design. The time from submission of the initial protocol to the reviewers to receiving comments (KPI1) and KPI3 (receiving revised protocol comments and sending to PI) had no real delays, these 2 processes were outperformed the expected KPIs of 80%. The possible reasons might be: (1) Time management: too busy with their routine jobs e.g. Lectures, round ward and their own research. (2) Too many protocols to be reviewed which is related to time management. In addition, full board protocol review type and randomized design protocol affected KPI2 (Table 1). We suggested that the most possible cause of delay could be because of the protocol of full board reviews were most likely more complicated and more detailed to be reviewed which would consume more time for reviewers. For the randomized research design also affected KPI3. It is suggested that time consuming include the step of gathering several comments from reviewers. Some difficulties in reading reviewers hand writing may cause the delay. The delay of sending protocol to reviewer that occurred in the year of 2013, was due to lack of staff leading to reducing the efficiency of processing document. Increasing number of staff with high potential performance would help to achieve target of KPI. As mentioned, some possible factors involved in the delay, but in order to solve the particular obstacles such as modification of SOPs by extending more time for reviewers to review full board research protocols which include the randomized research protocol was suggested. However, detail information of the particular factors associated with delay to better understand our way forward to improve protocol review process is nessessary to be identified in the present study.

## Materials and Methods

The authors created a survey with questionnaires distributed to the reviewers. A total of 62 out of 78 TU-EC1 members, main and alternate, completed them. Descriptive data were analyzed by STATA version 9.0. Time used from protocol submission to returning the initial review results to PIs in 2015 to 2018 were collected from protocol review records, then analyzed by mean and interquartile ranges (IQR), 25% and 75%. 934 human research protocol submission including 456 full board, 417 expedited and 61 exempted protocols for ethical review submitted during 2015 to 2018 were submitted to TU-EC1 for ethical approval.

### *Ethical consideration*

This research protocol was exempted after protocol submission to The Human Ethics Committee of Thammasat University No. 1 (Faculty of Medicine).

## Results

62/78 TU-EC1 main and alternative members replied. Reviewer gender distribution was almost equal: male (51.6%) and female (48.4%). In terms of university hospital source, they were mostly from Internal Medicine (25.8%). Others ranged from 1.3 to 20.5%, from Preclinical Sciences (20.5%), Pediatrics (10.2%), Psychiatry (7.7%), and Anesthesiology (5.1%). Four other departments, Obstetrics and Gynecology, Ophthalmology, Orthopedics, Community/Family Medicine reached 3.8%. Surgery composed 2.6%. The ENT (Ear, Nose, and Throat), Emergency Medicine, and Thai Traditional Medicine departments along with various other institutes (e.g. College of International Medicine) comprised 1.3%. Out of reviews total done, full board protocol reviews averaged 27.2$\pm$24.6%, significantly less than that of expedited 63.2$\pm$30.9%. PIs were mainly medical lecturers (62.3%), followed by students, residents and fellows (31.1%).

Full board consumed more time than expedited, indicated in Table 3. The major factors delaying the review process varied, but they were usually problems with the investigators' literature review (61.3%), research design (51.2%), and also research methodology (58.1%) e.g. limited details. Other observed factors were information sheets/ informed consent forms deemed to have inadequate design for patient comprehension, things like unnecessary information (58.1%), inappropriate language selections (38.7%), and overly complex formats (45.2%).

Trainings on appropriate protocols, identified pitfalls, responsible research (particularly human study ethics) and coaching/mentorship programs (currently in development) for new researchers and reviewers took place after these factors were identified. The average time used

**Table 1.** Median time (days, interquartile range) of time used in operating procedure of previous study (2011 to 2014)

| Operating procedure | Time based on SOP (days) | Median time (days, interquartile range) | | Achievement of KPI goals (%) (expected KPI = 80%) | |
|---|---|---|---|---|---|
| | | Expedited | Full board | Expedited | Full board |
| From submission of initial protocol to reviewers (KPI1) | 7 | 3 (1 to 5) | 4 (2 to 6) | 86.98% | 87.89% |
| From sending to reviewers to receiving initial comments (KPI2) | 7 | 10 (7 to 14) | NA | 39.02% | NA |
| From submission of initial protocol to reviewers (KPI1) | 7 | 1 (0 to 5) | 6 (6 to 7) | 94.44% | 97.36% |
| From receiving revised protocol comments to sending to PI (KPI3) | 7 | 1 (0 to 5) | 6 (6 to 7) | 94.44% | 97.36% |

**Table 2.** Possible factors affecting KPIs of previous study (2011 to 2014) (unpublished data)

| Factor | KPI1 | KPI2 | KPI3 |
|---|---|---|---|
| Type of protocol | $p = 0.545$ | $p = 0.549$ | $p = 0.448$ |
| Multicenter | | | |
| Non-multicenter | | | |
| Type of protocol review | $p = 0.880$ | NA | $p = 1.000$ |
| Expedited | | | |
| Full board | | | |
| Year of protocol review | $p = 0.034$ | $p = 0.907$ | $p = 0.552$ |
| 2011 | 94.55% | | |
| 2012 | 89.21% | | |
| 2013 | 77.92% | | |
| 2014 | 88.15% | | |
| Research design | $p = 0.152$ | $p = 0.012$ | $p = 0.01$ |
| Randomized | | 85.96% | 88.46% |
| Descriptive | | 71.84% | 85.96% |
| Experimental | | 76.92% | 89.17% |
| Other (pilot study, etc) | | 54.55% | 66.67% |

**Table 3.** Factors affecting protocol review delays: reviewers

| Type of protocol | Median time* (hours, IQR) | Overall submission issues | % | Information sheet and informed consent forms | % |
|---|---|---|---|---|---|
| Full board | 14.5 (1.5 to 18) | Literature review - Insufficient/unclear | 61.3 | Unnecessary details | 58.1 |
| Expedited | 2 (1 to 8.75) | Inexplicit Research design | 51.2 | Inappropriate language choice | 38.7 |
| | | Limited detail of research methodology | 58.1 | Too complex | 45.2 |

* Time used from protocol review to returning comments to EC-TU1

from protocol submission to protocol return (2015 to 2018) indicated review improvements were within acceptable SOPs of 30 days: Table 4.

## Discussion

Significant factors causing delay were revealed. Part of TU-EC1's mandate has always been to improve protocol review efficiency as it is ideal for research to begin as soon as possible. One of the major issues was incomplete submissions. Encouraging PIs to fill out application forms more carefully, with clearer details, is a good and simple step toward reducing delays. Other institutions' studies concur with this, citing variables leading to delay such as incomplete applications[4-6], poor administrative support[7], lack of well-

**Table 4.** Time used from protocol submission to returning protocol to PIs (2015-2018)

| Reviewtype | Median (days) (IQR) | | | |
|---|---|---|---|---|
| | 2015 | 2016 | 2017 | 2018 |
| Full board | 31 (21 to 40) | 26 (20 to 29) | 23 (19 to 32) | 27 (21 to 31) |
| Expedited | 18 (14 to 26) | 21 (15 to 27) | 21 (16 to 27) | 24 (20 to 31) |

trained EC members[8], and so on. These challenges have certainly slowed review times down for us and often appeared as overlapping factors. Till now, recommendations for improvement have been better standardization of the review process, ameliorated training for EC members, and EC board accreditation[9].

In addition, reviewers must be concerned with writing an explicit and correct review, as it is critical to evaluate the possibility of harm to participants. However, if the submission is incomplete or difficult to read, thorough evaluation is almost impossible. First, the literature review should clearly correspond to topic and enough information, making it easier for reviewers to judge the rationale's merits fairly.

Reviewers often stated that information sheets and informed consent forms did not correspond to each other: not only does this delay review, but this makes it difficult to engage participants in studies. Double or even triple checking participant information is critical. Guidelines for information sheets/informed consent forms already tell PIs to only distribute necessary details, use easy-to-understand language, and make forms simple; however, investigators should have a layperson proofread their forms before submission to ensure they are easily understood.

Study design and methodology were two major reasons review delay, Table 2. This suggests that if the appropriate study design and methodology were properly written up, it would reduce review durations. Reviewer concern for participants' rights, safety and welfare might be alleviated sooner than later.

TU-EC1 has actively supported training and/or consultations on how to write ethics committee application forms for new researchers; we have also provided updates for all researchers on revised SOPs and GCP (Good Clinical Practice). Submissions still need to be looked over several times by PIs, before sending to reviewers, using the provided checklists.

On the reviewers' side, automated periodical reminders, before due dates or for reassignment of new reviewers, are relatively simple to implement. Suggestions by the ethics committee, to ease the comment process, include adding line numbers; this would make forms more user friendly. Moreover, the development of an electronic IRB system, e-IRB, has been recently completed and shows a lot of promise as an effective evaluation tool.

The quality of EC and stakeholders, especially regarding accreditation, is still being debated with no clear conclusions having been drawn[10,11]. Other reports have supported EC roles in safeguarding participant rights and welfare while magnifying EC effectiveness[12,13]. The TU-EC1 was officially recognized by The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) and Forum for Ethical Review Committees in Asia and the Western Pacific (FERCAP) after an intensive accreditation process. The authors have noticed the recommendations from these organizations have enhanced our review process, which has most likely led to better participant protection.

Page and Nyeboer (2017)[13] proposed a model of the research ethics review to solve dissatisfaction in review delays. It demonstrated various components such as EC workflow, stakeholders, and accountabilities and provided a method of problem to develop solutions. The strategies only came about with clear problem identification. Some issues remained; however, these were eventually eliminated when stakeholders (including PIs, EC members and staff) deliberately adhered to the review process workflow in the decision-making process.

The authors suggested to use standard checklist or guideline in protocol review process for both reviewers and committees in order to reduce time of protocol review. In addition, training on risks and benefits of human research protocol must be provided for reviewers and TU-EC 1 members to have best practices in ethical consideration leading to fast review research protocol process.

Limited reviewers in some particular fields such as brain and heart expertise for protocol review could be associated with the delay review protocol process. Moreover, staffs of TU-EC1 need to update training on administration in order to keep track of reminder in review protocol process. Further changing study will explore deeply how to shorten the minute of full board consideration as the meeting discussion has been time consuming with some negligible issues.

## Conclusion

PIs must engage in more training to understand appropriate protocols; they also need to know inherent pitfalls, i.e. delays may happen if their submissions are incomplete. Moreover, increased reviewer recruitment from different fields would help: luckily, this is already underway. At all times, The Human Ethics Committee of Thammasat University No. 1 (Faculty of Medicine) must consider both reviewer and PI needs and limitations throughout this ongoing and evolving process of protocol review improvement.

## What is already known on this topic?

Our previous study revealed there was a notable delay in the protocol review process.

## What this study adds?

Factors causing delay in the review process were detected. The identified problems helped us develop strategies for a better protocol review process. Training, coaching and recruitment of more reviewers were suggested as improvements which would also help protect research participants.


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## Potential conflicts of interest

The authors declare no conflicts of interest.

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## ปัจจัยที่ส่งผลต่อกระบวนการทบทวนโครงร่างการวิจัยในการดำเนินงานของคณะอนุกรรมการจริยธรรมการวิจัยในคน มหาวิทยาลัยธรรมศาสตร์ ชุดที่ 1 (คณะแพทยศาสตร์)

สุมาลี คอนโด, ธนา ขอเจริญพร, ทิพาพร ธาระวานิช, ภาสกร ศรีทิพย์สุโข, ไวพจน์ จันทร์วิเมลือง

ในปี พ.ศ. 2545 คณะอนุกรรมการจริยธรรมการวิจัยในคน คณะแพทยศาสตร์ ชุดที่ 1 (TU-EC1) ได้ก่อตั้งขึ้นโดยได้เขียนแนวทางการดำเนินการมาตรฐาน ทั้งนี้จากการศึกษาก่อนหน้านี้ได้พบว่ามีความล่าช้าของกระบวนการพิจารณาโครงร่างการวิจัยที่ขอประเมินจริยธรรมการวิจัยในคน ผู้วิจัยจึงได้ศึกษาหาปัจจัยที่เกี่ยวข้องของความล่าช้าเพื่อพัฒนาปรับปรุงกระบวนการพิจารณาโครงร่างการวิจัยที่ขอประเมินจริยธรรมการวิจัยในคน ซึ่งจะช่วยให้ผู้วิจัยสามารถดำเนินการวิจัยได้ในเวลาที่เหมาะสม โดยออกแบบสอบถามสำหรับอนุกรรมการหลักและอนุกรรมการเสริม การวิเคราะห์ผลข้อมูลเชิงพรรณนาโดยใช้โปรแกรม STATA version 9.0 การวิเคราะห์ข้อมูลของระยะเวลาที่ใช้นับจากวันที่ทำการยื่นโครงร่างการวิจัยจนถึงวันที่ส่งผลการประเมินของการพิจารณาคืนแก่ผู้วิจัย จากบันทึกของโครงร่างการวิจัยที่ยื่นขอประเมินจริยธรรมการวิจัยในคน ในช่วงปี พ.ศ. 2558 ถึง พ.ศ. 2561 วิเคราะห์โดยหาค่าเฉลี่ย และพิสัยควอไทล์ (25% และ 75%) ปัญหาที่เกี่ยวข้องทำให้เกิดความล่าช้าที่ผู้ทบทวนส่วนใหญ่ได้แสดงในผลการตอบแบบสอบถาม คือการทบทวนวรรณกรรม ระเบียบวิธีวิจัย เช่น รายละเอียดข้อมูลมีจำกัด และรูปแบบการวิจัย ปัจจัยอื่นๆ ที่ทำให้เกิดความล่าช้าในกระบวนการทบทวนโครงร่างการวิจัย ได้แก่ การเขียนเอกสารข้อมูลสำหรับอาสาสมัครที่มีข้อมูลไม่เพียงพอ และเอกสารขอความยินยอมที่มีข้อความที่ไม่จำเป็น ภาษาที่ใช้ไม่เหมาะสม และมีความซับซ้อนเข้าใจยาก จากการศึกษานี้ได้แสดงให้เห็นถึงสิ่งสำคัญของการพัฒนาปรับปรุงกระบวนการทบทวนและประเมินโครงร่างการวิจัยของคณะอนุกรรมการฯให้มีประสิทธิภาพ ผู้วิจัยจะได้ประโยชน์หากได้เข้าอบรมการเขียนโครงร่างที่ใช้สำหรับการประเมินจริยธรรมการวิจัยในคนได้อย่างถูกต้องมากขึ้น นอกจากนี้การพบจุดบกพร่องหรือข้อควรระวังการมีความรับผิดชอบด้านจริยธรรมต่อการวิจัยในคน และการให้คำปรึกษากับนักวิจัยใหม่และผู้ทบทวนโครงร่างที่ใช้สำหรับการประเมินจริยธรรมการวิจัยในคนจะเป็นส่วนสำคัญในการสนับสนุนให้กระบวนการประเมินโครงร่างการวิจัยนี้เป็นไปอย่างมีคุณภาพ และประสิทธิภาพยิ่งขึ้น