CLINICAL STUDY MANAGEMENT MODEL: CASE STUDY OF IN-HOUSE AND FULLY OUTSOURCED STUDY

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ABSTRACT

The trend of outsourcing services has been increased in various fields including R&D and clinical research a few decades ago. Nowadays, both in-house and outsourcing clinical studies are still available in the market and pharmaceutical companies. This paper aims to understand management and challenges in two different resourcing model of the clinical study.

One in-house observational clinical research and another fully outsourced observational clinical study have been selected as the case study. Two clinical project managers from each study have been interviewed to collect data and explore the real case in five topics including management model, governance, stakeholders engagement, challenges, and experience sharing about resourcing models.

The selection of the management model must be depended on strategy, objective, and available resources. The in-house model suits for the keeping relationship and experience while full-outsourcing for efficiency. The appropriate tools and activities are required to governance and oversee the quality and performance of the project. The partnership program is recommended for the outsourcing model. Communication is a key success. The project quality of a fully-outsourced study should be more considered from a company perspective because the study has not been fully managed by the sponsors. The technical skills and socio-cultural skills enhance the project manager to manage the clinical study and work together with all stakeholders.

The paper provides an example of both in-house and fully outsourced clinical studies to understand management, challenges, and recommendation for the selection of the resourcing model and improvement for a future clinical study.

KEY WORDS: CLINICAL STUDY/ MANAGEMENT/ IN-HOUSE/ OUTSOURCING/ MODEL

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CHAPTER I
INTRODUCTION

Before becoming new medicines available worldwide, drug discovery and clinical trial processes are mandatory and compulsory to prove the safety and efficacy of those new treatment agents. The clinical trial is an important step to test medicine in humans and demonstrate that a new intervention has beneficial more than risks. Data from testing in a laboratory before and during clinical trials are required for submission and review by the Food and Drug Administration, Ministry of Public Health for drug registration purposes. Regarding benefit-risk acceptance considering by the expert reviewer of the Health Authority, new medicine will be approved and marketed for patients.

A clinical trial is also known as an interventional study which is one of two types of clinical studies. Clinical research or clinical study is a broad word of medical research in humans (NIH 2017). Two types of the clinical study are including clinical trials and observational studies. Besides clinical trials, observational studies are very important in medical fields. This kind of study serves the understanding of diseases, treatment pattern and long-term outcomes in real-life which may be a limitation in a clinical trial environment. Data from an observational study will be useful for improving medical and patient care. It may help to discover some possibilities of new indications of medicine.

The clinical study team and/or monitoring team are a function to handle the clinical research. Regarding most of the clinical trials initiated by the pharmaceutical company, the clinical research team is one of a unit in the pharmaceutical industry for a long time ago. So, it is called as an in-house clinical research management model. However, in a few decades, the organization and management model has been changed in some pharmaceutical companies. Some big pharmaceutical companies have a direction to downsize and reduce the cost of research. Therefore, these activities have been outsourced to the external vendors – Contract Research Organizations (CROs) (Landhuis 2018). Data from the association from 2007 to 2011, the pharmaceutical

company use CROs in clinical study rising 44% (Handerson 2013). The Contract Research Organization is a firm in charging of and focus on research activities for the biotech or pharmaceutical industry. This management model is known as the outsourcing model.

Nowadays, in the pharmaceutical industry, the different management model of clinical study has been used. Even though the rising number of CRO businesses, some pharmaceutical companies are still using the in-house clinical research team to be responsible for industry-initiated study while some firms have decided to implement the outsourcing model. The outsourcing model could be only contracting the external monitoring team/staff from the external firms - CRO or operation model as fully outsourced. For the fully outsourcing model, it means that the entire clinical study project management is serviced and managed by the vendor. In this case, the pharmaceutical company will be known as "sponsor" and oversee the status of the project.

There are pros and cons to each type of clinical research management model. In general, the outsourcing model is considered and selected in many pharmaceutical companies due to its advantages. This model requires less management cost as it is easier to control the overall project budget. In addition, there is no concern about human resources matters such as retaining and developing staff. On the other hand, for the in-house management model, the company has its own experience staff specific to the company culture. The communication gap is less than the outsourcing model and easier to monitor the project closely. Because of the benefits of each management model and the firm goal, both in-house and outsourcing models have still emerged in the pharmaceutical company and the clinical research market. However, besides advantages, the concern and limitation of each model should be considered before choosing and implement the management model to the clinical study.

The objective of this paper is to explore and understand the clinical study management between in-house and fully outsourcing models in multi-dimensional perspectives including project management, resources management, project cost, stakeholder management and challenges in the project. The example case study of two observational studies in different management models including one in-house and another one fully outsourced clinical study will be analyzed together with experiences

sharing by study staff will be gathered and described from the in-depth interviews as per mentioned perspectives. The expected benefits from this paper are to be a case study of different clinical study management model. The recommendation and limitation of each case study will be useful as the lesson learned and supporting information to consider and improve in clinical study activities for both in-house and outsourcing management model.

CHAPTER II
LITERATURE REVIEW

2.1 Clinical Study and Drug Development Process

Clinical Research (as known as Clinical Study) is a medical and/or health study using human volunteers. Its purpose is to produce valuable knowledge for understanding, preventing and treating human disease. There are two main categories of clinical research. (NIH 2017, ClinicalTrial.gov 2019)

2.1.1 Clinical Trials (Interventional studies): For this type of study, the specific interventions which may be drugs, devices, procedures, or others such as diet and behavior will be assigned to participants according to the research protocol or study plan designed by the investigators. The intervention in clinical trials may be the comparison of a new medical intervention to a currently available standard one, to a specific another active comparator, to a placebo which is non-active ingredients, or to no intervention that is also called single-arm design. Normally, the purpose of this study type is to determine the efficacy and safety of the new intervention comparing to the interested comparator by measuring certain outcomes. For example, investigators conduct the study of new medicines in patients who diagnosed with lung cancer to see the decrease of tumor size and clinical response.

2.1.2 Observational studies (Registries): For this kind of study, there is no new intervention involvement. The participants receive their routine medical care such as drugs, devices, procedures, etc., then the investigators collect data from medical records and assess outcomes according to a study plan or research protocol. For example, investigators observe and collect data to study in patients with lung cancer to learn about disease patterns and treatment regimens in the real-world. The observational studies are important to find out some investigative questions in which clinical trials are not addressed or unable to conduct due to ethical issues. There are 2 sub-categories

under observational studies including case-control studies and cohort studies (Song 2010).

Case-control studies: This research will be conducted in patients and analyzed historically for the disease etiology.

Cohort studies: It is a study in a group of people with defined interested characteristics and followed up to explore the specific outcomes. It can be either a prospective or retrospective approach.

Drug Discovery and development processes are the procedure to find and test new medicines before launching into a market. Normally, the drug development process takes time about 10-15 years to release one new medicine since the beginning stage which is a discovery period to the time it is available for patients. The average research and development cost for successful medicine is about $800 million to $1 billion. From 5,000 to 10,000 potential compounds in the drug development process, there is only one medicine has been green-lighted for approval and marketed (PhRMA 2007).

The overall process is starting from pre-discovery. This stage is to understand the disease and select a target of medicines' action. Then, a compound will be created and test to make it work. The compound which suits the target of action will be identified as candidate drug. It will be tested for the pre-clinical stage by researchers in the laboratory and in animal models for effectiveness and safety purposes. After all pre-clinical testing data satisfied and justified that it is safe enough, the drug candidate will be escalated to human trials which are called the "Clinical Trials" stage. Clinical Trials is the one of key procedure in the pipeline for drug development. They are divided into 4 phases with certain objectives to prove the efficacy and safety of the intervention (Chen 2018).

Clinical Trial phase 1 is to identify dose range and evaluate safety in a small group of healthy volunteers (20-80 subjects).

Clinical Trial phase 2 is to assess the efficacy of a new treatment in patients comparing to a placebo group. The number of participants will be about 100-300 patients.

Clinical Trial phase 3 is to confirm the findings and treatment effects of new medicines in a large patient population (1,000 – 3,000) by comparing the test drug to the current standard treatment.

Clinical Trial phase 4 is the post-marketing study to explore long-term safety and efficacy which involve a thousand patients.

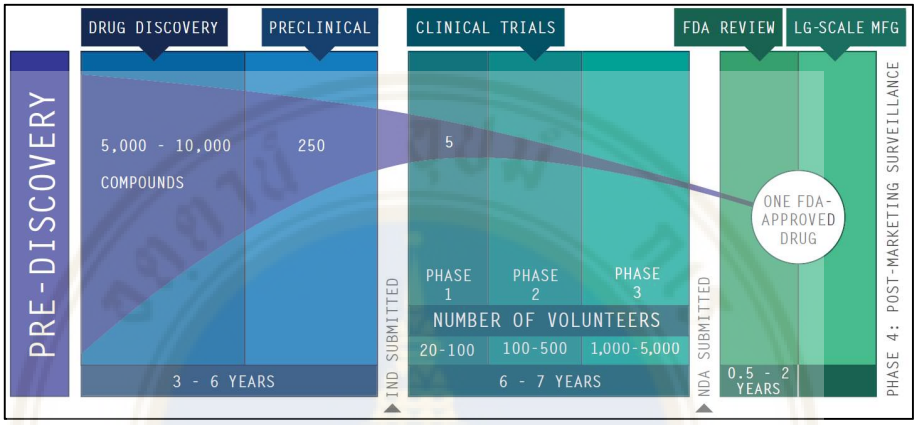

Figure 2.1 Drug Development and Clinical Trial Process (PhRMA 2007)

In each clinical research, there are various and control processes to be followed. The initiator (also called sponsor) must develop the study protocol and related materials to be used in the clinical research. The documents and resources to be identified and approved by its organization. Then, the potential physician will be approached and invited to be the investigator in the clinical study. The approval processes by the Health Authority and Ethics Committees are required before initiating the project. Once approved, the investigator can start recruiting and providing the intervention (if any) to the patients. All data will be recorded in the Data Collection Form and reviewed by the clinical study team. When patients have been completed a follow up visit, the database will be locked for statistical analysis followed by clinical study report preparation and publication of the results.

Figure 2.2 Clinical Study Process (MLKLibraryatSJSU 2019)

2.2 Project Management

Definition of a project has been provided by The Project Management Institute:

"*A Project is a temporary endeavor undertaken to create a unique product, service, or result*".

Clinical study/research is considered as a project because it has an established objective, a specific life span of a project, an involvement of various functions and professionals, not a routine job, and requires specific cost, time and performance. Project management is also defined as planning, directing, and controlling all human and resources to meet the specific requirements such as time, cost, and performance of the project.

Project Managers are ultimately responsible and accountable for project performance. They must work with cross-functional teams, vendors, subcontractors, suppliers, etc. to complete the projects.

Project Governance is established to improve project management. Its features are to provide senior management with 3 main things including An overview of all activities in the project; A big picture of organizational resources utilization; and the risk assessment in the project. There are two dimensions that driven the project execution which is technical and sociocultural. The technical side consists of formal, procedure, logic and disciplined. Another side is related to soft skills to shape and facilitate the team for a successful project.

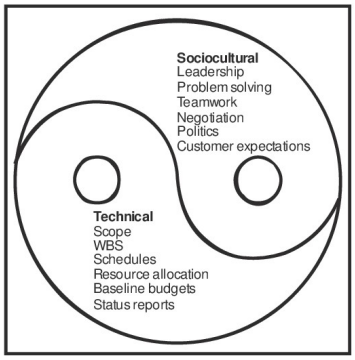

Figure 2.3 The Socio-Technical Dimensions of the project Management Process (Larson 2014)

2.2.1 Steps in Project Management

To manage the project/study, the following 7 steps from the beginning to close out the project are including; Establish goals, objectives, and scopes of the project; Team-up; Set project budget and timelines; Set action and how to implement the project/study; Project implementation and monitoring; Respond to challenges, problems, and deviations; and Post-project assessment together with lesson learned.

2.2.2 Determinants of Project Success

As per the project management aspect, there are 3 traditional criteria of project success which are **"Time"**, **"Budget"**, and **"Performance"**. These triple constraints are routinely assessed for project performance. Nowadays, a fourth criterion which is **"Client Acceptance"** has been added and become the new Quadruple Constraint. According to Atkinson, the understanding success model has been introduced and provided more clearly define project success or failure (Pinto 2016).

Table 2.1 Understanding Success Criteria (Atkinson 1999)

Iron Triangle	The information system	Benefits (organisation)	Benefits (stakeholder community)
Cost	Maintainability	Improved efficiency	Satisfied users
Quality	Reliability	Improved effectiveness	Social and
Time	Validity	Increased profits	Environmental impact
	Information–	Strategic goals	Personal development
	quality	Organisational-learning	Professional learning,
	use		contractors profits
			Capital suppliers, content project
			team, economic impact to
		Reduced waste	surrounding community.

2.3 Resourcing Models

Refer to project management, resourcing is a part of the initial stage. This point must be considered during the pre-study period. In general, there are 2 main models for resourcing matters which are in-house and outsourcing models. The selection of resourcing model must be considered in various aspects from strategic, tactical and operational levels as per following criteria: the complexity and size of the clinical research; appropriate resources availability (external or internal); CRO's competency and capacity; any internal objectives to develop or maintain professional; level of internal oversight requirement; and functions/activities to be outsourced (Finch 2017, Stamenovic 2017).

2.3.1 Resource in-house

This model is using the internal resources such as headcount/permanent staff in the company. For this paper, it also includes contractors. The company Standard Operating Procedures (SOPs) are quality documents to control and ensure internal activities.

The advantages of running in-house clinical research activities in a company are including Full control quality and costs; Direct stakeholder engagement.

However, there are some disadvantages of the in-house team. For example, it requires specialists with wide range experiences; A constant and steady number of researches required to fulfill resource demand; It is required to contract staff in many countries for multinational studies.

2.3.2 Outsourcing/Fully Outsourced

Outsourcing is a model that an existing internal activity in a company contracts out to another vendor/company. It can be a part of an activity or a whole activity. For a Pharmaceutical or Biotechnology company (in this case, it is called sponsor), a Contract Research Organization (CRO) will be a third-party vendor proving services of drug development and clinical study management. Due to the downsizing of pharmaceutical companies, CRO business started in the mid-1990s (Dimachkie 2012). The full study outsourced means all clinical research functions are outsourced such as

study management, regulatory submission, data monitoring, data management, statistics and programming, and medical writing (Finch 2017).

There are many advantages of outsourcing for a company including; Costs reduction (turn fixed cost to variable cost), Reduce internal resources/staff, high level of expertise, faster project completion, fulfill the deficiency of resources in a company and flexibility.

In term of limitation of outsourcing projects and trials, they consist of one CRO may not strong enough to operate all activities in clinical research; Speed and quality might be at risk due to interpretation and commitment of CRO; Loss of control by sponsor; Coordination breakdown; Interpersonal conflict due to different organization; Security issues; and sometimes the investigator prefers to work with sponsor staff than CRO team.

The oversight is required as a risk-based approach together with quality management in order to ensure that the vendor/CRO has completed activities as per the sponsors' expectations. According to Good Clinical Practice (GCP) – the international guideline of ethics and procedures for conducting clinical research, although the activities have been outsourced to CRO, the sponsor is accountable for the clinical studies. Therefore, it is mandatory for the sponsor to oversee the activities.

The following tools are samples using for oversighting the project.

- Oversight Plan (Protocol, study information document, contact details, issue logs, specification, etc.)
- Meeting and Minutes (kick-off and routine meeting)
- Feedback process and Lessons learned documentation

With these oversight tools, sometimes the difficulties of outsourcing clinical research management occur. The following information is example of a problem in outsourcing clinical study; Lack of communication between a company and CRO; Misinterpretation scope of work by CRO; Complexity of infrastructures; and over/under quality control of work resulting to insufficient or wasting too much time of oversight (Ray 2016, Finch 2017).

CHAPTER III
RESEARCH METHODOLOGY

3.1 Research design

The research methodology selected for this thematic paper is qualitative research to explore and describe the findings in-depth from the interview. The objective of this research is to explore and understand the management of clinical study in two types of resourcing model. They are in-house clinical study and fully outsourcing clinical study. The area of investigation consists of project management, resources management, project cost, stakeholder management and challenges in each project. Regarding this intention of primary data collection, the qualitative research is fit and enable to understand the detail, situation, and rationale in each dimension of questions initiated by researchers. It serves to gather insight and realistic perspective from richer information provided by the subject/interviewee comparing to the questionnaire/survey. The qualitative research technique for data collection in this paper is an in-depth interview. The detail of the case study, interviewee and research questions have been mentioned accordingly.

3.2 Methodology

3.2.1 Clinical Study Selection Criteria

Regarding the aim of this paper is to explore two different resourcing models in clinical research fields, the example case study of both in-house clinical research and fully outsourcing clinical research have been chosen for review and analysis. From accessibility, permission and confidentiality concerns, two observational studies can be retrieved as for the case study in this thematic paper. Both are classified as clinical studies and initiated by the pharmaceutical company to describe the diseases and treatments in real-world practice.

For confidentiality purposes, pseudonyms will be used in describing the general information of two example case studies. The short brief introduction of two clinical studies has been mentioned below. The general information of both clinical projects such as study design, resourcing model, and resources management will be tabulated and described in Chapter 4: Findings analysis.

Study A: This clinical study is an observational study conducted in one country with more than thirty participating hospitals. The resourcing model of this study is an in-house study. The study team and monitoring team are all internal staff in the company. The duration of the project is approximately 6.5 years starting from late 2012 to 2019.

Study B: This clinical research is also an observational study initiated by the regional level. There are eight countries enrolled in this study including the country conducted in study A. Study B has been fully-outsourced to one of big CRO in the world. CRO is responsible for all of the activities since study start to the end of study activities such as study report. The company representative is in charge to oversee the project. The study duration is about 6 years from 2013 to 2019.

3.2.2 Interviewee Selection Criteria

To align and understand in-depth of each case study selected for this paper, the researcher decided to approach one person who involved in each case study – Study A and Study B. The role of interviewee should be at least project manager or project coordinator because these positions contribute and have information not only the project activities but also some strategic and tactics rationale of the clinical project.

From the criteria above, the researcher will collect data from two project managers who have experience and involve in the case study. As per data privacy and confidentiality purposes, pseudonyms are also used in describing the background of each project manager and mentioned in this thematic paper. For Study A, the information will be collected from Ms. Adele while Ms. Beyoncé will provide information for Study B. The interview will be done approximately 45 minutes per interviewee. According to the interviewees' schedule, the data collection was done with Ms. Beyoncé on 1st November 2019 via telephone conversation because she is based in

overseas, followed by Ms. Adele on 7th November 2019 at her office in Bangkok. Below is the general background of both Ms. Adele and Ms. Beyoncé.

Ms. Adele: She is a person who involves in the study preparation and study start-up period of Study A. More than 8 years, she has been in clinical research fields with the pharmaceutical company. She used to be the local representative to work with the regional study team of the company for the global clinical trials. She also has the experience to deal with local CRO for some clinical studies. She used to oversee both observational studies and clinical trials.

Ms. Beyoncé: She is a project manager of Study B. Before joining the internal team of the company, she used to be in a clinical research team of both pharmaceutical companies and CRO. She also has experience in clinical research fields for more than 10 years including clinical trials and observational studies.

3.3 Interview Questions

The research questions for interviews are developed from the project management framework including information from literature review. They can be divided into 5 main topics with 15 questions as shown in Appendix A. These questions are designed to be opened-end. They will be used to guide for interviews but not limit as to open for the discussion.

CHAPTER IV
FINDINGS ANALYSIS

The general information for both Study A and Study B was shown in the table below. The interviews were conducted with Ms. Adele and Ms. Beyoncé to provide opinions and information for Study A and Study B, respectively. The information was consolidated in 5 main categories.

Table 4.1 Summary of Study A and Study B Characteristics

	Study A	**Study B**
Study Design	Prospective, Observational study	Prospective, Observational study
Resourcing Model	In-house	Fully outsourced
Size	1 country More than 30 hospitals	8 countries More than 50 hospitals
Duration	6.5 years Late 2012 to 2019	6 years 2013 to 2019

4.1 Strategy, Objectives and Management Model

Study A: The in-house management model has been selected for this study because of 2 main reasons. Firstly, an estimated project cost provided by Contract Research Organization (CRO) was a very high price comparing to using internal resources. The CRO calculates the cost per activity and per working hour. For example, at that time, one telephone call between the CRO with the hospital for working will be charged 500 Thai Baht per time. Any extra request for the CRO to contact the hospital or on-site visit with the doctor or nurse at the hospital will be added to the study budget.

On the contrary, the internal resources are hired as full-time staff in the team/company. If any additional request or visit required, there is no add-on cost charged to the study.

Secondly, the complexity of communication in the fully outsourcing model is considered. If the company would like to implement some actions, the company needs to contact the CRO representative first. The information will be cascaded to the regional project manager (if any), then local project manager, followed by the local project coordinator (also known as "Clinical Research Associate: CRA"). This loop communication is quite complicated than an in-house model. The company can implement the action directly with the local project manager and/or local project coordinator. For the complexity of the communication loop, it can lead to miscommunication and transcription issue including incorrect actions at the local level.

In addition to the rationales above, another goal of the in-house resourcing model is to keep the relationship between the company and the doctors. During the study period, the local team will work together with the doctors and company staff. This will help to engage the physician in the scientific field. Some insights could be collected during the study and external stakeholder engagement. It is not only supporting the study but also the company. Therefore, Study A has been managed by the local clinical team instead of the fully-outsourcing model. At that time, from internal assessment in terms of the number of studies, the number of hospitals and the workload of activity in each local project coordinator, the internal resources are available to handle this study. During the study start-up period, it required resources to spend time working on documents and work with all hospitals, only one project coordinator may not cover all activities. So, the project manager allocated two staff for supporting these activities during the pre-study period.

According to the quadruple constraint concept, in this Study A, the requirement is most important because the ultimate goal is to have a result from the study for publication. The data is required to be utilized further for supporting and improving the treatment in the patients. The data cleaning, data review, and data recheck were done during study conduct and took 4-5 months after data completion to ensure the quality of data. Client acceptance is highly important as well because it is required to get an opinion from the doctors who are experts in real-world practice. The relationship between the team, company and the doctors who participate in Study A is

mandatory. At least a monthly study update must be done to keep communication between the study team and the doctors. The study team tries to keep the budget as plan and strict to the defined timeline. The budget has been monitored with a range of 5% buffer. However, these two components are flexible to ensure that the requirement and client acceptance are meet the study team expectation.

Study B: Study B is a fully outsourced clinical study. The resourcing model was decided at the global level. Study B is a big scale project which involves 8 countries and more than 50 hospitals across the region. If this study is managed by the local clinical team, it is required for the core study team and the company global project manager to deal with 8 local clinical teams. With the fully outsourced model, the global team only contacts with one representative, the project manager from the vendor or CRO. In addition, there is a resource constraint in a few countries. Therefore, Study B has been fully outsourced to the CRO. Moreover, the global team expects the expertise of the CRO to manage Study B in different countries and different region.

The procurement and vendor selection process is in place. Before choosing the CRO, the internal quality and professional team will perform a quality check by visiting the vendor, reviewing all processes and documents, interviewing the staff. This process takes a long period, then the result from the vendor qualification process will be announced by the audit team. Then the qualified CRO can be included in the procurement process including auction and negotiation. For Study B, the partnership CRO has been selected as the vendor. This CRO has been qualified and joined as a partnership program with the company for more than 6 years. One benefit of the partnership program for the company is to have collaboration in strategic planning of the clinical study footprint for the new drug since the clinical trial phase 1 to phase 3. The CRO can support decision making on what, how and when to launch the clinical study.

For the quadruple constraint concept, the requirement is the most important. Same as other clinical studies, the output or deliverable is the necessary which cannot be deviated. If the output is poor or less quality, all of the investment in the study will be less meaningful. The time depends on the outcome of the deliverable. The milestones are defined at the beginning and can be revised reasonably. The cost and client acceptance are also important but less concern than the outcome. For example, the

global team decided to delay the publication because they would like to include all comments from the internal reviewers and external experts who are participating physicians in the study.

To manage resources, initially, there were only 2 main contributors from the company including the global project owner from the medical team and global project manager from the clinical team. It made a huge workload and stressful for the 2 internal staff. Then, the global team set up the internal staff who have a specialty in data management and statistical analysis to support the global project manager and work with the data manager from the CRO. In terms of budget management, the global project manager will review all invoices against the agreement. Any payment excluding from the contract will not be accepted by the global project manager. Then, the CRO project manager will work internally to control the budget and activities as defined in the agreement.

Analysis: The strategy and objectives of conducting the clinical study are a key decision of the resourcing model. The resource availability is also a factor for the decision. The reasons for the in-house managing model in Study A are including budget concern, flexibility, less complexity of communication loop, internal resource availability and focus on external customer engagement. For the Study B, due to large scale of the clinical project, to avoid the huge effort from the company side, and limited resources of the local clinical team in some countries, the global team decided to outsource the study to the partner CRO which is a qualified vendor as per the company procedure and partnership program. The CRO can also support the company in clinical study pipeline planning and execution from its expertise. This case is aligned with the global trend of collaborative partnerships between CROs and Sponsors (Hughes 2013) and why the outsourcing clinical study is required (ClinicalInvestigation 2014).

The requirement/performance is the priority for both Study A and Study B because of the goal to deliver the good quality of the data as per Good Clinical Practice (GCP) (DrugControlDivision 2009). The budget and timeline will be accepted and flexible to support the constraint of the requirement. Especially for Study A, the client acceptance is the second priority which aligned the objective and strategy to conduct the study. The resource allocation is considered to manage the tasks and workload in the team.

4.2 Project Governance

Study A: For project governance in Study A, it has been implemented since the pre-study period until the study termination. The dedicated study team will be established. Regarding the local study, the core study team is including the medical manager who is the project and budget owner; clinical project manager who oversees and manages the study operations; the study director who is the chairman of the study. The project review meeting has been conducted every month to review the status of the study against milestones and budgets. The issue and action plan for further steps are also discussed in this meeting. The monthly clinical team meeting will be led by the project manager and attended by the project coordinator to understand the up-to-date activities in each hospital and identify issues if any. The meeting with another function such as the data management team is arranged to follow up and ensure the activities succeed within a timeline since the study start-up. More frequent meeting with the data management team is done especially after data completion to monitor the data review and data recheck process.

Besides, Standard Operating Procedures (SOP), the tools and documentation are very important for a clinical study to ensure the quality and compliance of the project. Meeting minutes are required for all meetings and filed in the study document file (called "Trial Master File"). This is to comply with the Good Clinical Practice that "No document, nothing happened". Another mandatory document is the Monitoring Plan. Monitoring Plan is a document to define how the quality control implemented in the study. For Study A, it is required that the project coordinator (also known as "the monitor") must visit the hospital to review medical record against with data in the data collection form every 6 months to ensure the accuracy of data in the study (also called "monitoring visit"). The report from the monitoring visit must be reviewed by the project manager for quality purpose and issue detection. The project manager may conduct a co-visit with the project coordinator to ensure the quality of the project.

The Risk Management Plan (RMP) is another document to manage the identifiable risk. It has been prepared since the study start-up and reviewed through the study period. An example of identifiable risk is the slow recruitment of patients into Study A. To manage this risk, the project manager will project the patient enrollment

curve and monitor the actual recruitment against with plan. Once the recruitment behind the schedule in 2-3 months, the new hospitals will be approached to participate in the study to contribute to the patient enrollment achievement. The RMP can be revised and added more information according to the situation.

Study B: The project governance conducted by the high-level committee which is called the governance team. The focused topics in the meeting are to review deliverables, timelines, and budgets. Any major and critical issues will be escalated from the CRO project coordinator to the CRO project manager, followed by a CRO contact person for the company. The global project leader will raise those important issues to the governance committee. The meeting is arranged monthly. The dashboard will be used and tracked the status of the study with color in "Red", "Yellow", or "Green" which means "delay", "potential delay" and "on-track", respectively. In addition to the project governance committee, the operations meeting has been conducted for specific functions and in-depth discussion with the operational level. For example, the meeting between the global project manager and the CRO project manager. The CRO may invite data manager or project leader in each region in the meeting also. The frequency of this meeting is every week at the pre-study period, then change to monthly meetings after the end of patient enrollment.

The supporting tools and processes are also set up for project governance purposes and quality assurance. The global project manager can access to the data collection form system to review information. The CRO clinical study document database is also opened access for the global project manager to do randomly quality check. The global project manager can perform oversight visits annually to review the related important document such as financial documents and master service agreements. Especially for the CRO in the partnership program, there is the operational partnership manual to define all SOPs of the CRO and what the process is for each activity. Even though the supporting tools and mentioned processed, it is quite difficult to understand and ensure the full quality at an operational level. The global project manager can do only a random check. This is different from the in-house management model. The project manager can fully control the project and operational level via an in-house project coordinator.

For the RMP of Study B, as it is a fully outsourced study, the CRO is a person to prepare the document and send it to the company for review and approval. The possible risk will be identified using a score to classify the severity of each risk. The mitigation or contingency plan will be also described in the RMP document. The RMP has been established since the early stage of the clinical study until the end of the study. It can be revised as appropriate according to the identifiable risk.

Analysis: For both Study A and Study B, project governance has been implemented since the study initiation. The tools and activities are including meeting, minutes, dashboard, newsletter, study protocol, SOP, monitoring plan and RMP. This process is to comply with the GCP to have established processes and documentation. As the fully outsource study for Study B, the CRO is responsible to prepare RMP and all required documents. On the contrary, as the in-house project, the internal staff will manage all documents for Study A which is the in-house study. The relevant person in the clinical study team will join the meeting to review and monitor the project status. For the Study A – the in-house study, the quality control can be done and fully oversee by the local clinical team whereas there are limitations for the company to get in touch with all information and situation in Study B which is the fully outsource study.

For Study B which is a fully outsourced study, the operational partnership manual is the supporting tool in governance like the other Sponsors and CROs collaborative partnership program. In the market, the formal governance structures implementation would help to improve strategic, operational processes. This will facilitate the effective and smooth execution of the clinical study (Hughes 2013).

4.3 Stakeholders Engagement

Study A: Stakeholders identified in Study A are including both external and internal customers. The internal customers consist of the medical team (the project owner), the clinical team (operations management), the drug safety team, and the commercial team. The pharmaceutical company must gather and submit the safety report to Health Authorities. The clinical team needs to inform and work with the drug safety team for safety reporting. The commercial team may support to advise and connect the clinical team to a new physician when the clinical team has no experience

or never work with a new doctor before. To manage these stakeholders, communication is a tool to keep everyone on the same page. If any issue, the clinical team needs to consult the project owner (medical team) for decision and solution as soon as possible. The monthly meeting with the medical team and drug safety team is also scheduled to communicate the study status.

For the external customers in Study A, they are including physicians/nurses at the hospital, Health Authorities, and Ethics Committees. The clinical team needs to keep a relationship with doctors/nurses because they are the main contributors to recruit patients and collect data for the study. The monthly email or telephone contact must be done to keep engagement. Physical meetings such as on-site visits will be conducted as mentioned in the monitoring plan. For Study A, it requires to do monitoring visits every 6 months. The ad-hoc visit can be arranged if any issue. To manage Health Authorities and Ethics Committees, the guideline provided by them must be followed to avoid the issue and misunderstanding.

Study B: The internal stakeholders are including global medical team who is the project owner; local medical team who can advise the list of potential participating physicians for the study and also support for some issues at the country level; global clinical team who can help in term of governance and some operational aspects such as data management and statistical analysis consultation to work with the CRO team. The meeting has been scheduled monthly to provide the study status update to the governance team and operational team. For the local medical team, the newsletter of the clinical study will be shared by the clinical team every month. Moreover, the drug safety team also involved in Study B as per the safety reporting requirement.

The CRO is the main external stakeholder in Study B. The meeting has been set up to keep communication and follow up on the status. The frequency of the meeting depends on the period and critical activities of the study required closely monitoring. The participating physicians/nurses are also the key external stakeholders in Study B. However, the company does not contact them directly which is different from the in-house clinical study. The CRO and the CRO project coordinator is the main contact point for the participating doctors/nurses. The local medical team can contact the hospital in case of any issue required local support from the company. In addition, the

Health Authorities and Ethics committees are the stakeholders and are engaged by the CRO.

Analysis: According to the nature of the clinical study, the stakeholders in Study A and Study B are the same. Only one different for the external customer in Study B – the fully outsource study is the CRO. The internal customers consist of the medical team (the project owner), the clinical team (project and operation management), the drug safety team, and other functions in the company. For external customers, they are including the participating physicians/nurses, Health Authorities, and Ethics Committees. The communication is required to engage all stakeholders and keep everyone update on study status. The guideline for each institute to be followed for smooth working.

4.4 Challenges and Lesson Learned

Study A: Overall outcome from managing the Study A is satisfying. The enrollment and study results are on-track. External customer engagement is achieved. There is no negative complaint about the operational perspective from participating physicians/nurses or key external experts. The budget spending is acceptable within a 5% buffer. Some activities such as the data cleaning process take a longer time than expected. However, the study team understands and accepts this delay because data and results are a key priority. It is the study team and the company's responsibilities to ensure and certified that data is reliable. It will be used and generalized to patient care.

Two challenges highlighted for Study A are managing data, and turnover of the project owner. For managing data, according to the clinical study is not the main job for physicians/nurses, they have routine work which is providing patient care in the hospital. Therefore, the data entry by participating doctors/nurses is not fit the timeline defined by the study protocol. For example, the data completion should be done within 5 days after the patient visit. It affects the data review and data checking process. So, the understanding of physicians/nurses' daily job must be aware of. The practical timeline would be set up and discussed with the participating doctors/nurses at the beginning of the study period.

Another challenge is changing of medical manager who is the project owner. The clinical study developed by the medical team. The turnover is nature. However, the gap during the hand-over process may occur. Some background information or details of the rationale behind the study may not fully be communicated to the new project owner. Especially, the long-term clinical study, it would be a loss of some information. The well maintains of documentation and supervisor must be required to ensure the seamless transition of the project owner. It can be also applicable to all staff involving in the clinical study.

Study B: Study B succeeded to complete the patient recruitment within the timeline and deliver the interim analysis results. For the patient recruitment, the company project manager helped the CRO to set up the plan, patient enrollment re-allocation plan and closely follow-up. Therefore, patient enrollment in Study B becomes successful. However, the release of the main results was delayed due to a huge lot of feedback from both internal and external reviewers. The overall outcome is achieved as per requirement. For the budget, it is acceptable and not deviate from the plan. It might be from the CRO attempt to control the budget internally and absorb some additional cost due to the long-term relationship and partnership program.

Regarding the large scale of the clinical project, there are many challenges in the Study B. Two challenges were raised for this paper. The first challenge in Study B is communication and strategy alignment. The decision from the global team was to fully outsource this study to the CRO. However, the local clinical team and local medical team in some countries did not agree with this resourcing model due to the country context. The best way to work with the medical doctors in that country is to have the company engage them directly. The participating physicians/nurses are uncomfortable and unhappy if no physical meeting with them. With the fully outsourcing model, the CRO project coordinator can have a face-to-face meeting at the hospital only 2 visits. This limitation is not satisfied with both the local team and participating doctors/nurses. Once the project started in this country, there are many burdens from the external party and less support from the local team due to the perception of fully outsource study. The global team needs to have a clear direction and communicate to the local team to define the involvement of the local team.

The second challenge in Study B is the quality of the project. Regarding the observation studies and few numbers of hospital visits by the CRO project coordinator, the quality may not the same as in clinical trials. To ensure the data quality, the project coordinator must perform Source Data Verification (SDV) which is the process to check if any discrepancy between the medical record and data collection form. But for this study, the project coordinator can only do the remote monitoring which only reviews data in the data collection form. The monitoring visit at the hospital can be allowed only 2 times due to the scope of work and budget. The data review by the company medical team and external experts might compensate to recheck the data in Study B. In the future, another option for quality assurance is to have the audit for the clinical project. In addition, the high turnover rate in the CRO may lead to incomplete information and poor handover which will affect the quality of the project too.

Analysis: Both Study A and Study B achieved the required dimension as per the Quadruple constraint concept. For Study A, client acceptance is also a success. These are the key priorities, so the team pays attention to this point and achieves it as planned.

From observation, the challenges in Study A are at the operational levels. They are managing data and turnover of staff. These are also the common problem in the clinical study including Study B. They are mentioned by Ms. Beyoncé who manages Study B. The broader scope of the problems is raised and address in this paper. Because of the big clinical study involving multi-country and the CRO, the challenges are strategic communication internally and the quality of the project from a few numbers of hospital visits.

Refer to published data, some results suggest the clinical study by CROs are on average, completed 30% faster than the clinical trials conducted in-house (Carroll 2005). However, some opposing data show that sponsors report 70% of clinical studies conducted by CROs requiring more budget and/or time (Hughes 2013). Approximately 40% of responders report the expensive and/or slower performance of the clinical trials from the survey (Hughes 2013). This delay is from a lack of cooperation between the CROs and Sponsors. Therefore, Study B seems good among the clinical studies conducted by CROs worldwide. The probable reason is from the company and the CRO

in Study B work closely and effort from the company project manager to support the CRO.

4.5 Experience sharing and Opinions

Ms. Adele - Study A: For the in-house study, it is quite flexible to have a project coordinator manage the clinical study with participating physicians/nurses. Especially, in Thailand, senior medical doctors prefer having a face-to-face meeting more than a telephone conversation. So, the in-house model is fully served in this kind of activity. With this support, the relationship and collaboration between the clinical team, company and the participating physicians/nurses are more strengthen. Therefore, the in-house management model is suitable for the observational studies and matches with goals and strategy of the medical team. On the contrary, the physical meeting or ad-hoc request by participating physicians/nurses will be limited in the fully outsourcing model due to budget and an agreeable number of activities. This limitation may lead to poor communication between the participating doctors/nurses and the project coordinator. If it is a serious issue, it can affect the reputation of the company regarding poor operations.

However, the in-house management model is required resources investment and long-term development of skillful internal staff such as project manager and project coordinators. The training and staff welfare must be maintained. One consideration is that the clinical study is a project, not a routine job. It means that it happens for a period. In the case of the company has a smaller number of clinical studies, the job assignment and number of internal staff need to be determined carefully. In the worst case, the downsizing of the company for the clinical team might be executed, the reduction of internal staff will be implemented. This will make the remaining staffs feel insecure and affect the performance.

The fully outsourcing model may cause a higher cost to manage the project especially, the additional charge from the CRO for the ad-hoc request. The CRO can also deliver the service with their expertise. However, there is a high expectation from the company to the CRO. The company may treat the CRO as a vendor that can manage everything as per the company order within timeline and quality. One concerning point

is the quality of the project and operations. The CRO has experience and is the contact person with participating physicians/nurses. Comparison to the in-house study, the company may not know what the real situation or issues are at the hospital. The audit may be required for quality assurance of the project.

The technical skill such as medical knowledge would be fundamental for a person who involves in the clinical study. Besides basic knowledge, soft skills are very important and useful in managing the clinical project. The main responsibilities of both clinical project managers and project coordinators are working with people. Therefore, soft skills facilitate activities. Communication skills, problem-solving skills, and teamwork are highlighted and frequently used. The task cannot be done by one-man show but need contribution from all of the stakeholders. The issue must be solved immediately with good and clear messages. Without these skills, the wrong actions from poor communication will be done and the project cannot be succeeded.

Ms. Beyoncé - Study B: The advantage of an in-house clinical study is the clinical team has full control in the study. The company project manager will know full detail in the clinical project. The project coordinator can cascade information and issue found at the hospital directly to the project manager and the company. The recovery action can be implemented immediately to solve the problem. It is easier to control the quality of data and document because everything needs to be managed by the company staff. There is no constraint for the ad-hoc request such as physical meetings with the participating physicians/nurses at the hospital. However, it is difficult to manage internal staff and keep feeding the project to the team otherwise the lay-off maybe happened.

For a fully outsource study, as a hirer, the company has more power to deal with the CRO or vendor. The company can push the request and keep tracking the status of the clinical study which required the effort from the CRO. It seems like less operational management required from the company side. The CRO can serve the resources and their expertise to the company in conducting the clinical study. This kind of model is very helpful to manage the large scale of clinical study in various countries. The CRO will have more experience to deal with Health Authorities and processes in different countries. The trend of fully outsource study is increasing because it requires less effort from the company.

The disadvantage of a fully outsourcing model is limited access to the detail of the study. As the company does not contact hospitals directly and has no effort to review all documents, the quality of the project should be considered. Even though the report and issues will be communicated to the company. However, it should be kept in mind that there is a case that the CRO may not cascade all of the information to the company. The company is willing to be aware of all issues in the clinical study, but the CRO may disclose only some issues or until the issue cannot be resolved by themselves. To manage this point, the company project manager needs to be a meticulous person. If any experience the CRO sector, it would be beneficial. During the project ongoing, the project manager must review the document carefully and dig into the details to find out what the rationale behind it is. This is not only to ensure the quality of the project but also prevent and detect the issue before turning to a serious problem.

The understanding of the clinical trial process and SOP are mandatory to manage the clinical study. The soft skills are also the key drivers in project management. The project manager is the person who works between the company and the external party. Collaboration and teamwork are important. Communication is a basic skill to use in managing the project. The smooth working or burden depends on communication. It must be clear and for all relevant persons. For fully outsource studies, the experience in the CRO is helpful to understand their culture and work process. It is also required negotiation skills and being thorough in all documents such as invoices, agreements, and reports. The project manager must keep following up and tracking the status of the study together with the CRO performance.

Analysis: The quite similar opinions are shared by Ms. Adele and Ms. Beyoncé. An in-house resourcing model serves the full control of the project by the company; flexibility; fast in action; and enhance customer engagement. However, the company needs to keep constant the number of projects and professional development to maintain the in-house clinical team.

For a fully outsourcing model, it may require less effort from the company as all of the tasks managing by the CRO. It is a good option for the company when there is no internal resource or less experience in some therapeutic areas. The CRO can utilize its expertise to provide service. In addition, the partnership program is beneficial to the company to manage the clinical trial pipeline. However, the quality of the service must

be considered and closely monitored. This point is also addressed in some published articles. There are some issues and controversy for the outsourcing clinical trials such as the quality of the outsourcing clinical trials (ClinicalInvestigation 2014), and the unethical trials management by the CRO (Soni 2013). To outsource clinical study, the collaborative or partnership program between the Sponsors and CROs is recommended. It is not only for governance purpose but also the company advancement in term of strategic and operational excellence in long-term business (Hughes 2013)

Besides the technical knowledge such as diseases and clinical study regulations, soft skills are very important and supportive in managing the clinical project. The communication skill is highlighted in the case study. Moreover, teamwork and problem-solving skill are also necessary for all functions in the clinical study. These are compatible with the socio-technical dimension. For the outsourcing study, the project manager may need more experience and meticulous to deal with the CRO. Data the survey is also aligned with both case study and the socio-technical dimension. The survey suggests the needed skills for the company project manager/sponsor staff including both analytical and behavioral skills (Hughes 2013). The analytical skills consist of project management, report interpretation, audit management. The behavioral skills are influencing skill, problem-solving, communication, Emotional Intelligence, conflict, and relationship management.

CHAPTER V
CONCLUSION & RECOMMENDATIONS

5.1 Conclusion

This thematic paper is to explore and understand the resourcing model from the case studies which are in-house study (Study A) and fully outsourced study (Study B) by interviewing the clinical project staff - Ms. Adele and Ms. Beyoncé, respectively. As a clinical study is also considered as a project, the project management concept has been used to scope the questions for exploring both Study A and Study B in 5 main dimensions mentioned in Chapter 4. The 4 key learnings from the case studies are concluded as below.

Keeping in-house for relationship and experiences, Fully-outsourcing for efficiency: The in-house management model works well for maintaining the relationship between the company/sponsor and external customers. The internal clinical study team staff such as project coordinator and project manager can have direct contact with participating physicians/nurses and/or key medical external experts. This management model also fits the local context in some countries that the medical doctors prefer the face-to-face meeting with the sponsor more than a remote visit or with the CRO. The in-house clinical study also enhances internal staffs' skills and experiences development. For the fully outsourced study, the Contract Research Organization (CRO) provides its professional and contribution in case of the company has limited internal resources or expertise which might be from business expansion or new in that therapeutic area. With the fully-outsourcing model, the clinical project can be operated by requiring less effort from the sponsor as all tasks will be handled by the CRO.

Collaboration partnership with CRO for long-term pipelines and quality: The partnership between the company and CRO provide mutual benefits for business growth in both the management and operational level. With the traditional way of contracting, the vendor will focus only to deliver the project management services. For the long-term collaboration, both sponsor and the CRO can develop the business

and clinical projects together with more trust from sharing the processes. The partnership manual will allow more visible in terms of project governance and quality management. For all clinical studies, project governance must be implemented at the beginning of the study and keep monitor until the study termination. The tools and activities such as meeting, minutes, dashboard, newsletter, study protocol, Standard Operating Procedure (SOP), monitoring plan, audit, monitoring visit and Risk Manage Plan (RMP), are useful in quality control and review. Good Clinical Practice (GCP), local regulation and company policy must have complied. In the meantime, the project manager and team must oversee the project to ensure the quality of the project.

Communication does matter: Communication is a key success driver in managing the project and for all stakeholders. Lack of communication or miscommunication may lead to non-compliance with a result of project failure. This is applicable to both in-house and outsourced studies to deal with both internal and external customers. The stakeholders for both study models are quite the same. For a fully outsourced study, the company project manager needs to deal with the CRO. The communication and compliance with the guideline enhance good collaboration.

Dig down and multi-skills for oversight: The governance and skillful/experienced project manager are required to oversee all types of the clinical study project. The project managers must have not only technical skills but also soft skills/behavioral skills. Especially for the fully-outsourced study, the sponsor does not perform activities by itself. Therefore, the project manager needs to dig down for understanding all of the situation and for quality assurance of the project.

In conclusion, there are pros and cons to the in-house and fully outsourcing model. The selection of the management model for clinical study must be depended on strategy, objective, and available resources. The appropriate tools and activities are required to governance and oversee the quality and performance of the project. The similar challenges have been observed for both studies, but it depends on the scale and complexity of the study. The project quality of a fully-outsourced study should be more considered from a company perspective because the study has not been fully managed by the sponsors. The technical skills and socio-cultural skills enhance the project manager to manage the clinical study and work together with all stakeholders.

5.2 Recommendation

To select the management model for the clinical study, firstly, the strategy, objective and available internal resources must be defined and evaluated. If the company is planning to conduct an observational clinical study to collect data and keep the relationship between the company and the external customers such as physicians and nurses in the hospital. The in-house clinical study should be recommended in case of the internal resources are available. The in-house study is likely to fit with the study initiated by the Medical Affairs department in a pharmaceutical company. The in-house observational clinical study will highly match the 3 key tactics for Medical Affairs are including Evidence Generation, Scientific Exchange and Stakeholder Management (Deloitte 2015). The in-house study will be flexible, and the company can control all activities together with arranging the visit with the external customers who are participating physicians/nurses.

In the case of the large-scale multi-national clinical study and/or limited resources/expertise, the fully-outsourced study would be recommended. The qualified vendor process must be performed before contracting with the CRO. For long-term business growth, the partnership program should be implemented to align the working processes; build the long-term plan and excellent launch of clinical study; and co-develop knowledge and system. The sponsors should monitor and keep tracking the deliverable, timeline and budget. For the quality control process, the company project manager should oversee closely and be meticulous enough to ensure the project quality. The audit and/or visit should be implemented to the reliable of the project. The "Trust but verify" concept would be applicable to this type of study.

Same as a project manager, the clinical project manager or the person who is planning to be the clinical project manager should have both technical and socio-cultural skills. Project management skill is mandatory. The communication skill is very important in managing the clinical study and all stakeholders. The feedback from both internal and external parties are required and for improvement purpose.

5.3 Limitation

In this paper, two observational studies including one in-house and another one fully-outsourced clinical research have been selected as the case studies. However, regarding limitations in terms of confidentiality and accessibility, the project size of both clinical studies is different. Study A which is in-house study is local clinical research conducted in only one country whereas Study B is bigger due to it is regional clinical study. According to this point, there is a limitation to conduct a direct comparison between Study A and Study B. Moreover, another limitation is both studies are observational studies that are different from clinical trials (interventional studies). The generalization of the findings from this paper may be limited to clinical trials because of the interventional studies' complexity in terms of resources, activities, and management. In addition, due to the company policy, the clinical study cost for both Study A and Study B cannot be disclosed. Therefore, the budget cannot be included in this article for analysis.

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APPENDICES

Appendix A: Interview Questions

Topic	Questions
Strategy, Objectives and Management Model	1. What is the resourcing model used in the study? and Why? For outsourcing model, is there any partnership between company and the CRO?
	2. What is the goals and rationale behind of the mentioned study related to resourcing model?
	3. In the study, among Time, Cost, Requirement and Client Acceptance, which element is most important and constraint? and How to management them?
	4. How to management the resources such as human resources, materials, etc. in the study? For outsourcing model, how to select the CRO?
Project Governance	5. When and how to implement the project governance?
	6. What are supporting tools used in governance purpose? For example: oversight plan and documentation, meeting and minutes.
	7. What are the risk identified in the project? and How to manage and minimize those risk?
	8. How do you ensure the quality of the project?
Stakeholders Engagement	9. Who are the stakeholders in the study? and how to manage both internal and external stakeholder?
Challenges and Lesson Learned	10. What are the results of managing project? As per Quadruple constraint concept, is this project successful? How?
	11. What are the challenges and lesson learned from managing the study for improvement in the future?

Topic (Cont.)	Questions (Cont.)
Experiences sharing and Opinions	12. What are pros and cons of in-house study?
	13. What are pros and cons of fully outsourced study?
	14. What are the recommendation and suggestion to manage those kinds of study?
	15. Are the socio-cultural required in managing the project? Is it required more for the project manager in fully outsourced study?

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