IIT Made Easy

Investigator Initiated Trials Made Easy
“Absence of evidence is not evidence of absence.”

Carl Sagan
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Acknowledgements

On behalf of Quintiles, I would like to thank my co-editors, Professor Yung-Jue Bang, President of Biomedical Research Institute and Director of Clinical Trial Center at Seoul National University Hospital, South Korea and Professor K. Arnold Chan, Director of Clinical Trial Center at National Taiwan University Hospital, Taiwan, for volunteering their time and expertise to review the manuscripts.

We would also like to express our utmost gratitude to all our authors, Professor Danny Liew, Professor Ock-Joo Kim, Professor Pik Pin Goh, Associate Professor Sith Sathornsumetee, Dr. Lye Mun Tho, Dr. Sheau Wen Lok, Dr Jana Baskar, Dr. Nantha Kumar, Dr. Loke Meng Ong, Dr. Amir Kalali, Dr. Vikas Sharma, Dr. Kerry Gordon, Srinivas Pai Raikar, Raghavendra Kalmadi, Lisa Marie Saldanha, David Horsburgh, and Lilian Chan, who have kindly donated their time and for sharing their knowledge and experience.

This book was made possible by the support of many of our colleagues and peers within Quintiles. To all these people, we express our sincere thanks.

A special mention to Dr. Karen Wai, Senior Director & Head of Integrated Site Services, Quintiles Asia. The idea of this book would not have become a reality without her support.

Thank you,

Dr. Stephanie Tan
Associate Director
Integrated Site Services, Quintiles Asia
When I was a medical student, I recall being told by someone many years older than me that science had reached a plateau, that the most important discoveries had already been made, and that all great inventions were now of historical record. Though I instinctively disagreed with this perspective, as a young man I lacked the knowledge, experience, and self-confidence to effectively challenge and successfully debate this contention. And indeed, only a decade later, the home computer, the mobile phone, and the internet were introduced and have changed the way each of us approaches our daily life, proving how wrong that position was. But strange as that position seems, it is not as rare as we think. For about the same time as I was having the argument about science, a highly acclaimed book was declaring the rather premature “End of History” to the nods and murmured agreement of many notable historians and social scientists.

The fact of the matter is that the greatest obstacle to discovery and innovation is to think there is nothing to be discovered, that things are as they should be, that disease and suffering are inevitable. And if we unknowingly fall prey to this false thinking, we cease to ask the simplest of questions and fail to seek the tools by which to answer them. For those of us committed to healthcare, this attitude of “non-discovery”, this apathy of “un-inquisitiveness” is especially tragic, for it effectively abandons all those patients who count on us to ease their suffering and collectively condemns them, with a shrug of our shoulders, to the falsehood of the status quo and the prisons of the past.

It gives us immense pleasure to see the creation of this handbook, which provides the basic tools for physicians to pursue scientific enquiry in their own institutions and in their own practices for the benefit of patients everywhere. In science as in medicine, it is understood that we build on the foundation laid by those who came before us. And, if we see far and achieve great things, it is because we stand on the shoulders of giants. But equally, if we hold hands and stand shoulder to shoulder, our small drops of contribution will create a collective flood of hope for those we serve.
This handbook, the first of its kind, is a great collaborative effort between academia and industry, bringing together the top thinkers and most experienced investigators and clinical trialists from across Asia, ignoring national and corporate boundaries. Without exception, all those who contributed their expertise and valuable time, did so out of commitment to facilitating the spirit of inquiry towards our collective goal of pushing the frontiers of medicine and improving the lives of our patients.

It is a great honor for us at Quintiles to have been able to coordinate the development of this book, and we are especially thankful to our two co-editors, Professor Bang and Professor Chan, for leading this effort.

We hope you find this handbook useful.

Best wishes,

Dr. Amar Kureishi
Regional Chief Medical Officer
Head of Drug Development, Quintiles Asia.
15 Dec 2014
Drug development and the improvement of available treatments is often thought to be the sole responsibility of pharmaceutical companies or commercially-focused research arms. However, independent, patient-focused studies led by physicians play a vital role in improving and expanding patient care in the real world, regardless of commercial value. These studies are called Investigator Initiated Trials (IITs).

What is an Investigator Initiated Trial?

IITs are unsolicited clinical, outcomes, or disease-state studies. IITs are research independently proposed and conducted by institutions, physicians, and researchers who seek to advance medical and scientific knowledge.

There are various names for the same type of trials. An IIT is also called an IST (Investigator Sponsored Trial), an IIS (Investigator Initiated Study), a NCT (Non-Commercial Trial), a PLS (Physician Led Study), an ACT (Academic Clinical Trial), and an IDCT (Investigator Driven Clinical Trial). The term “trial” can be substituted by the term “study” or “clinical trial”. And the term “investigator” can be replaced by “physician” or “academic”. This creates a myriad of terms defining the same thing: a clinical trial where the sponsor is not a commercial entity. 

What is the definition of an investigator?

A clinical investigator involved in clinical trials is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator’s care; and for the control of drugs under investigation.
Who is a sponsor?

A sponsor is an individual, company, institution, or organisation that takes responsibility for the initiation, management, and regulatory compliance for a clinical trial. There can only be **ONE** sponsor per trial.

A sponsor-investigator is an individual who both initiates and conducts an investigation, taking on the regulatory obligations of both. The term refers only to an individual. A pharmaceutical company, hospital, or an academic institution cannot be a sponsor-investigator because it is not an individual person. An **IIT** is a clinical research study initiated and conducted by a sponsor-investigator.³

What is the sponsor-investigator responsible for?

The sponsor-investigator for an **IIT** is responsible for all facets of the trial including concept and protocol development, budget development, ethics and review board submissions, and trial management. An example of the different steps involved in the IIT process is shown below.
Why are Investigator Initiated Trials important?

The generation of new knowledge through research and development has been the major factor contributing to improvements in health in the 20th century. Non-commercial IITs are driven by a real-world awareness of patient need and are critically important in establishing an evidence base for health interventions that would otherwise not be commercially viable. IITs are important in the generation of local, context-specific knowledge to increase effectiveness of existing interventions and address unmet health problems.

The benefits of IITs are that they:

- Promote innovative thinking
- Explore use of marketed drugs for new indications, in subsets of approved populations, in new dosage regimens, or in new combinations with other treatments
- Provide pharmaceutical companies with clinical data for further understanding of their drugs in the real world
- Refine safety and effectiveness information for already approved drugs
- Foster scientific exchange and collaboration
Table 1: What are the differences between Investigator Initiated Trials and Industry Sponsored Trials?  

<table>
<thead>
<tr>
<th><strong>INVESTIGATOR INITIATED TRIAL (IIT)</strong></th>
<th><strong>INDUSTRY SPONSORED TRIAL (IST)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Purpose</strong></td>
<td></td>
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<tr>
<td>The primary focus is on improving and expanding patient care of an already approved drug. The study itself will ideally culminate in a publication. Conclusions may be considered hypothesis generating. Academic researchers tend to have greater interest in niche indications and a better knowledge of local medical needs.</td>
<td>The main objective of industry sponsored trials is regulatory submission. The overarching goal generally is to develop a product intended for large markets to ensure financial success.</td>
</tr>
<tr>
<td><strong>Funding Mechanism</strong></td>
<td></td>
</tr>
<tr>
<td>IITs are supported by an individual, institutions, or pharmaceutical company.</td>
<td>ISTs are mostly funded by companies’ research and development budgets.</td>
</tr>
<tr>
<td><strong>Study Conduct</strong></td>
<td></td>
</tr>
<tr>
<td>Investigators follow certain guidelines, e.g. Good Clinical Practice (GCP) and Common Technical Document (CTD), as well as Standard Operating Procedures (SOPs) of their institutions. The company providing the study agent must oversee safety aspects of the study and review any publications. IIT progress is outside the company’s control with regards to recruitment, number of study sites, resolution of operational issues, and so forth.</td>
<td>Adherence to regulatory guidelines and company SOPs during the design stage as well as in trial conduct ensures integrity and credibility of the trial. Sponsor responsibilities such as GCP compliance and suitability of company capabilities, facilities, and procedures are verifiable from technical and scientific standpoints, SOP review, staff, and facilities assessment.</td>
</tr>
<tr>
<td><strong>Data Collection and Analysis</strong></td>
<td></td>
</tr>
<tr>
<td>The development of an action plan and definition of critical time points are required in advance. The database structure likely differs from that of the company, therefore data cannot be imported into company systems.</td>
<td>The company owns and has access to source data. The quality of output is ensured and a complete safety database is available.</td>
</tr>
</tbody>
</table>

Bibliography and References:
Seoul National University Hospital (SNUH) has been looking after public health over the past 100 years, leading the development of medicine in Korea. It was established in 1885 as Korea’s first national hospital under the name of Kwang Hye Won and is one of the oldest and biggest hospitals in South Korea. After it became the affiliate hospital for Seoul National University’s College of Medicine and College of Dentistry, it was recognized as a special corporate body under the name of Seoul National University Hospital. SNUH is a general and teaching hospital.
How do you formulate a research question?

After identifying a gap in our current knowledge, we start the research process by formulating questions. These questions typically come from problems involving diagnosis, etiology, prognosis, and treatment or prevention of diseases during routine patient encounters in clinical practice.

They are usually derived from a complex thinking process culminated from available knowledge and a careful analysis of the health problem by the researchers. The research questions may also arise when new diagnostic tests or new treatments become available to compare with what we already have.

Good research questions are generally defined as:

- Answerable – Can the question be practically answered?
- Important – Will the answers be important to you, other clinicians in the field or patients? What is the potential impact of the study results?
- Interesting – Is it worth the effort? Is it answering a gap in current knowledge or representing unmet medical need? Is it innovative? Is it high quality?
- Approvable – Is it ethically justifiable and approvable by institutional review board (IRB)/ethics committee (EC)?
- Fundable – Is it interesting enough to potential sponsors such as funding agencies or pharmaceutical companies to support? IIT trials would serve as the basis for application for a subsequent larger outcome trial
- Publishable – Are the results going to be publishable? Are there any other groups working on the same questions? Decide on your target journals. Discuss with your mentor or senior investigators in your department. You may even consider reaching out to editorial teams to gauge their interest in the topic as a potential paper
As a tool to help develop a good research question. FINER stands for:

- Feasible – Adequate number of subjects, adequate technical expertise, affordable in time and money, and manageable in scope
- Interesting – Interesting to investigator, peers, and community
- Novel – Confirms, refutes, or extends previous findings, new findings
- Ethical – Amenable to a study that IRB will approve
- Relevant – To scientific knowledge, to clinical and health policy, to future research

Check for components of a well-formulated question: consider the PICOT (Patient problem or Population; Intervention; Comparison; Outcomes; Time) format. For instance: Does agent X improve a 12-month progression-free survival rate in patients with recurrent intracranial atypical meningioma compared with no treatment? P = patients with recurrent intracranial atypical meningioma; I = agent X; C = no treatment; O = progression-free survival rate; T = 12 months.

Generate a conceptual or theoretical framework to refine the research question. In addition, consultation with mentors and experts and attending relevant conferences are a “must” to help refine the research question. Be prepared that this process usually takes time, which may include a period of refining or modifying the question according to input received. Act fast to fix the question, otherwise someone else will be ahead of you.

What are the different types of study designs?

Most Investigator Initiated Trials (IITs) are intervention trials and they can be classified into four to five types of study and phases of development. Note that type and phase are not synonymous but they often go together. For instance, the most typical Phase I trial is human pharmacology study, whereas the most typical Phase II trial is therapeutic exploratory study. However, Phase II trials can involve human pharmacology study or can be therapeutic confirmatory. Likewise, therapeutic confirmatory study type can be developed into Phase I to IV studies.
## Phases of Drug Development

<table>
<thead>
<tr>
<th>PHASES OF DRUG DEVELOPMENT</th>
<th>TYPE OF STUDY</th>
<th>OBJECTIVES</th>
<th>EXAMPLES</th>
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</thead>
</table>
| **Phase 0**                | Pharmacokinetic/Pharmacodynamic (PK/PD) to assess target modulation by drug | * Interrogate the drug target  
* Identify biomarkers of drug effect in human samples | * Effect of kinase inhibitors on target protein phosphorylation in patients’ tumors |
| **Phase I**                | Human pharmacology                                | * Assess tolerance  
* Define PK and PD  
* Explore drug interaction  
* Estimate activity | * Dose-tolerance study  
* Single or multiple dose PK/PD studies  
* Drug interaction studies |
| **Phase II**               | Therapeutic exploratory                            | * Explore use for the targeted indication  
* Identify optimal dose for subsequent studies  
* Provide basis for confirmatory study design, endpoints, methodologies | * Trials of relatively short duration in well-defined narrow patient populations using surrogate endpoints or clinical measures  
* Dose-response exploration studies |
| **Phase III**              | Therapeutic confirmation                          | * Demonstrate/confirm efficacy  
* Establish safety profile  
* Provide an adequate basis for assessing the benefit/risk relationship to support licensing  
* Establish dose-response relationship | * Adequate and well controlled studies to establish efficacy  
* Randomized parallel dose-response studies  
* Clinical safety studies  
* Studies of mortality/morbidity outcomes  
* Large sample size  
* Trial with an active comparator |
| **Phase IV**               | Therapeutic use                                    | * Post-registration trial  
* Refine understanding of benefit/risk relationship in the “real-world” setting or sub-populations and/or environments  
* Identify less common adverse reactions  
* Refine dosing recommendation | * Comparative effectiveness studies  
* Studies of mortality/morbidity outcomes  
* Studies of additional endpoints  
* Large sample trials  
* Pharmacoeconomic studies |
Description of trial design should include the type of design (parallel, cross-over, factorial, cluster, split body, single group, and N-of-1), the allocation ratio, and the framework (superiority, equivalence, non-inferiority, or exploratory). Non-inferiority trials are intended to demonstrate that the effect of a new treatment is not worse than that of an active control by more than a specified margin. They have several inherent limitations and the results are generally not as credible as those from a superiority trial. The details of each design and framework are beyond the scope of this chapter.

The most common type of randomised trials is a two-arm, parallel, superiority with 1:1 allocation of experimental treatment versus control. Adaptive designs are becoming more popular but need to have pre-specified rules for adaptation and be documented in the protocol.

How do you design a protocol to answer your hypothesis?

The purpose of having a protocol is to explain how you run the trial to answer your research questions. It serves as a complete document package to describe the objectives, design, methodology, statistical and ethical considerations, and organisation of a clinical trial. It helps to convince funders to support your study and IRB/EC to ethically approve your trial. It can also help protect research participants in terms of safety and confidentiality.

Before you design your protocol, it is often helpful to browse protocols of similar type from your mentors or colleagues at your institution or from clinical protocol registries (see below) or databases that will give you an idea and expedite the learning process of how to design clinical protocols.

It is important to be well versed with the landscape of the clinical area. In almost all cases, a systematic review of current evidence is required as the first step for protocol development.

- Critically evaluate previous work done in this area
- Be aware of conflicting evidence or approaches
- Look at trends in the field, particularly for relevant ongoing and future trials
- Search multiple databases such as PubMed, MEDLINE, Embase, Scopus, etc.
- Look at systematic reviews such as Cochrane’s
- Beware of publication bias. Only positive studies tend to get published. Therefore, it is important to search other resources such as clinical trial registries (ClinicalTrials.gov, WHO International Clinical Trials Registry Platform (ICTRP), the European Clinical Trials Database (EudraCT), Japanese UMIN Clinical Trials Registry (UMIN-CTR), Chinese Clinical Trial Register (ChiCTR) and ISRCTN), meeting abstracts, and regulatory databases)

Writing the background and rationale is a very important step to develop a protocol. It helps others, including potential funders and IRB/EC, to understand why you want to do the study. It also reflects how critically and thoroughly you have examined the current evidence and knowledge gaps in the field. This section should be focused on relevant information about the magnitude of the problem, current standard of care and prior experimental treatments, rationale for choosing this intervention, comparator, study population, outcomes, and potential impact in various aspects for both positive and negative trial results.

Set the specific and testable hypotheses, which are directly linked to trial design and analytic methods. There should be one primary objective to test your hypothesis. Secondary objectives are to answer a few other important questions. Consider correlative biomarker (tissue, circulating cells or protein, or imaging) studies in the secondary or exploratory objectives to strengthen your protocol. Outcomes need to match hypotheses and should be measurable. Criteria and timing for response assessment should be clearly stated.

Elaborate the study procedures in the full protocol with a brief trial scheme in the synopsis. Include a potential adverse events list and reporting requirements. Contingency plans for unforeseen adverse events should be stated in the protocol.

Other important elements in the protocol include dose modification for adverse events, statistical considerations, patient and trial monitoring, data management, ethical considerations, and publication plan.
There are several guidelines and checklists such as SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013, ICH GCP E6, CTEP, and others to follow when you write a protocol. Your funding agencies and local IRB/EC usually have the protocol format for you to follow.

Collaboration?

Clinical research is typically multidisciplinary. You need to form a good team at the start of your journey from concept to protocol design, then approval and implementation. First, you may ask for advice from your mentor or trusted senior investigators who have experience in clinical trials in either industry sponsored studies or IITs. They can be very helpful and give you tips of how to get things done at your institution as different places have different cultures and research environments.

Experienced statisticians or biostatisticians are resourceful persons whom you should engage very early when you begin to design a protocol. In fact, most statisticians want to be involved early rather than late. Remember that they cannot do much with the result data if the study was not designed properly but is already completed. Their input for overall design, study objectives, study population, endpoints, sample size estimation, and other statistical considerations is crucial.

For example, in a randomised control trial comparing a drug versus placebo, in order to calculate sample size, points to be considered include whether the study is meant to test superiority or non-inferiority, the estimated magnitude of difference between drug and placebo groups, Type I and II errors, rate of attrition, and whether interim analyses are planned.

You may ask your colleagues from relevant disciplines to join the study. It is important to involve co-investigators whom you can work with. In fact, it sometimes may be beneficial to invite competitors to collaborate and consolidate efforts into a single study – which could serve to maximise resources (such as targeting a limited pool of study subjects) and avoid conflicts down the road.

Clinical research associates and research pharmacists are essential for data management and drug dispensation, respectively. Pharmacists will need to play a key role in record keeping for drug accountability as well as being responsible
for receipt, storage, formulation, and dispensation. Unused medications must be returned and documented, with the sponsor duly notified.

For protocols with novel therapeutic agents and correlative biomarkers, input from preclinical scientists such as molecular biologists, pharmacologists, or geneticists may be helpful. Access to an accredited laboratory facility to process and store patient samples is required and you may need to consider equipment such as centrifuges or a liquid nitrogen facility with a back-up power source. Increasingly, clinical trials incorporate a concurrent molecular or basic science aspect as patient samples obtained from a well-run clinical trial are an extremely valuable resource, which may be stored for future projects not directly tied into the current trial.

What are the factors to consider when designing a protocol to answer your research question/hypothesis?

First, you need to understand regulatory and scientific requirements and the procedure for the processing at your institution prior to protocol design and implementation.

You may need to submit a concept or a letter of intent outlining the study if you request funding support from sponsors such as a pharmaceutical company or government agency. Following approval from the sponsor, you will begin working on the protocol to be submitted to institutional disease-specific protocol committee (if available) for scientific review and prioritisation and then to an IRB or EC for evaluation of the protection of human subjects in research.

Do not forget to search clinical trial registries, meeting abstracts, and regulatory (such as FDA and EMA) databases as a lot of completed clinical trials, particularly those with negative results, have never been published. Awareness of current trends and advances in technology may help in protocol development.

Try not to duplicate work unnecessarily as it is a waste of time and resources and it is difficult to publish.

Think about feasibility (enough subjects to accrue; any competing studies; single-center vs. multi-center or collaborative group studies) and determine available resources.
Conduct a protocol strategy meeting among your study team. Draft a timeline and know the due dates for document submission to IRB/EC.

Register the protocol in one of the clinical trial registries such as ClinicalTrials.gov or WHO ICTRP.

Maintain consistency between protocol sections including objectives, outcomes, outcome measures, and analysis method.

Follow the format of your IRB (organisation and clarity of information). Make sure that you have all required elements in the protocol.

What factors to consider when deciding on inclusion and exclusion criteria?

Inclusion and exclusion criteria must be clear and consistent to specify trial participants. Each item can affect the recruitment, attrition, and outcome events. Eligibility criteria should not be either too restrictive or too broad as the results from the study should be generalisable to clinical practice in a real-world setting.

Inclusion criteria: demographics including age, gender, normal healthy subjects vs. subjects with specific disease of interest, concomitant disorders, general health condition e.g. performance status for cancer trials, adequate liver, kidney, cardiac, and bone marrow functions, previous or current treatment, contraception for subjects (women with childbearing potential and fertile men), capability for informed consent.

Exclusion criteria: serious co-morbidities that may affect life expectancy, current and prior exposure to certain medications, prohibitive concomitant medications, history of allergy to a component of the study drug, pregnancy, currently participating in another trial, other relevant factors that may affect results and outcomes.
Points to Remember!

1. Interesting and important answerable questions – Results can lead to changes in clinical practice

2. Scientific merit – Systematic review of current evidence for background and rationale of the trial

3. Hypothesis is specific and testable

4. Simple design to test the hypothesis

5. Patient centric (e.g. how easy is it for patients to comply with it). Have you considered asking patients for input?

6. Single primary objective

7. Correlative studies as a secondary objective to see why the intervention works or doesn’t work. Which subgroup of study participants derives benefit from experimental treatments?

8. Appropriate outcome measures

9. Clear delineation of inclusion and exclusion criteria – Not too broad or too restrictive. Subject withdrawal criteria should be included

10. Specify contingency procedures with precise criteria for dose adjustment, stopping rules or discontinuation for individual subjects, parts of trial, or entire trial

11. Complete and accurate statistical considerations (sample size estimation, level of significance, criteria for termination of trial and preplanned methods, and timing of statistical analysis of trial results)

12. Ethically justifiable with anticipated optimised benefits and minimised risks – Approvable by IRB/EC

13. Patient’s consent form contains sufficient information required by international, national, and institutional guidelines and the language is simple, non-technical, and suitable for a layperson

14. Good data management system with clean database
15
Good monitoring system for trial processes (e.g. randomisation codes), subject compliance, and reports of adverse events

16
Good quality assurance (e.g. certified central laboratories, end-point validation procedures)

17
Results should be important with generalisable impact to practice in the local and global communities

18
Protocol is visible to physicians both inside and outside your institution. This can be achieved by study initiation meetings, grand rounds, seminars, and on-line information such as a list of active protocols through the website of your department or hospital

19
Before signing off and submitting a protocol, check for consistency throughout the protocol. Make sure that information in the consent form matches with the main protocol. Proofread and check for typos so that the reviewers can focus on protocol contents. Maintain the updated version number and date of your protocol and consent

Bibliography and References:

National Taiwan University Hospital (NTUH) started operations under Japanese rule in Daitoutei (today’s Dadaocheng) on June 18, 1895, and moved to its present location in 1898. The Hospital was later annexed to the Medical School of Taihoku Imperial University and renamed Taihoku Imperial University Medical School Affiliated Hospital in 1937. The present name was adopted after the Republic of China took over the hospital upon Taiwan’s retrocession in 1945. On October 19, 1991, the completion of a large new building complex on the so-called East Site marked another milestone in the history of the NTUH. Today, the (new) East and (old) West sites together have more than 4,000 employees, serving 2,000 inpatients and 8,000 outpatients daily. The hospital remains the best-known and most highly renowned medical center in Taiwan. The hospital is a world-renowned medical center for liver diseases. Advanced surgical, angiographical, and endoscopic procedures are routinely performed.
Why do we need informed consent for research?

Not only is informed consent a legal and regulatory requirement, it fulfills one of the fundamental principles of ethics in clinical research, which is respect for every person. This involves promoting their autonomy by ensuring that adequate information is available to help them reach their own decision.

A person’s autonomy may be diminished by many factors, such as age (very young or very old), state of mind (situation or a mental disorder), socio-economic status, and possibility of undue influence, plain threat, or coercion. Unfortunately, history has provided many examples which demonstrate violation of this fundamental principle in the name of research.

Is a signed informed consent form synonymous with informed consent?

No! Obtaining informed consent from a participant is more than just a signature on a form. A signature may represent a participant’s agreement to participate, but does not imply understanding. However, the informed consent form (ICF) can be a useful guide to serve as a basis for verbal discussion between the researcher and participant.

In other words, informed consent should
represent informative and meaningful dialogue between investigator and participant, and not just a lengthy document. The informed consent process does not cease once the ICF has been signed nor is the ICF a substitute for discussion. Rather, informed consent is an ongoing process performed by all members of the research team throughout the duration of the study.

Nevertheless, for the purpose of this book, most of the information in this chapter will focus on the ICF. It is important, however, to remind oneself that the ICF is only a part, albeit an essential one, of the informed process.

What information needs to be included in the ICF?

Here are the underlying concepts that need to be considered when writing the ICF and conducting informed consent:

- Sufficiency – Is the necessary information being provided?
- Clarity/Comprehension – Is the information provided clear and understandable?
- Capacity to consent – Is the participant capable of providing consent?
- Voluntariness – Is the decision free from coercion and undue influence?

The exact amount and type of information differs depending on national and institutional regulations. Most institutions will have their own ICF templates – this is often a good place to start! In general, all ICFs should contain the following information as a minimum:

- A statement that the study involves research
- An explanation of the purpose of the research
- Expected duration of the participant’s participation
- A description of the intervention or study drug, as well as the major procedures that will be carried out as part of the study. It can be hard to know how much to disclose, but a helpful reminder is to focus on procedures that are above “standard of care”
  * Make it clear which aspects of the study are experimental
- The reasonably foreseeable risks or inconveniences to the participant and, when applicable, to an embryo, foetus, or nursing infant
- The reasonable expected benefits. Be transparent about this – if no intended clinical benefit to the participant is expected, make that clear
- Alternatives to participation in the research
- Any compensation or pro-rated payment to the participant for study participation
- A statement that participation is voluntary and that the participant may choose not to participate or withdraw from the trial at any time without compromise of the participant’s medical care
- Confidentiality of participant’s medical records, study findings, and steps taken to ensure that. You may also want to discuss who would have access to the participant’s medical records as part of study procedures, monitoring, and follow-up
- Contact details for essential personnel involved in the study
- An explanation of what happens after the research ends. This may include a statement of if and how results from the research will be disseminated to participants

**Is there such a thing as too much information?**

Sometimes we look at the ICF for a particular trial and wonder if the amount of information presented is simply too overwhelming in detail and quantity for the participant in front of you. This represents yet another problem with the informed consent form; it is not tailor-made for each individual participant.

For instance, a well-read 30-year-old professional and an 80-year-old partially deaf gentleman with mild memory impairment may both be eligible participants of a clinical trial, but one may benefit from different amounts of information, or information that is presented to them differently. This is not to say that the process of informed consent should be skipped altogether in the elderly man, but rather that the information should be presented in a way that would most likely be meaningful to him.

As a general guide, understanding of the following is considered essential in any clinical trial:

- Diagnosis
- Prognosis
- The nature and purpose of the intervention
- Alternatives
- Risks and benefits
Is informed consent foolproof?

In an ideal world – yes. Unfortunately, in everyday practice, there are problems with the informed consent process as evidenced by multiple studies. Here are just a few reasons why the informed consent is not perfect:

- Readability of the consent forms
  This is an area that can be easily improved. Ever read a clinical trial consent form in its entirety from start to finish? It is an extremely tedious, time-consuming process. Now, imagine your patients having to read those. Consent forms these days are just too long, too wordy, use too much medical jargon, and are sometimes written in a way that makes little sense to a layperson.

- Patient vulnerability
  A potential participant can agree to participate in a study and yet that decision may not reflect his/her autonomy and free will. A participant may be vulnerable for many reasons (e.g. having very limited options of treatment, limited or no access to standard care, cultural or gender roles affecting decision making capacity etc.) and it is important to look for them.

Guidance from Institutional Ethics Committees may be sought if there is a possibility that the participant population may be vulnerable.

- Poor recall
  Even healthy volunteers with a high educational level are only able to recall a small amount of informed consent information. Patients with advanced disease, other stressors, or those with lower educational attainment can be assumed to have even greater difficulty remembering large amounts of information.

- Potential conflict of interest
  The treating physician is sometimes also an investigator on a clinical trial. Once a physician decides to enroll a patient in the trial, a new dynamic to the traditional doctor-patient relationship will develop. To avoid or minimise potential conflicts of interest, it is important for the investigator to remember that, as a treating physician, their primary focus is the patient’s well-being. It is even more essential in this setting to maintain equipoise and ensure that no undue coercion is involved in the process of informed consent.
Common Practical Errors while conducting informed consent

- Use of expired versions of the form, or unapproved forms
- PI or consent personnel forgetting to sign or date the form
- The participant has failed to sign AND date the form
- Failure to provide a copy of the ICF, or providing all but the last page of the consent form to the participant
- Keeping only the last page of the consent form in the study file
- Failure to re-consent when new information becomes available, or the current version of the ICF has been superseded
- Not giving the patient sufficient time to make a decision
- No documentation that consent process took place
- Enrolling non-English speaking participants without using a proper interpreter (a family member is NOT an appropriate translator)

How can we improve the ICF and the informed consent process?

1. Write simply. Different countries provide different guidelines regarding the targeted reading levels for informed consent content. In general, a reading level of Grade 6-8 is recommended.

Consider the following sentences:

"Investigations for this study will include screening for the presence of the Hepatitis A and B virus, as well as HIV. This is necessary, as the nature of the study requires that the immune system be fully functional in order for the treatment to be properly assessed."

Or

"We will need to do blood tests for HIV (AIDS virus), Hepatitis A and Hepatitis B. This is because we need to know your immune system is working normally."

The second sentence obviously reads better for potential participants. The informed consent form is after all meant to be a plain language statement. Here are a few suggestions on how to
write simply yet effectively:

- Use short sentences and short paragraphs
- Use bullet points to break up slabs of text
- Write in the active tense; address the reader directly as “You”
- Use familiar words and remove unnecessary medical jargon

*Tip:* If you find yourself having to read over a sentence or paragraph more than once to fully grasp its meaning, chances are that it is highly likely your readers are going to have trouble understanding it. Use Word’s readability checker to help assess the readability of your form.

2. Allocate adequate time for potential extended discussions with participants. Having another family member or friend is always helpful. Ensure that if a participant is unable to read, that an impartial witness be present during the entire informed consent discussion. A signature by the witness is also required on the ICF.

3. Always check understanding with the participant. Try using the “teach back” method, e.g. “Can you tell me in your own words what we talked about regarding…..?”

4. Encourage participants to ask questions. Reinforce that this is a voluntary process, and that they can choose to withdraw from the study at any time.
Points to Remember!

1. Informed consent is essential to maintain respect towards a study participant and ensure autonomy.

2. An Informed Consent Form (ICF) is an important document but not synonymous with a meaningful informed consent dialogue between researcher and participant.

3. Check that the ICF and informed consent process covers all essential principles related to participants' safety, respect, beneficence, and rights. Seek guidance from IEC/IRB as needed.

4. Use simple language. Avoid unnecessary medical jargon.

5. Remember that informed consent is not a single event. It is an ongoing process for the entire duration of research.

6. Always check that the correct version of the ICF is in use.

Bibliography and References:


University Malaya Medical Center (UMMC) is a government-funded medical institution located in Pantai Dalam, in the southwest corner of Kuala Lumpur. It was established in 1962. UMMC is part of the University of Malaya. On August 5, 1968, the new UMMC was officially opened by His Majesty the Yang Dipertuan Agung, Duli Yang, Maha Mulia Seri, Paduka Baginda, Yang Dipertuan, Agung Tuanku, Ismail Nasarudin, Shah Ibni Alharmahum, and Sultan Zainal Abidin. Both UMMC and the Faculty of Medicine strive to live up the University motto: “Ilmu Punca Kemajuan” (Knowledge is the Key to Success). UMMC is one of the organisations in the Ministry of Higher Education. The main objectives of UMMC are health services, learning, and research.
CHAPTER 4

Budget Creation

Dr. Jana Baskar, Srinivas Pai Raikar

Introduction

Finance is a crucial factor required for the successful conduct and completion of an Investigator Initiated Trial (IIT). Often, investigators have an interesting hypothesis, typically endeavouring to address a clinical question that has not been adequately studied before, but are unable to test such due to financial constraints.

Careful planning of the finances before embarking on IIT is of utmost importance to ensure successful completion of the study. Budget preparation should focus on evaluation of the protocol and resource assessment at the site level. Understanding the protocol requirements and assessing the available resources (e.g. facilities and equipment, personnel etc.) at the site level to match these requirements will help in the budget preparation for an IIT.

How should one obtain funding?

Funding can be sought typically in the form of research grants from either public or private research institutions. In such instances, these institutions usually publish the eligibility criteria along with the process by which to apply for such grants on their respective websites.

Funding and or drug supply can also be sought from biotech, pharmaceutical, and medical device companies in the form of an IIT grant request. Each company would have its own process by which this is administered but in all cases the first step would be to reach out to the respective company representative, which should be a member from the medical department.

When should the budget for an IIT be created?

Quite commonly budgets are drafted after a protocol has been created. However, this should not be the case. In fact, one should start thinking about costs at the conception of a research idea. Especially, in the case
where funding is being sought from a pharmaceutical, biotech, or medical device company it would be advisable to submit a draft budget at the concept stage.

A draft budget can be created based on certain assumptions which are essential in every trial. There are two common ways to establish a budget. Either an approximation can be made on a per patient basis which can be subsequently extrapolated to determine the total cost of the trial based on sample size numbers, or the cost for each resource can be estimated line item-by-line item and these can then be added to give the total cost of the trial.

Beneath are some assumptions that may be considered when drafting a budget:

- IIT timelines – projected start and completion date, total number of months for enrollment and follow-up
- Whether this is a single or multi-centre IIT
- Sample size
- Estimated number of subjects needed to be screened
- Total number of patient visits (including unscheduled visits)
- Number of investigators participating in the IIT
- Study product – in the case of an interventional study, how this will be sourced, storage and pharmacy costs, method of administration, and also frequency and duration of treatment
- Type of Case Report Forms (CRFs) – paper vs. electronic
- Data management costs
- Personnel – the type (i.e. study coordinator, investigator) will vary based on the requirements of the protocol, the experience of the individual, and other commitments he or she may have
- Any external support or services (e.g. courier services, laboratory fees for processing specimen)
- Indirect costs also referred to as overhead or facilities and administration costs. These are usually calculated based on a percentage of the study budget and may be negotiable in certain cases

The table on the next page shows the essential components to consider when drafting a budget for IIT.
Table 2: Breakdown of the costs estimated for an IIT

<table>
<thead>
<tr>
<th>TASK / SERVICE</th>
<th>COST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development of Informed Consent Form (ICF), Patient Information Sheet (PIS), patient diaries</td>
<td></td>
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<tr>
<td>Meetings and trainings (including PI meeting in case of multicentric IIT)</td>
<td></td>
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<tr>
<td>Study Coordinator fees</td>
<td></td>
</tr>
<tr>
<td>Contracts inclusive of investigator fees based on Fair Market Value (FMV) and institutional overheads</td>
<td></td>
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<tr>
<td>Regulatory</td>
<td></td>
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<tr>
<td>Institutional Review Board (IRB)/Ethics committee (EC) submission including IRB/EC fees</td>
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<tr>
<td>Case Report Form (CRF) development</td>
<td></td>
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<tr>
<td>Data Management Set up</td>
<td></td>
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<tr>
<td>Monitoring</td>
<td></td>
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<tr>
<td>- Visits (pre-Study, initiation, monitoring, close out, incl. preparation and report); preparation of monitoring guidelines; standard reports;</td>
<td></td>
</tr>
<tr>
<td>- Unblinded clinical research associate (CRA) for pharmacy monitoring (depending on protocol if applicable)</td>
<td></td>
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<tr>
<td>Randomisation if applicable</td>
<td></td>
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<tr>
<td>Medical writing (Clinical Study Report)</td>
<td></td>
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<tr>
<td>Document retention / Maintenance</td>
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<tr>
<td>Drug Supply Management in case of IP including shipment/pharmacy fees</td>
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<tr>
<td>Laboratory/imaging/electrocardiography (ECG) costs</td>
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</table>

Certain study costs would generally merit a more detailed breakdown in order to be able to fairly defend the overall study budget. An example of this would be Investigator fees.
**Investigator fees**

A fee is assigned to every task conducted by the investigator or research coordinators. It is important that the costs quoted for each task is in accordance with the principles of Fair Market Value (FMV). Summation of the costs of all the tasks performed by the investigator will produce a fee for each investigator for the duration of the study. The investigator also needs to be aware of the institutional policies for investigator fees in IITs. The table below is an example of tasks to consider when calculating the budget for an investigator’s fee.

**Table 3: Breakdown by tasks for Investigator fees**

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<tr>
<td>Informed Consent</td>
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<td>Eligibility Consent</td>
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<td>Physical exam &amp; Vitals</td>
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<td>Study drug dispensation</td>
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<td>Adverse event</td>
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<td>Concomitant Medications</td>
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<td>Any other Assessments</td>
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<td>Questionnaires if any</td>
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<td>In-hospital visits</td>
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<tr>
<td>Review of Reports</td>
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<tr>
<td>Phlebotomist</td>
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<td>Treatment compliance</td>
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</table>

**Additional: Overheads @ X%**

**Total Cost (inclusive of Overheads)**

**Total cost in USD inclusive of tax**

**Screen Failures @ Y%**
Points to Remember!

1. Budget preparation requires careful and thorough planning.

2. Funding can be sought typically in the form of research grants from research institutions (private and public) or the form of an IIT grant from a biotech, medical device or pharmaceutical company.

3. The two required elements for construction of a budget are: protocol evaluation and resource assessment at the site level.

4. A draft study budget can be created based on certain assumptions which are essential in every trial.

5. There are two common ways to construct a budget. Either an approximation can be made on a per patient basis or the cost for each study item can be estimated individually, line by line.

6. It is important that the costs quoted for each task is always estimated in accordance with the principles of Fair Market Value.

Bibliography and References:
Royal Melbourne Hospital (RMH) is the oldest hospital in Victoria, Australia, built just prior to the gold rush era that led to a boom in Melbourne’s population. It is one of Victoria’s leading public teaching hospitals, and operates across two campuses, RMH City Campus and RMH Royal Park Campus. RMH City Campus first began as The Melbourne Hospital in 1848 and RMH Royal Park Campus as the Immigrants’ Aid Society in 1853. The Royal Melbourne Hospital is a privileged member of Melbourne’s world-leading Parkville Precinct, and enjoys strong relationships with many of the city’s major universities and research institutes.
Collaborating with Industry

Investigator Initiated Trials (IITs) have become a cornerstone of collaboration between the pharmaceutical industry and independent researchers representing individuals, academic institutions, and co-operative groups.

Why collaborate?

The pharmaceutical industry seeks to improve patient care through support of scientific advances in medicine. As part of this commitment, IIT programs support innovative clinical and basic science studies that address important medical and scientific questions related to compounds and therapeutic areas of mutual interest.

There should be no association with the support provided and an incentive to promote or increase the prescription of marketed drugs. To this end, many pharmaceutical companies choose to insulate the budgetary support for IITs from any marketing or commercial-related financial programs.

Who sponsors IITs?

The sponsor of IITs by definition will be the investigator or the body who enters into the agreement with the specific pharmaceutical industry entity.

Hence the study sponsor and/or investigator will bear all obligations related to responsibility for study conception, design, operational execution, data handling, data analysis/interpretation, subsequent reporting/publication, and ensuring compliance with all local laws and regulations.

How should investigators prepare for IIT proposals?

In order to minimise any risk of directed research, the pharmaceutical collaborator
will generally not be involved with the generation of trial-specific protocols.

However, most pharmaceutical companies will broadly define the main areas of strategic interest as related to their compounds. These areas of strategic industry interest may be found in specific investigator guides or on company-hosted websites. Investigators should also be encouraged to enter into a science-based discussion with appropriate noncommercial contacts (e.g. Medical Scientific Liaisons) in the company around areas of company scientific interest.

Most pharmaceutical companies will have a specific process of review of the investigator’s proposal.

The overarching principles that govern evaluation of IITs include:

- The validity of the scientific question being addressed, ensuring that any data generated by an IIT complement the existing body of evidence and also answer valid scientific questions
- The robust scientific nature of the IIT being conducted in terms of ethical trial design considerations

- A commitment by the investigator to disseminate the findings in an appropriate, transparent, and timely manner. This should most appropriately be in a peer reviewed platform
- The scientific credentials of the investigator and his site staff in order to carry out and execute trial in a robust and safe manner

To this end a company may require that the investigator submit his proposal in a specific template. It may also be required that Good Clinical Practice (GCP) credentials of the investigator and staff be submitted along with trial proposal. It is recommended that GCP training has occurred within the preceding 3 years to IIT submission for industry support.

The company may also request for a publication history of the investigator and evidence of appropriate medical and scientific qualifications.

How are IIT proposals reviewed?

As many pharmaceutical companies have a central review process, the review of IIT
proposals may be a multi-step process with input from the country of submission, regional, and global stakeholders. As such, investigators should request approximate timelines for review.

After initial review, concerns from industry reviewers may be communicated to investigator who can then choose to modify the trial design in order to allay specific concerns. There should not be any doubt that the final decision on trial design should be made by the investigator.

However, industry reviewers may include those with specific skill sets such as toxicologists or biostatisticians. Hence investigators may wish to take into account specific areas of concern highlighted about trial design.

What support is needed for IIT proposals?

Support for IITs may be in the form of drug, comparator drug, financial funding, and/or the provision of specific scientific services.

This will be governed by an appropriate legal agreement between the pharmaceutical entity and the investigator/sponsor. Payment will usually be structured around significant milestone events (e.g. ethics committee approval for the trial). Many companies now require local company medical affairs input to certify that budgets proposed for the trial are within the Fair Market Value norms for the conduct of such trials in that particular country.

Pharmaceutical industry entities are committed to a high degree of financial transparency and may thus publish their specific financial commitments to IITs on a website or submit to review by a regulatory body.

Many pharmaceutical companies will monitor the IIT investigators’ compliance and adherence to their contractual obligations, such as the disclosure of IIT findings, agreed upon milestones, and safety information reporting. As regulatory bodies may ask for safety and efficacy findings from IITs for New Drug Applications, it is imperative that IITs be conducted with the highest standards of scientific rigor.
Where are IIT outcomes published?

Final publication of IIT outcomes must be decided on by the investigator/sponsor. The pharmaceutical company may offer specialised editorial services such as medical writing etc. but should have no editorial input.

As many IITs may have ramifications on the prescription of existing marketed molecules, the investigator may consider sharing the data from the trial before publication. This may be full datasets or even simply the conclusions from the manuscript. One should note that guidelines on data sharing vary from journal to journal. Some may not allow sharing of data before publication in the journal. Points to consider when planning to submit results for publication include:

- Would the generated data raise concerns among practitioners about the current usage of the drug among patients?
- Would regulatory bodies need to be updated on any unexpected safety data?
- Would data showing efficacy in a hereto unknown indication mean the industry partner needs to do its own review to formulate guidance for other physicians?

The benefits of informing the industry partner is that it will enable them to have prepared answers for possible medical queries from other healthcare professionals on the IIT and implication on molecules currently being used.

How is intellectual property managed?

In broad terms, the investigator owns the intellectual property to any research that is done. In the case of IITs, most pharmaceutical companies will detail ownership of the data generated in the contract that outlines the level and degree of support. It is recommended that this is reviewed carefully by the investigator and their affiliated educational/clinical institute.

Summary

IITs are an integral part of the collaboration between industry and researchers. Mutual understanding of the processes involved and the need to uphold a high degree of scientific rigor and independence are hallmarks of success in this area.
Can I ask the company for assistance in writing the synopsis and protocol?

It is important that there is no element of directed research. Hence while companies are able to review and give feedback on trial design etc. they will not assist in writing the concept or protocol.

Do I have to make all of the changes to trial protocol recommended by the company?

As the trial sponsor, the investigator is ultimately accountable for the safe and efficient conduct of the trial. It is recommended that close and open communication links be developed with the review board of the company to find a mutually agreeable common protocol.

What happens once the protocol and budget are approved?

The company will then work with the Investigator and/or the relevant affiliated clinical, research, or academic entity to draft a contract for the support of this trial.

Do I need to let the company know how the trial is progressing?

Generally the company will structure payments based on milestones. Hence significant events (e.g. ethics committee approval, first patient first visit (FPFV)) should be communicated to the appropriate local company contact.

Can I get assistance with statistical analysis from the company?

This again varies from company to company. In the interest of compliance and not being seen to influence the trial in any way, some companies may not allow direct involvement with analysis of data. Some may allow biostatistics assistance from specialised company
employees. Others may be able to offer financial assistance for analysis by a third party vendor.

**Do I need to share the data with the company before presentation of data in a peer reviewed platform (e.g. abstract presentation at congress/submission of manuscript to journal)?**

The investigator should look at the contract to see if there are any detailed clauses pertaining to the sharing of data. Generally, while the investigator has no obligations to share data before a presentation to the public, he may wish to consider sharing of the data if there is significant safety impact or impact on how the molecule is currently being used.

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**Bibliography and References:**

Siriraj Hospital is the oldest and largest hospital in Thailand, located in Bangkok on the west bank of the Chao Phraya River, opposite Thammasat University’s Tha Phrachan campus. It is the primary teaching hospital of the Faculty of Medicine Siriraj Hospital, Mahidol University. With a capacity of more than 2,000 beds and more than one million outpatient visits per year, Siriraj is one of the largest and busiest medical centers in South East Asia. The medical school accepts about 250 medical students and more than 100 people for postgraduate residency training each year. Siriraj is the largest public hospital in Thailand. Due to its excellent reputation, its tertiary care unit is the referral center for all hospitals in Thailand.
To ensure that the rights, safety and well-being of trial subjects are not compromised, all clinical trials need to be reviewed by an ethics committee (EC) or institutional review board (IRB).

Fundamental ethics considerations include the following:

- Patient participation must be voluntary and the patient’s decision to participate or not is made freely under informed circumstances; no undue influence or coercion is permitted (details of informed consent are found in Chapter 3 – Informed Consent and the Informed Consent Form)

- Risks to subjects are to be minimised; risks to subjects are reasonable in relation to anticipated benefits. Data safety for monitoring need to be planned to ensure the safety of subjects during the trial

- Ensuring subject confidentiality is maintained in accordance to any applicable laws and regulations

- Vulnerable populations are taken into special consideration to ensure they have equal rights and opportunities

- There is social, clinical, and scientific value to the study, so that the aim of the research is to find an answer to a question that will benefit society as a whole

If your hospital does not have a full-fledged ICH-GCP compliant EC, there are always alternatives you can leverage, for example a central ethics committee in your country/state or even an independent review board (sometimes known as commercial IRBs) can be approached if you get a ‘No Objection’ from your own hospital EC.
So how do I go about making an EC submission?

- **Design Protocol & Study Documents**
  (e.g. Informed Consent Form (ICF) etc.)
- **Obtain Study Grant**
  (For details please refer to chapter 4)
- **Compile EC submission package**
  (and make necessary number of copies)
- **Submit to EC**
- **EC reviews the submission package and issues queries/comments/recommendations**
- **Address any queries &/or make necessary changes**
- **Yes**
- **Approval letter received**
  - **Study can start after all other approvals are in place**
- **No**
  - **Re-submit to EC**

**Useful Tips:**

- **If you are not sure of what documents you need to submit, check with the EC Secretariat.**
  The EC Secretariat would have the most accurate information with regards to what the board members are looking for. ECs should have Standard Operating Procedures (SOPs) that you can ask for.
  
- **Note:** Along with the protocol, informed consent form and other patient materials, including those used for recruitment (e.g. posters, newspaper advertisement), EC’s may also want to review the investigator’s qualifications (i.e. CV) and Good Clinical Practice training documentation. Some ECs may review the investigator and site study budget and different countries may also have specific ‘country requirements’ for the budgets, which you need to consider.

- **Take note of submission deadlines (initial submission, re-submission, reply to queries), because if you miss a submission deadline your study may be pushed to the next meeting which could be anytime from one month to three months away.**

- **Check if you (Principal Investigator-PI) are expected and/or allowed to attend the EC full board meeting.**
  Very often having the PI presenting the study design and rationale to the EC can help answer potential queries all at once and reduce a back and forth of queries that can potentially delay approval timelines.

- **Administrative support is important to ensure all the necessary documents and application forms are correctly completed so there is no time wasted in redoing simple administrative tasks.**

- **Ensure payment to EC is made in a timely manner.**
  Some ECs may not table the study for review without payment, some will review but will not release comments and some may not release approval letters.
Ensuring the safety and well being of the study subjects is the key responsibility of the EC and to help you ensure your EC submission package meets the basic areas of interest to the EC, we have listed some points to keep in mind:

### Points to Remember!

<table>
<thead>
<tr>
<th>Point to Remember</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearly highlight the purpose, and rationale of the clinical trial</td>
<td>Even though this will be in the protocol, clearly highlighting this in the EC application form is good</td>
</tr>
<tr>
<td>If the study has a placebo arm, then a supporting document providing the justification for this should be submitted to the EC</td>
<td>Ensuring that the protocol covers for rescue medication/intervention, etc. for the study subjects is helpful</td>
</tr>
<tr>
<td>If the study has a active comparison arm, explicitly say that the comparator is standard of care, to ensure there is no bias to the study arm as being more superior to the comparator</td>
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<tr>
<td>Be ready to elaborate on the justification behind the subject inclusion and exclusion criteria and the subject sample size calculation</td>
<td>ECs look very closely at this criteria to ensure that the right patients are being recruited for the study and ensuring there is sufficient supporting data to arrive at these criteria and numbers is essential. If possible, consider having a statistician sign off on the sample size estimation</td>
</tr>
<tr>
<td>Provide a safety monitoring plan to EC if the trial involves more than minimal risk</td>
<td>Data Safety Monitoring Boards (DSMB) are common for studies with high-risk patients and ECs will often ask for the working guidelines of this group</td>
</tr>
<tr>
<td>Specify the compensation for injuries from the trial</td>
<td>In addition to what would be documented in the protocol for patient compensation, providing the study insurance certificate would be good</td>
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</table>

*Continue on next page*
Continuing review

It is important to note that maintaining ethical considerations should not end when initial approval is obtained. In fact, ethics approval is usually for a period of time rather than the duration of the study. Most, if not all, ECs will require a periodic study report to be submitted for the EC’s review at set intervals as part of an on-going review of the study. This may be required every 12-months or even 6-months, depending on the EC’s guidelines.

Points to Remember!

- Clearly state the travel compensation and/or reimbursement given to the subject (if any)

  In order to provide assurance to the EC that the compensation/reimbursement being provided to the study subjects is reasonable and not an enticement to take part in the trial, it will be good to have this amount stated in the ICF that is submitted to the EC

- Clearly address data confidentiality concerns and the procedure for biological sample handling/destruction

  Ensure that data confidentiality is appropriately addressed in the protocol. For studies where biological samples are collected, especially tissues samples, the time for which they will be stored, the storage location/facility, and the tests to be done on them should be addressed very clearly in the protocol and ICF (sometimes needed). Future testing of the sample should also be addressed appropriately

Bibliography and References:

ALL INDIA INSTITUTES OF MEDICAL SCIENCES

India

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A robust, ‘analysis-friendly’ database that is compliant with regulatory and ethical requirements is crucial for the successful undertaking of clinical trials. This chapter covers key data management topics relevant to the conduct of clinical trials. There are two sections, and as with the rest of this handbook, both are aimed at researchers undertaking Investigator Initiated Trials (IITs).

The first section introduces basic concepts of data entry and database construction, and is targeted towards investigators planning to lead small, mostly single-centre studies. The section assumes that such investigators have limited relevant experience in the conduct of clinical trials.

The second section provides an overview of the clinical data management (CDM) process and systems used in larger, mostly multi-centre studies. The section is most relevant to investigators with some relevant experience in the conduct of clinical trials.

Part 1: Basic data management issues

Database programs

Many researchers involved in small studies use Microsoft Excel for data collection. It must be noted that Microsoft Excel is not a database program per se, it is an electronic spreadsheet. Hence this format is not ideal and should only be used when no other options exist, and only for studies with relatively few variables and minimal requirement for data processing.

A larger, more complicated study would benefit from using a relational database, such as Microsoft Access. Relational databases store data in multiple tables and are ‘3 dimensional’, as opposed to the single, ‘flat file’ nature of a spreadsheet. For example, consider a clinical trial with one baseline visit and four follow-up visits. At each of the visits, demographic, clinical, and outcomes data are collected. Tables of data can be
created for each of the five visits, but related data from any of the tables (for example, clinical information from all five visits) can be extracted and assembled.

Regardless of the program used, it is mandatory to create a data dictionary that defines all the variables in a dataset. A typical data dictionary defines each variable, provides relevant references (for example, indicates the corresponding question in the case report form [CRF]), describes the potential values of each variable (including values for missing data, if applicable), and includes explanatory notes as required.

Data from Microsoft Excel or Access are easily exported into statistical software packages (for example, SPSS, STATA and SAS) for analyses, as long as basic rules of data entry (see below) are followed. Not all features in Microsoft software (for example, comments in Excel) are transferable, and hence a good data dictionary is important.

If a researcher is familiar with a statistical software program, then he/she may enter data directly into this program. Data in statistical software programs are maintained as flat files (as with Microsoft Excel). The main disadvantages of directly entering data into statistical software programs are less flexibility (for example, annotations are not easily made) and the need to have the program available ‘in the field’.

**Data security**

It is critical that personal and sensitive information about study subjects remains secure, whether these exist in paper or electronic form. All data containing personal and sensitive information must be placed under locked storage. For electronic data, this means that files must be adequately password protected.

Any personal identifying information (for example, names and medical record numbers) should not be included in electronic databases. Instead, subjects should be identified by a unique study ID that preserves their anonymity. A list linking study IDs to personal identifying information needs to be created and stored separately and securely.

**Database setup**

In general, within a spreadsheet or table of a relational dataset, each column should
define a variable and each row (other than the first) should define an observation or a study subject. The first (or maybe the first two or three) rows are assigned to the variable names. An excerpt of a hypothetical dataset created in Microsoft Excel, containing data for only five subjects, is provided in Figure 1. In this example, each row defines a study subject.

**Figure 1: Example of a dataset created in Microsoft Excel**

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>subject_id</td>
<td>date_birth</td>
<td>date_recruited</td>
<td>age</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>16-Dec-37</td>
<td>2-Feb-11</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>6-Jun-68</td>
<td>4-Feb-11</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>3-Mar-15</td>
<td>18-Feb-11</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>8-Dec-65</td>
<td>27-Mar-11</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>15-Jul-54</td>
<td>5-Apr-11</td>
<td>57</td>
</tr>
</tbody>
</table>

Variable names should be kept short but still be sufficiently self-explanatory. Detailed information about each variable should be maintained in a data dictionary.

As commonly occurs in a clinical trial, study subjects will each contribute more than one observation of data because of repeated follow-up. That is, subjects attend multiple visits during a course of a trial, and data are collected each time. As mentioned, if data are being collected in a relational database, then a table can be created for each visit. For flat files (spreadsheets and datasets contained within statistical software packages), the longitudinal nature of the data can be expressed in one of two ways: ‘long’ or ‘wide’ formats.

In ‘long’ datasets, each row represents an observation, and because each subject undergoes multiple observations, each subject’s data appear in multiple rows. An example is provided in Figure 2. In this hypothetical example, data from two visits are shown, with Visit 2 taking place approximately three months after Visit 1.

**Figure 2: Example of a ‘long’ dataset created in Microsoft Excel**

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>subject_id</td>
<td>visit_number</td>
<td>unique_id</td>
<td>date_birth</td>
<td>date_visit</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1001</td>
<td>16-Dec-37</td>
<td>2-Feb-11</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>2</td>
<td>1002</td>
<td>16-Dec-37</td>
<td>3-Mar-11</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>1</td>
<td>2001</td>
<td>6-Jun-68</td>
<td>4-Feb-11</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>2</td>
<td>2002</td>
<td>6-Jun-68</td>
<td>3-Mar-11</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>1</td>
<td>3001</td>
<td>3-Mar-45</td>
<td>18-Feb-11</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>2</td>
<td>3002</td>
<td>3-Mar-45</td>
<td>24-Mar-11</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>1</td>
<td>4001</td>
<td>8-Dec-65</td>
<td>27-Mar-11</td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>2</td>
<td>4002</td>
<td>8-Dec-65</td>
<td>26-Jun-11</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>1</td>
<td>5001</td>
<td>15-Jul-54</td>
<td>5-Apr-11</td>
</tr>
<tr>
<td>11</td>
<td>5</td>
<td>2</td>
<td>5002</td>
<td>15-Jul-54</td>
<td>1-Jul-11</td>
</tr>
</tbody>
</table>

Note that values for some variables are fixed, because they are independent of the visit number. In the example illustrated in Figure 2, the variables ‘subject_id’ and ‘date_birth’ remain constant for each subject. The values of all other variables change according to the visit number.
In ‘long’ datasets, because the value for ‘subject_id’ is no longer unique to each observation (the same value appears in multiple observations), a separate variable should be created that is unique to each observation. In the example illustrated in Figure 2, the variable ‘unique_id’ was created through concatenation of ‘subject_id’ and ‘visit_number’ (‘subject_id’*1000 + ‘visit_number’).

In ‘wide’ datasets, each row uniquely represents a study subject, and separate variables are created to represent data collected from different observations, over different times, of the same subject. An example is provided in Figure 3. As with the hypothetical example illustrated in Figure 2, data from two visits are shown, with Visit 2 taking place approximately three months after Visit 1.

Note that the variable ‘subject_id’ is unique (not repeated), and variables for which values change according to the visit number have to be specified according to the visit number. In the example illustrated in Figure 3, separate variables have been created to capture the date of each visit, as well as the age of the subject at each visit. In a clinical trial, most other information will also be visit-specific, such as updated data on outcomes and adverse effects.

Within statistical software packages, datasets can easily be converted between ‘long’ and ‘wide’ formats.

**Data entry**

From the outset, it is important that data be entered in a manner that is friendly to analyses. Otherwise, a significant amount of time will have to be subsequently devoted to data ‘cleaning’. To appreciate what constitutes ‘analysis-friendly’ data, an understanding of data types is first required.
Variables can be classified into 2 main types: categorical and numeric, within each of which are 2 further subtypes:

1. Categorical
   - Nominal
   - Ordinal
2. Numeric
   - Discrete
   - Continuous

As the name implies, categorical variables are expressed in categories rather than numeric values. Nominal categories have no order, while ordinal categories do. Variables for which only two categories exist are also called binary variables. Numeric data can be stratified into those with discrete values and those that exist on a continuum.

As exemplified by systolic blood pressure variable in Table 4, numeric data can be converted into categorical (ordinal) data. However, when entering data, it is good practice to preserve numeric data in numeric form so that precision of the information is maintained. Categorisation of numeric data leads to loss of information (for example, the category ‘120-140’ encompasses all values between 120 and 140 inclusive). Furthermore, if needed, categorisation of numeric data can always be undertaken after the initial data entry.

Data can also be entered in date formats, as exemplified in Figure 1 with the variables ‘date_birth’ and ‘date_recruited’. Although the data are expressed as dates, they are actually numeric values, being a measure of time since a reference date. For example, in Microsoft Excel, dates are actually the number of days since the reference date of 31 December 1899. Hence 1 January 1900 is ascribed the value 1 and 16 December 1937 is ascribed the value 13,865. (To see this in Microsoft Excel, change the format of the relevant cells from date to number.) Having dates entered as numbers allows for their mathematical manipulation to derive time. For example, in Figure 1, values for the variable ‘age’ (in years) were derived

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>SCALE</th>
<th>TYPE OF DATA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancies</td>
<td>0,1,2,3,4...</td>
<td>Discrete</td>
</tr>
<tr>
<td>Weight</td>
<td>kg (eg 67.3, 81.2)</td>
<td>Continuous</td>
</tr>
<tr>
<td>Radiation exposure</td>
<td>Yes / No</td>
<td>Nominal (Binary)</td>
</tr>
<tr>
<td>Country of birth</td>
<td>USA, Aust, UK, other</td>
<td>Nominal</td>
</tr>
<tr>
<td>Job stress level</td>
<td>Low, Medium, High</td>
<td>Ordinal</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>&lt;120, 120-140, &gt;140</td>
<td>Ordinal</td>
</tr>
</tbody>
</table>
by subtracting ‘date_birth’ from ‘date_visit’ to obtain the number of days that had transpired between these 2 dates, and dividing this value by 365.25 (mean number of days in a year).

Finally, data can also be entered as free text. It must be noted that free text is not analysable in any quantitative sense and should be avoided, or at least minimised. When free text is exported to statistical software programs, columns containing free text are assumed to be categorical (string) variables. However, the categories will be meaningless.

As a general rule of thumb, numeric data (including in date form) are more analysis-friendly than categorical data. They have a natural order and can be mathematically manipulated. This means that ideally (but not crucially), categorical data should be coded as numbers so that they can be maintained in numeric variables. For example, “No” could be coded as 0 and “Yes” as 1, and the categories “Mild”, “Moderate” and “Severe” could be coded as 1, 2 and 3, respectively. The codes assigned to each category should be maintained in the data dictionary.

In general, with binary categorical variables for which the values are either positive or negative (for example, “Yes” or “No” and “Present” or “Absent”), use 1 to denote the positive response and 0 to denote the negative response. With ordinal categorical variables, use ascending numbers to correlate with the increasing order of responses (for example, 1, 2 and 3 to denote “Mild”, “Moderate” and “Severe”, respectively). These assumptions are intuitive, and during data analysis, many statistical software programs assume by default that categories follow an order as per their numeric codes.

If categorical data are not to be numerically coded, it is important to ensure that during data entry, the spellings of categories that are the same are kept identical. For example, “Male” and “male” will not be recognised as being the same and will be assumed to be two different categories. In Microsoft Excel and Access, entry of categorical data can be facilitated by the use of drop-down menus. This avoids the need for typing, which ensures consistency of spelling and also saves time.

Another point of note regarding categorical variables is that they should be both mutually exclusive (that is, only one category is relevant for each observation) and exhaustive (that is, all options are considered). In terms
of the latter, many categorical variables need to include “Other” as an option.

For numeric variables, ensure that cells contain only numbers; do not include any text such as units of measure (for example, “56 years old”, “120 mmHg”) or explanatory notes (for example, “56 (to confirm)”). Even punctuation marks need to be avoided (for example, “56?”). When data are transferred to statistical software packages, inclusion of non-numeric data in any cell (even just one) will lead to the assumption that the relevant variable is non-numeric.

For both categorical and numerical variables, there are frequently missing data. Specific values can be used to denote missing data (for example, “Missing” or “999”) or the field can simply be left blank. Keep in mind that if numeric values are used to denote missing data, then these values need to be specified as such. Otherwise, they will be interpreted literally (for example, interpreted as the value 999).

Part 2: Clinical data management

What is clinical data management?

Clinical data management (CDM) refers to the process of collecting, cleaning, and managing of clinical trial data in compliance with regulatory and ethical standards. The primary objective of CDM is to provide high-quality data by keeping errors and missing data to a minimum, so as to maximise available data for analyses. To meet this objective, best practices are adopted to ensure that data are reliable, complete, and processed in accordance with appropriate regulatory frameworks as well as Good Clinical Practice (GCP) guidelines.

Regulations, guidelines, and standards in CDM

CDM has guidelines and standards that must be followed, one of which is Code of Federal Regulations (CFR), 21 CFR Part 11. This regulation is applicable to records in electronic format that are created, modified, maintained, archived, retrieved, or transmitted. This demands the use of validated systems to ensure accuracy, reliability, and consistency of data, with
the use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records.

Adequate procedures and controls should be put in place to ensure the integrity, authenticity, and confidentiality of data. If data have to be submitted to regulatory authorities, they should be entered and processed in 21 CFR Part 11-compliant systems. Most available Clinical Data Management Systems (CDMS) facilitate compliance with the above regulations.

**The CDM process**

The CDM process is designed to deliver an error-free, valid, and statistically sound database. To meet this objective, the CDM process starts early, even before the finalisation of the study protocol.

**Case Report Form design**

Development of a CRF is the first step in the CDM process. A CRF is developed after reviewing the protocol wherein the CDM personnel will identify the data items to be collected and frequency of collection with respect to the visit schedule. CRFs could be paper or electronic in nature and are developed with inputs from biostatisticians, medical advisors, project managers, clinical team leads, and sponsors.

CRFs are the official documentation of the trial for both sponsors and regulatory authorities, and together with the source documents and the trial master file/investigator site file, will be closely examined during monitoring, audits, and inspections.

This section highlights some of the most important points to consider during the CRF design process.4

Some best practice in CRF design:

- The arrangement of the data fields should be clear, logical, and user friendly
- Where possible, provide tick box options and keep free text to a minimum
- Take into account the flow of study procedures and the typical organisation of data in a medical record

Note that there are three types of data collected: non-time dependent, time dependent, and cumulative. Non-time dependent data are
collected at a snapshot in time. Such data include subject demographics and medical history. Time dependent data are collected repeatedly over time. A typical example is vital signs recorded at multiple visits. Cumulative data are collected over time but not linked to a specific visit. Adverse events and concomitant medications are typical examples.

A well-designed CRF can help define a structured database and collect valid and consistent data in a clinical trial. It reduces time for data query management and increases the efficiency of statistical analysis and output generation. Along with the CRF, filling instructions (called CRF completion guidelines) should also be provided to study investigators for error-free data entry.

**Database design**

The next step is the design of the database to capture the clinical trial data. As mentioned, databases should have built-in compliance with regulatory requirements and be easy to use. Study details like objectives, intervals, visits, investigators, sites, and patients are defined in the database and CRF layouts are designed for data entry. These entry screens are tested with dummy data before their application to the real data capture.

**(Some) tools for CDM**

Many software tools are available for data management, and these are called CDMS. In multicentre trials, a CDMS is essential to handle large amounts of data. Most of the CDMS are commercial, but a few are open source (free) tools. Some clinical trial sponsors use custom-made CDMS to suit their operational needs and procedures. Commonly used commercial CDMS include Oracle Clinical, Oracle Clinical RDC, Oracle Inform, Medidata RAVE, and others. In terms of functionality, these software tools are more or less similar and there is no significant advantage of one system over the other.

Among the open source tools, the most popular are OpenClinica, OpenCDMS, TrialDB, PhOSCo and others. These CDMS generally offer functionality that approaches that of commercial tools.
Development of study guidance documents

It is important to develop a data management plan (DMP) document for various data management activities. The DMP document serves as a guideline and is developed for activities like database design, data collection, data cleaning (edit check specification), quality control measures, data coding, serious adverse event (SAE) reconciliation, data transfers, data imports, non-CRF data reconciliation, and database lock activities.

Data collection

Data collection is undertaken using the CRFs that exist in paper or electronic format. The traditional method is to employ paper CRFs to collect data responses, which are then transcribed into the database. Paper CRFs are filled in by investigators according to the completion guidelines. With electronic CRFs, the investigator or a designee logs onto the CDMS and enters data directly. Other than avoiding the need for paper, the main advantages of electronic CRFs are minimisation of transcription errors and faster resolution of discrepancies.

Data validation

Data validation is the process of testing the validity of data in accordance with the protocol specifications. Edit check programs are written to identify the discrepancies in the entered data, which are embedded in the database. These programs are written according to the logic condition mentioned in the edit checks specification document. Edit check programs are initially tested with dummy data containing discrepancies.

A discrepancy is defined as a data point that fails to pass a validation check. It may be due to inconsistent data, missing data, range checks, and deviations from the protocol. In electronic CRF based studies, the data validation process is run at the time of data entry. Discrepancies are then resolved by investigators or study coordinators.

Discrepancy management

This is also called query management/resolution. It is the most critical activity in the CDM process. Discrepancy management includes reviewing discrepancies, investigating the reason, and resolving them with documentary proof or declaring them as irresolvable. Discrepancy management
helps in cleaning data and gathers evidence for the deviations observed in data. Almost all CDMS have a discrepancy database where all discrepancies will be recorded and stored with audit trail.

The CDM team reviews all discrepancies at regular intervals to ensure that they have been resolved. Based on the types identified, discrepancies are either flagged to the investigator for clarification or closed in-house without seeking clarification from the investigator. Queries are sent to site for discrepancies that require clarification from the investigator.

Investigators and/or designates will review the query and provide appropriate resolution either by confirming the data or making a change to the data. If the response provided by investigator/site is not appropriate, then a re-query is issued to the site to elicit a further response.

**Medical coding**

Medical coding helps in identifying and properly classifying medical terms associated with a clinical trial. For classification of events, medical dictionaries are used. Technically, this activity needs the knowledge of medical terminology, understanding of disease entities, drugs used, and a basic knowledge of the pathological processes involved.

Functionally, it also requires knowledge about the structure of electronic medical dictionaries and the hierarchy of classifications available in them. Adverse events occurring during the study, prior to and concomitantly administered medications, and pre- or co-existing illnesses are coded using the available medical dictionaries. Commonly, Medical Dictionary for Regulatory Activities (MedDRA) is used for the coding of adverse events as well as other illnesses and World Health Organization Drug Dictionary (WHO-DD) is used for coding the medications.

Medical coding helps in classifying reported medical terms on the CRF to standard dictionary terms in order to achieve data consistency and avoid unnecessary duplication. For example, the investigators may use different terms for the same adverse event, but it is important to code all of them to a single standard code and maintain uniformity in the process. The right coding and classification of adverse events and medication is crucial as an incorrect coding
may lead to masking of safety issues or highlight the wrong safety concerns related to the drug.

**Serious adverse event reconciliation**

A serious adverse event (SAE) is defined as any untoward medical occurrence that happens during a clinical trial. For example, an event that results in death, is life threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, and congenital anomaly/birth defect.

SAE reconciliation is a process of verifying/reconciling common data elements present in clinical and safety database. It is done to ensure SAE data are consistent and accurate between the two databases.

**Data transfers**

Clinical data are extracted from the database at regular or pre-defined intervals during the course of the study. The extraction of data involves development of data transfer program and guideline document which describes the methodology to be followed for this process. The data thus extracted are sent to biostatisticians for review. Any observations and/or findings identified by biostatisticians are shared with CDM team who will investigate and take appropriate actions.

**Data imports**

Data that are not collected in the CRF, but are generated as part of the clinical trial are called non-CRF data. Typical examples are laboratory data, ECG data, and randomisation data. Non-CRF data are imported into the CDMS at pre-defined frequencies through data import programs for data review and cleaning purposes.

**Database locking**

After a proper quality check and assurance, the final data validation is run. If there are no discrepancies, the datasets are finalised in consultation with the biostatistician. All data management activities should have been completed prior to database lock. To ensure this, a pre-lock checklist is used and completion of all activities is confirmed. This is done as the database cannot be changed in any manner after locking. Once the approval for locking is obtained from all stakeholders, the database is locked and clean data are extracted for statistical analysis.
Generally, no modification in the database is possible. But in case of a critical issue or for other important operational reasons, privileged users can modify the data even after the database is locked. This, however, requires proper documentation and an audit trail has to be maintained with sufficient justification for updating the locked database. Data extraction is undertaken from the final database after locking. This is followed by its archival.

**Bibliography and References:**

**Points to Remember:**
1. A robust, ‘analysis-friendly’ database that is compliant with regulatory and ethical requirements is crucial for the successful undertaking of clinical trials.
2. For small, mostly single-centre studies, Microsoft Access provides a suitable database format. If possible, avoid Microsoft Excel.
3. Data security is key.
4. Data can be classified into two main types: categorical and numeric.
5. Numeric data are more analysis-friendly, and categorical data can be converted into numeric data by coding categories numerically (e.g., “No” = 0 and “Yes” = 1).
6. For larger, mostly multi-centre studies, use of Clinical Data Management Systems (CDMS) is necessary.
7. CDM refers to the process of collecting, cleaning, and managing of clinical trial data in compliance with regulatory and ethical standards.
West China School of Medicine/West China Hospital of Sichuan University (WCSM/WCH) is a prestigious medical center located on the banks of the Jinjiang River in Chengdu, a famous historical and cultural city of China. After 120 years of development, particularly during the reform and opening-up period, WCSM/WCH has become a comprehensive medical teaching and research center with diverse disciplines, abundant faculty resources, advanced medical techniques, modern medical equipment, and strong potential in medical research. WCH is the largest single-site hospital in the world and a leading medical center of West China, treating complicated and severe cases, especially in the fields of living donor liver transplantation, severe acute pancreatitis, and clinical anesthesia. The hospital has 4,800 beds and covers an area of more than 470,000 sq m and service area of 400,000 sq m. In 2011, more than 3.5 million patients visited the outpatient department, 173,000 patients were discharged from inpatient departments, and more than 93,900 operations were performed.
Why do we need to take statistical considerations into account in a clinical trial?

Clinical trials are usually set up with the hope that the health intervention under study may be beneficial in a specific population of potential patients. However, the trial itself will be carried out only in a sample drawn from that population. Statistical principles are required not only to ensure the trial is designed to answer the question about whether the health intervention is beneficial, but also analysed appropriately to ensure any interpretation of the results can be generalised to the whole population.

One key challenge is that no two patients in a sample (or a population) are the same, and so will not react identically to the health intervention. This variability can be a problem if it is large, since it will become difficult to differentiate between real treatment differences and natural variation. And the smaller the clinical trial (in terms of sample size), the larger the variability is likely to be. The application of sound statistical principles is needed to obtain a robust conclusion from the study.

Which is more important, design or analysis?

Most definitely, the design of the clinical trial is more important. Whereas any errors in analysis can be corrected, in the case of trial design (to quote from a famous statistician): “To consult the statistician after an experiment is finished is often merely to ask him to conduct a post mortem examination. He can perhaps say what the experiment died of.”

As well as seeking to minimise variation through good study design (e.g. giving medications and taking measurements at the same time each day), another key consideration is the avoidance of bias. The
presence of bias can lead to a situation where the results of the study sample are not a good representation of the population, and could arise (for instance) by only selecting patients likely to be fully compliant, or by only giving the health intervention to the most severe patients. In this latter case, it would be impossible to determine if any difference between ‘intervention’ and ‘control’ patients was due to the intervention itself or the severity of their disease.

What are the key elements of a well-designed trial?

Minimisation of variability (i.e. maximising precision) and avoidance of bias are the two most important statistical considerations for clinical trials, and a large component of the ICH “E9 Statistical Principles for Clinical Trials” guideline is devoted to these two topics. The most common methods for reducing bias include randomisation and blinding.

Randomisation is a technique which introduces a deliberate element of chance into the assignment of treatments to patients in a clinical trial. This helps to minimise any bias in treatment allocation. Essentially, randomisation tends to produce ‘intervention’ and ‘control’ groups which are evenly distributed in terms of factors that influence the likelihood of developing the outcome of interest in a clinical trial.

If these factors, called confounders, are unevenly distributed between the two groups (for example, one group was significantly older than the other), then any observed difference in the outcome of interest between the two groups may reflect the difference in confounders rather than the effect of the intervention. Blinding is intended to limit the occurrence of bias which could arise from knowledge of treatment allocation – this could apply to patient recruitment, treatment allocation, data measurement, handling of withdrawals, etc.

Two other features of a well-designed trial are also noteworthy:

- Single, well-defined primary objective – It is important to clearly define a single primary objective for the trial. This may be the superiority of a new treatment over a control, or perhaps to show a new treatment is not worse than (non-inferior to) a control. In any case, it is vital to link the appropriate primary endpoint to the primary objective. For instance, if a trial
is set up to show that a new treatment yields weight loss compared to a control group, then change from baseline in patient weight is likely to be the primary endpoint. Ideally, the primary endpoint in any trial should be:

- Related to the primary objective
- Easy to diagnose or observe
- Objectively measured (rather than subjectively) where possible (it is noted that patient reported outcomes have an inherently subjective component)
- Capable of being observed independently of treatment assignment
- Clinically relevant
- Chosen at the study planning stage

- **Sample size** – With an insufficient number of patients, the study may not have enough power to detect a clinically meaningful treatment effect, thus would not achieve its primary objective. Equally, too many patients may also be undesirable, not only due to spiralling costs but also because some patients may be unnecessarily exposed to what might turn out to be an ineffective treatment. This is unethical. We will return to the concept of power shortly, but statisticians should always be consulted when considering the sample size for a trial.

**What are the key elements of good statistical analysis?**

First and foremost, **estimation** is as important as **significance testing**. By estimation, we mean quantifying the treatment effect in the population. This usually involves calculating an average value, along with its variability, based on the data observed in the sample (i.e. in the trial). Most commonly, you might see **means** and **standard errors** or, better still, means and **confidence intervals** for the treatment effect. The most appropriate average measure will depend on the type of data under observation.

For binary endpoints (such as success/failure), percentages or incidence measures (for example, 5 per 100 persons per year) will usually be displayed. You might also come across relative risks and odds ratios in this context. Continuous data are usually summarised through means or medians, with appropriate measures of variability. The variability around a mean is sometimes expressed by the standard error, while the variability around a median (50th percentile) is sometimes expressed by the 25th and 75th percentiles. The interval between the 25th and 75th percentiles is called the inter-quartile range.
Significance testing is carried out to determine if an observed treatment effect (in the sample) is far enough away from what is called the “null hypothesis” (the opposite of what you hope the trial will find e.g. no treatment effect) to effectively rule out the null hypothesis as a viable option. This is expressed via a **p-value**, which denotes the probability of observing a result as extreme as we have observed in the trial if the null hypothesis was true.

For instance, if the response in the intervention arm was estimated to be better than in the control arm, then a corresponding small p-value would mean that this result was unlikely to have occurred by chance. That is, had the null hypothesis been true, the probability of finding the observed result, purely by chance, would have been low. Now consider the following potential decisions arising from a significance test in a particular clinical trial:

<table>
<thead>
<tr>
<th>Decision (trial)</th>
<th>Truth (population)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment effect exists</td>
</tr>
<tr>
<td><strong>P&lt;0.05</strong> (treatment effect)</td>
<td>Correct decision (power)</td>
</tr>
<tr>
<td><strong>P&gt;0.05</strong> (no treatment effect)</td>
<td>Incorrect decision (false negative), occurs with probability $\beta$</td>
</tr>
</tbody>
</table>

Conventionally in clinical trials, a p-value $< 0.05$ is felt to be sufficiently small to conclude a statistically significant treatment effect (i.e. $\beta = 0.05$ in the above table). Equally, we usually aim for **power** to be $> 0.8$ (which is equivalent to $\beta = 0.2$). That is, at least an 80% chance of finding a treatment effect in the trial if there is a real treatment effect in the population.

Bias is also a potential issue during statistical analysis. Common ways to combat this include avoiding multiple significance testing where possible (e.g. by choosing a specific primary endpoint at one pre-specified time point), compensating for any necessary multiple significance tests (if every test has a 5% false-positive rate, then the chance of at least one false positive in any one or more of the multiple tests can be as high as 20% using just five significance tests) as well as ensuring all data are accounted for in the analysis, including dropouts (the **intention-to-treat principle**).
Is the interpretation of results a straightforward statistical exercise?

No, it isn’t. Just because a statistical test yields a p-value, that will not tell the whole story. The clinical relevance of the result will be important, as well as its statistical significance. This is why statistical testing alone is insufficient (e.g. if $p < 0.05$, which is better: the new treatment or the control?) and estimation is crucial. Only by reviewing the estimated size of the treatment effect (and its confidence interval) can a judgment be made on its clinical relevance. Moreover, it must also be established that the trial result can be generalised to the intended population. For these reasons, interpretation will also require clinical as well as statistical input.

How should we ensure our planning takes all relevant statistical considerations into account?

Very simple – ask a qualified statistician for advice! According to ICH E6 “Good Clinical Practice”¹: “The sponsor should utilize qualified individuals (e.g. biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analyzing and preparing interim and final clinical trial reports.” In many academic settings, you can usually find biostatisticians on the staff of the Medical or Public Health School.
Points to Remember!

1. Statistical thinking is even more important in design than analysis.

2. The key statistical considerations in trial design are minimisation of variation and avoidance of bias.

3. Never have more than one primary objective for a clinical trial.

4. Always get input from a qualified and experienced statistician when designing a study (e.g., sample size) and determining appropriate methods of statistical analysis.

5. For the primary objective to be met, the primary results of the trial must be clinically relevant as well as statistically significant.

Bibliography and References:

Cipto Mangunkusumo Hospital (commonly abbreviated as RSCM which stands for Rumah Sakit Cipto Mangunkusumo in Indonesian) is a government hospital located in central Jakarta, Indonesia. The name of this hospital derives from Dr. Tjipto Mangoenkosmo, a prominent Indonesian independence leader and Sukarno's political mentor. RSCM is a national referral hospital center. In April 2013, the RSCM became the first government hospital in Indonesia to be accredited to world-class service standards.
CHAPTER 9

Conclusion

David Horsburgh, Professor Danny Liew, Dr. Stephanie Tan

The aim of this handbook is to act as an introductory guide to the IIT process and provide a theoretical and practical foundation for researchers wishing to undertake their own clinical trials. Each chapter addresses a key issue in the IIT process, as well as its associated challenges, as identified through the authors’ own experiences.

Below are some concluding remarks.

The importance of IITs

IITs are a vital part of improving patient care and address a very different set of scientific questions to industry sponsored trials. In particular, IITs allow for:

- Real-world perspective
- Identification and assessment of new therapies or new uses for existing therapies
- Questions with a clinical, rather than commercial focus
- Platforms for further research

These unique benefits should act as a focal point for planning future IITs.

Good trial design is key

Running IITs is complicated, but any potential challenges can be minimised simply by following the motto that good study design helps lead to good study delivery and results. From the outset, the purpose, type, and rationale of the study need to be clearly defined.

Ask the following key questions to help determine the scope and requirements for your IIT:

- What is the aim of this study? (e.g. is it trialng a new drug or an approved drug on a new target population? is the focus on safety or efficacy?)
- What is the unmet clinical need that is being addressed with this study?
- How will this study benefit patients or further knowledge of this drug/treatment/disease?
- What patient population is needed for this study and how many subjects do I need to recruit for statistical validity?
- What direct benefit do patients receive from being involved in this study?
- If this study is trialling a new treatment combination, are all permitted medications and comparators already approved for my target patient population?
- Does my study design involve a placebo arm and if so, how are patients on the placebo arm managed?
- What ethical considerations do I need to address for this study?
- What risks to the patient or reduction in the quality of treatment are possible if involved in this study? Is sufficient background support or rescue medication available?
- What institutional support is available? (i.e. in terms of study coordinators, statistical input, data management, etc.)
- Is my immediate research team capable of conducting this study in terms of experience and available time?

Create a roadmap

Budgeting and regulatory and ethical submissions are some of the key challenges that investigators will face going into the IIT process. These factors are common reasons for failure. In order to grasp the scope of the IIT process and prepare in advance, adhere to the following simple steps:

- Create a draft budget early on in the process, even prior to protocol finalisation. This will help determine where additional costs may arise. The sooner the required resources can be identified and allocated, the more likely the study will run smoothly
- Identify required regulatory and ethical submissions and plot the submission milestones for the entire study. This will greatly reduce the possibility of last-minute or late submissions and will allow you to see what periods may require increased resources
Consider the challenges

The number of IITs conducted globally is on the rise. Almost 80% of big pharmaceutical companies now have dedicated departments to handle IITs.¹ Public and non-profit organisations are an increasing source of funding while the average IIT spend among the top industry companies is now close to US$25 million per year.²

However, with that has come increasing scrutiny on IITs. Unfortunately, it also does not mean funding for trials is easier to obtain. Challenges include:

- Competition for funding is high
- Gaining approval for large-budget IITs is difficult
- Quality may be inconsistent due to reduced monitoring
- Not all IITs provide useful data to support the original hypotheses
- Limited support from institution or availability of research teams

All these challenges need to be addressed individually. However, good trial design, awareness of statistical and regulatory requirements, and quality control measures will help to improve the successful completion of a trial.

Get help

Get help and get it early. Advice and support can (and should) be sought from more experienced colleagues, academic units, institutional ethics committees, institutional offices for research, and regulatory authorities. Therapeutic area-specific consortiums and associations may also provide information and guidelines as well as access to experienced colleagues.

In Summary – A Bright Future and the Need for IITs

The need for IITs is always expanding as new drugs come onto the market. These studies are crucial in ensuring the benefit to patients is maximised. However, IITs also provide researchers an entry point into the clinical trial landscape and an avenue to pursue their own areas of interest and own research training.
The aim of this handbook is to address some main challenges as identified by experienced investigators and knowledgeable parties in the industry. It is intended to guide researchers through the first few of what hopefully will be many steps into the important world of IITs.

Bibliography and References:


Philippine General Hospital (PGH) is a tertiary state-owned hospital administered and operated by the University of the Philippines Manila, the University of the Philippines System’s Health Sciences Center. It is the largest government hospital administered by the university and is designated as the National University Hospital. It is located at Ermita, Manila in the Philippines. It is the biggest hospital in the country with a 1,500-bed capacity. On an average year, about 600,000 patients pass through the hospital’s halls. PGH celebrated its centennial in 2007, one hundred years since the US government passed a law establishing it. The hospital saw the worst of tropical epidemics during its early existence and the worst of the war in the 1940s. It is one of very few Philippine hospitals that remained open all throughout the war.
Professor Yung-Jue Bang MD, PhD

Professor Yung-Jue Bang, Professor of Medical Oncology, is the President of Biomedical Research Institute and Director of Clinical Trials Center of Seoul National University Hospital. He graduated from Seoul National University College of Medicine in 1979. He is certified in the specialties of internal medicine and hematology/medical oncology. He has been working for Seoul National University College of Medicine since 1986. He has served in many positions, including Director of Cancer Research Institute of Seoul National University (2000 – 2006), President of the Korean Cancer Study Group (2006 – 2008), Vice President of Korean National Enterprise for Clinical Trials (KoNECT) (2009 – 2014), Chairman of Department of Internal Medicine (2010 – 2014), and Chairman of the Korean Cancer Association (2012 – 2014). Dr. Bang has co-authored more than 350 papers in peer-reviewed journals including New England Journal of Medicine and Lancet. He is primarily interested in the development of new anticancer therapeutics, both clinical and translational, especially in gastric cancer. He is the Principal Investigator of a number of international clinical trials including ToGA study, CLASSIC study, and GOLD study.
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Dr. Nantha Kumar graduated from the National University of Singapore and subsequently obtained his membership in the Royal College of Surgeons (Edinburgh). He subsequently trained and worked in a number of tertiary hospitals in general surgery and surgical oncology. He has also been a co-investigator in both investigator and company sponsored clinical trials. He transitioned to join the pharmaceutical industry in 2008 and has subsequently worked in multinational pharmaceuticals such as GlaxoSmithKline and Bayer Healthcare. He also has experience with cutting-edge biotechnology companies such as Celgene. He has set up and managed complex trials in oncology and hematology in Asian sites. He has also worked extensively in clinical development and medical affairs and served to bridge industry and clinicians in Asia.

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Srinivas Pai Raikar is the Director and Head of Site Management Asia Pac at Quintiles based out of Singapore. He has 22 years of combined global biopharmaceutical and clinical research experience. He has been closely involved in conceptualisation, planning, and execution of four key Investigator Initiated Trials (IIT) as well as supporting budget creation for IITs. Srinivas is currently heading site management, leading the initiatives focused on building site relationships and partnerships through the team of strategic site relationship managers (SSRMs) and working closely with Quintiles preferred sites. Prior to joining Quintiles, he worked in a leadership position at Excel Life Sciences, a site management organisation and held various positions for over 15 years in Pfizer. Srinivas completed his management studies at Narsee Monjee Institute Mumbai and received his Bachelor in Chemistry from Goa University.

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Lisa Marie Saldanha

Lisa Marie Saldanha, a pharmacist by training, has over 10 years experience in the clinical research industry. Currently Head of Regulatory & Start-up, Asian region for Quintiles, she leads a team of more than 100 people across Asia in the delivery of clinical trial start-up (regulatory and ethics submissions, contracting and document management). Lisa’s experience spans across both the pharmaceutical as well as CRO industry, in direct management and operational experience in clinical operations, project management, protocol and country feasibility, and study start-up.

David Horsburgh

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