



MINISTRY OF HEALTH MALAYSIA

**FRAMEWORK ON
TRADITIONAL AND COMPLEMENTARY
MEDICINE RESEARCH IN MALAYSIA**

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Foreword

by the Minister of Health



Research in Traditional and Complementary Medicine (T&CM) is essential not only to demonstrate the safety and efficacy of its practices and products, but also to highlight its role within the national health care system. In past decades, the World Health Organization (WHO) has developed a series of guidelines related to T&CM research as international standards for reference by its member states. Following the direction of WHO, the Ministry of Health Malaysia (MOH) is committed to the promotion, innovation and development of T&CM research.

The task of developing this Framework on T&CM Research in Malaysia was challenging as it had to be suitable for use by researchers in various T&CM practice areas in Malaysia, as well as being acceptable for both T&CM and conventional medicine stakeholders. In addition, this framework also highlighted specific requirements for research involving Malaysia's own biological resources.

I sincerely applaud the effort and commitment of all individuals, institutions, agencies and professional associations who have worked tirelessly in making this framework possible. It is my fervent hope that this framework will be a significant step towards conduct of more T&CM research with high translational value that could benefit the health of all Malaysians.

YB DR. ZALIHA MUSTAFA



Foreword

by the Director-General of Health

T&CM has a long history of meeting the health needs of the global population alongside conventional medicine. In recognising the role of T&CM in its national health care system, the MOH has taken proactive measures to regulate T&CM to ensure that T&CM practices are safe and effective for the benefit of Malaysian citizens. However, concerns relating to safety, quality and effectiveness of T&CM have often been raised due to insufficient scientific evidence to support its claims. In addition, T&CM theoretical framework are often not considered in T&CM research. Hence, it is critical to strengthen the local research capacity in order to generate more reliable evidence on the safety, quality and effectiveness of T&CM.

The Framework on T&CM Research in Malaysia is intended to facilitate practitioners, researchers, academicians, authority bodies and T&CM industry players who are interested in designing, conducting and evaluating T&CM research in Malaysia. It encompasses the general and specific requirements for the conduct of T&CM research after considering the principle and design of a research that is suited to T&CM, whilst in compliance with the present policies and guidelines in Malaysia. This framework is the primary source of reference and can be adapted by any of the aforementioned stakeholders.

It is my hope that this Framework could lead to more research in T&CM, encourage more interested parties to conduct research in T&CM, and eventually increase the quantity and quality of research in T&CM. This would thus encourage research expertise in T&CM and produce scientific evidence for future policy decision making in T&CM in Malaysia.

I would like to express my utmost gratitude to the WHO for providing technical support in the preparation of this Framework. My sincere appreciation is also extended to all the stakeholders who committed their time and effort in contributing invaluable input for the Framework preparation. Last but not least, congratulations to the T&CM Division and Herbal Medicine Research Centre, Institute for Medical Research who initiated the development of this Framework as one of the efforts to drive T&CM towards evidence-based practice.

**TAN SRI DATO' SERI
DR. NOOR HISHAM BIN ABDULLAH**

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Thanks are also due to the relevant institutes/divisions under the MOH; Ministry of Natural Resources, Environment and Climate Change; Ministry of Agriculture and Food Security; and local T&CM industry stakeholders for contributing their comments and suggestions.

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List of Abbreviations

ARRIVE	Animals Research: Reporting In Vivo Experiments
CARE Guideline	Case Reports Guideline
CENT for TCM	CONSORT Extension for Reporting N-of-1 Trials for Traditional Chinese Medicine
CHM	Chinese herbal medicine
CONSORT	Consolidated Standards of Reporting Trials
CTIL/CTX	Clinical Trial Import Licence/ Clinical Trial Exemption
DRGD	Drug Registration Guidance Document
EQUATOR	Enhancing the Quality and Transparency of Health Research
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GSP	Good Scientific Practice
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IP	Intellectual property
MDA	Medical Device Authority
MOH	Ministry of Health Malaysia
MREC	Medical Research and Ethics Committee
MyIPO	Intellectual Property Corporation of Malaysia
NCCR	National Committee for Clinical Research
NPRA	National Pharmaceutical Regulatory Agency
NRDHM	National Committee for Research and Development of Herbal Medicine
NRT	Non-randomised controlled trial
OECD	Organisation for Economic Cooperation and Development
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
R&D	Research and development
RCT	Randomised controlled trial
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
STARD	Standards for the Reporting of Diagnostic Accuracy Studies
STRICTA	Standards for Reporting Interventions in Clinical Trials of Acupuncture
STRICTOC	Standards for Reporting Interventions in Clinical Trials of Cupping: extending the CONSORT Statement
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SUSAR	Suspected Unexpected Serious Adverse Reaction
T&CM	Traditional and complementary medicine
TENS	Transcutaneous electrical nerve stimulation
TIDieR	Template for Intervention Description and Replication
TCM	Traditional Chinese Medicine
WHO	World Health Organization

Glossary

Definition of T&CM

T&CM

A form of health-related practice designed to prevent or treat or manage ailment or illnesses or preserve the mental and physical well-being of an individual which includes traditional Malay medicine, traditional Chinese medicine (TCM), traditional Indian medicine, homeopathy, Islamic medical practice and complementary therapies and excludes medical or dental practices used by a medical or dental practitioner respectively.⁽¹⁾

Terms relating to T&CM research

T&CM research

It refers to the use of the methods which are generally accepted in the evaluation of health services, including comparative effectiveness studies and mixed-methods designs to assess the quality, safety and effectiveness of T&CM.⁽²⁾

T&CM theoretical framework

A conceptualised approach in applying T&CM related theories, principles and features to understand, analyse, categorise the workings of the human body and causal factors of disease as a guide to clinical decision-making process.⁽³⁻⁵⁾

Research with consideration of T&CM theoretical framework

It refers to T&CM research designed and conducted within the T&CM theoretical framework.

Research with partial consideration of T&CM theoretical framework

It refers to T&CM research designed and conducted mainly in alignment of conventional medicine framework with some consideration of T&CM theoretical framework.

Research without consideration of T&CM theoretical framework

It refers to T&CM research designed and conducted within conventional medicine framework with no consideration of T&CM theoretical framework.

Terms relating to T&CM diagnosis and approach

Individualised approach

Treatment which is tailored to the individual at a particular point in time, with changes made to the treatment regime depending on the patient's response and the objectives of the treatment.⁽⁶⁾ This is one of the principles adopted in many T&CM modalities, which often poses a challenge in the design of T&CM research.

Pattern Diagnosis

In some T&CM modalities the disease is viewed as Pattern(s), manifesting as a disparate but mutually related set of objective signs and subjective symptoms occurring throughout the whole body which may arise from disharmony between the environment and the body.⁽⁶⁾ Thus, the T&CM approach to healing aims to re-establish equilibrium between the environment and the body.⁽⁷⁾

Many interchangeable terms are used, depending on contexts, including Diagnostic Pattern, or Pattern Differentiation, or Syndrome Diagnosis. The patient's Pattern or Syndrome are unique at its initial presentation and may change at various stages throughout the course of a disease, hence warrant an individualised treatment approach.

Terms relating to herbal research

Active ingredients

Active ingredients refer to constituents with known therapeutic activity, when they have been identified. Where it is not possible to identify the active ingredients, the whole herbal medicine may be considered as one active ingredient.⁽⁸⁾ Therapeutic activity refers to the successful prevention, diagnosis and treatment of physical and mental illnesses; improvement of symptoms of illnesses; as well as beneficial alteration or regulation of the physical and mental status of the body.⁽⁹⁾

Characterising compound

A natural constituent of a plant part that may be used to assure the identity or quality of a plant preparation, but is not necessarily responsible for the plant's biological or therapeutic activity.⁽¹⁰⁾

Biological activity refers to a change in the baseline function of an animal or part of an animal brought about by the administration of test substance.⁽¹⁰⁾

Crude plant material

Minimally processed (usually only collection, washing, drying, and sometimes cutting) leaves, flowers, fruit, seed, stems, wood, bark, roots, rhizomes or other plant parts.^(9,11)

Finished herbal product

Finished herbal products consist of herbal preparations made from one or more herbs. If more than one herb is used, the term “mixture herbal product” can also be used. Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished products or mixture herbal products to which chemically defined active substance have been added, including synthetic compounds and isolated constituents from herbal materials, are not considered to be herbal.⁽⁹⁾

Herb

Herbs include crude plant material such as leaves, flowers, fruit, seed, stems, wood, bark, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered.⁽⁹⁾

Herbal materials/plant materials

Herbal materials include, in addition to herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries, these materials may be processed by various local procedures, such as steaming, roasting, or stir-baking with honey, alcoholic beverages or other materials.⁽⁹⁾

Herbal medicine

A plant-derived material or preparation with therapeutic or other human health benefits which contains either raw or processed ingredients from one or more plants. In some traditions, materials of inorganic or animal origin may also be present.⁽¹⁰⁾

Herbal preparation/medicinal preparations of plant materials

Herbal preparations are the basis for finished herbal products and may include comminuted or powdered herbal materials, or extracts, tinctures and fatty oils of herbal materials. They are produced by extraction, fractionation, purification, concentration, or other physical or biological processes. They also include preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey, or in other materials.⁽⁹⁾

Natural products

Products consist solely of one or more naturally occurring substances of a plant, animal or mineral, of parts thereof. The Malaysian regulatory on natural products include traditional medicines, herbal products, homeopathic medicines and natural products with therapeutic claim.⁽¹²⁾

Pharmacovigilance

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.⁽¹³⁾

Therapeutic claim

A claim that is not documented in established pharmacopoeia or monographs, or a claim which is not the traditional use of the ingredient. It may include corroboration and verification of traditional use to relieve a symptom or help to treat a disease, disorder or medical condition, and it must be substantiated by scientific evidence.⁽¹⁴⁾

Traditional medicine

As defined under the Control of Drugs and Cosmetics Regulations 1984, traditional medicine refers to any product used in the practice of indigenous medicine in which the drug consists solely of one or more naturally occurring substances of a plant, animal or mineral, of parts thereof, in the unextracted or crude extract form, and homeopathic medicine. It shall not include any sterile preparation, vaccine, any substance derived human parts, any isolated and characterised chemical substances.

Traditional preparation of medicinal materials

Extemporaneous preparation of traditional medicinal materials (plants, animal/mineral origin) as per traditional records/instructions (e.g. books/pharmacopoeia), which is prescribed by certified traditional medicine practitioners directly to the patients for recommended indication(s), within recommended dose, and according to established diagnosis and management plan.

Terms relating to T&CM procedure-based therapies

T&CM procedure-based therapies

Therapies that use various techniques, primarily without the use of medication, to provide health care.⁽¹⁵⁾

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Section 1

Introduction

Section 1 : Introduction

1.1. Scope of Framework

Rationale

T&CM should be appropriately supported by evidence-based studies in order for it to be further integrated into the mainstream health care system in Malaysia. However, there is a lack of a specific guidance on T&CM research in Malaysia; hence there is a need to produce such a framework.

Objective

The main objective of this framework is to guide researchers in conducting T&CM research and encourage innovation in T&CM research in Malaysia.

Process

The development of this framework has taken into consideration of important local and international guidelines for the conduct of research. Input from engagement with various stakeholders, higher education institutions and T&CM practitioners have been compiled and consolidated to ensure that this framework is comprehensive (but not exhaustive).

Target population

Researchers, T&CM practitioners, T&CM industrial stakeholders, academicians, and authority bodies.

1.2. Overview of T&CM Research in Malaysia

T&CM has been utilised by Malaysians for many centuries for health maintenance and its demand has increased in recent decades. It has been identified as an important component of the health care system which shall co-exist with modern medicine and contribute towards enhancing the health and quality of life of all Malaysians.⁽¹⁶⁾ In order for T&CM to contribute optimally towards the national health care system, the Government of Malaysia has strived to facilitate regulation of T&CM practice, practitioners and products in Malaysia; integration of T&CM practice into the

national health care system; and set directions to enhance economic development of the T&CM industry through policies, guidelines, and blueprints.⁽¹⁷⁾ Safe integration of T&CM in Malaysia should be supported by research and development (R&D).

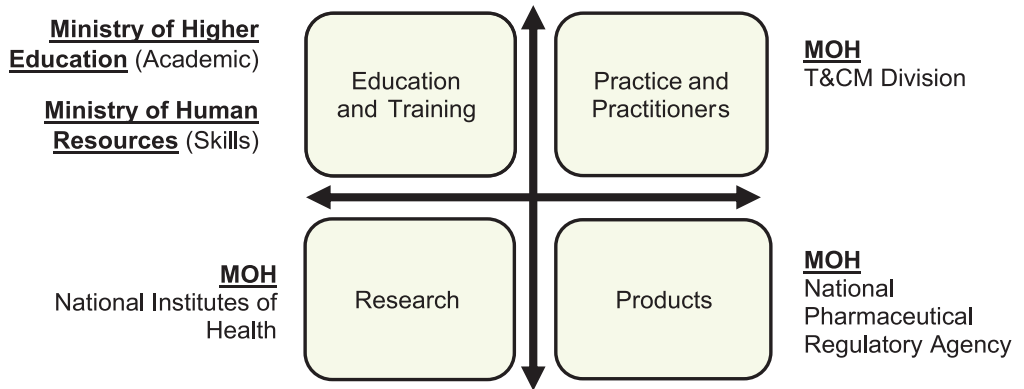


Figure 1. Overview on the Governance of T&CM in Malaysia

The four main pillars of governance for T&CM in Malaysia which are education and training; practice and practitioners; products; and research are described in Figure 1.

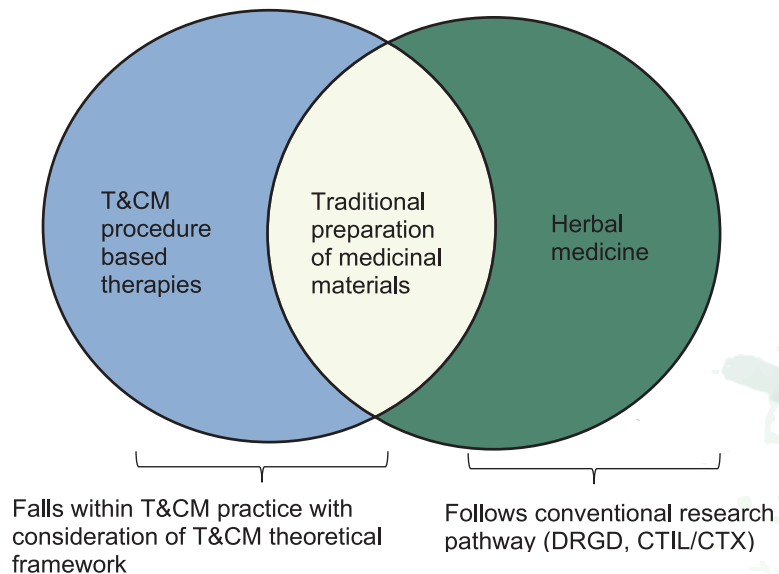


Figure 2: T&CM Research in Malaysia

In Malaysia, T&CM research encompasses both T&CM practice (which includes procedure-based and/or use of herbal medicine within the practice) and herbal medicine as a whole, as depicted in Figure 2. Herbal medicine may be investigated for use in clinical research based on conventional medicine concepts (with or without

considerations of T&CM theoretical framework) or within the T&CM practice itself, based on specific T&CM theoretical framework.

When the investigated herbal medicine is formulated to finished product (e.g. capsule, tablet, syrup etc.), it should follow the research pathway to meet the product-related and specific data requirements laid out by the National Pharmaceutical Regulatory Agency (NPRA), with reference to the Drug Registration Guidance Document (DRGD) and the Malaysian Guideline on Clinical Trial Import Licence (CTIL)/Clinical Trial Exemption (CTX). The T&CM practice as a whole is governed by the T&CM Act 2016.

1.3. Issues and Challenges in T&CM Research in Malaysia

Based on stakeholder engagements, several issues and challenges have been identified related to the conduct of T&CM research in Malaysia:

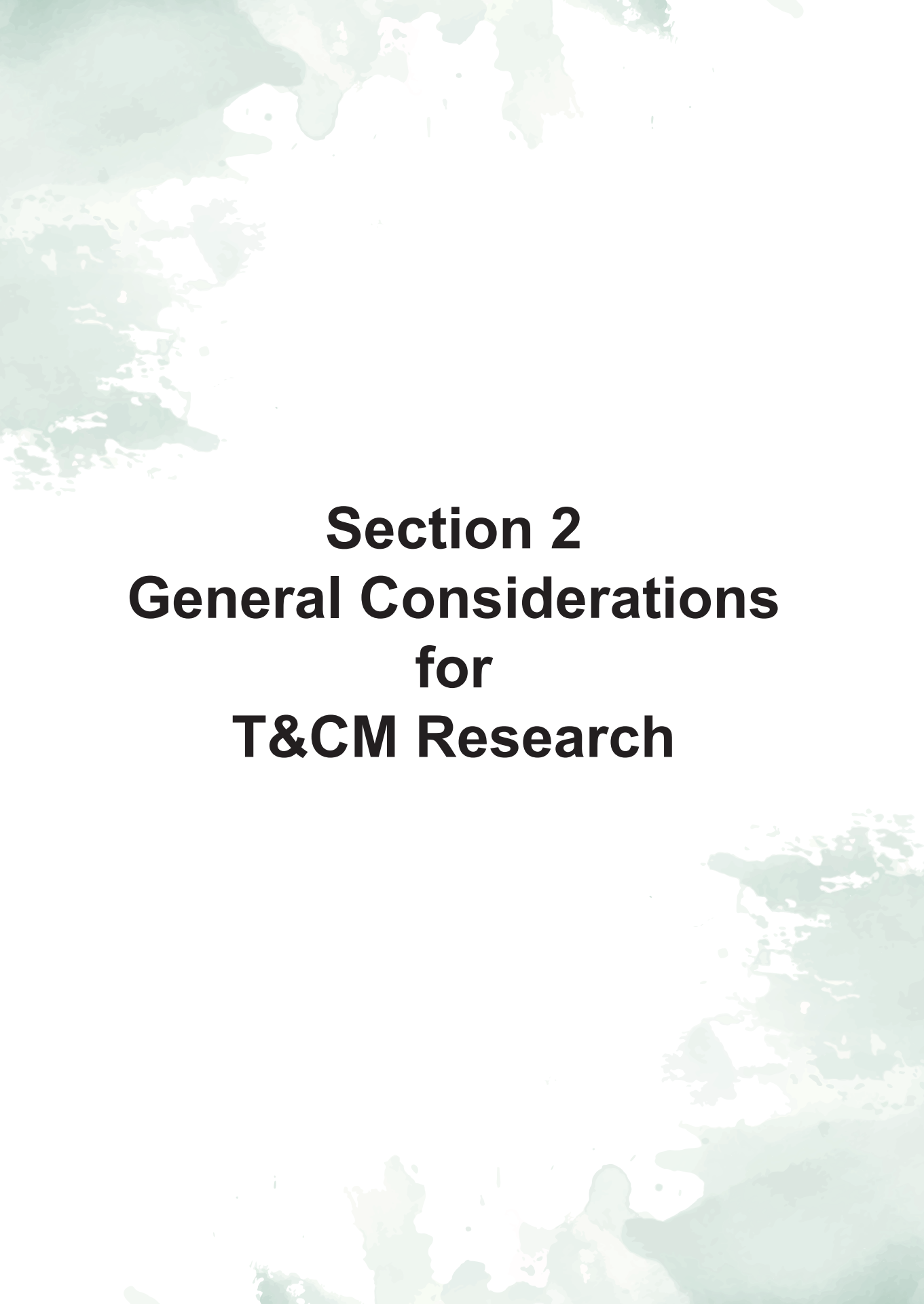
- T&CM is evaluated through the perspective of conventional medicine despite both having different approaches to disease, i.e., conventional medicine is disease-focused, symptoms-oriented and standardised, whereas T&CM focuses on holistic and individualised approach. Hence, conventional clinical research design may be difficult to apply to T&CM practice;⁽¹⁸⁾
- Lack of research priorities in T&CM and insufficient expertise such as a national advisory panel/expert committee to advise on matters related to research on T&CM as well as poor resource allocation for T&CM R&D; and
- Lack of capacity to conduct T&CM research among interested parties as follows:
 - Limited access to research materials (e.g. scarce availability of literatures in the indexed mainstream medical journals);
 - Inadequate guidance/guidelines and training for research related to T&CM;
 - Lack of international collaboration opportunities with countries that have more established T&CM research capabilities.

1.4. Research Direction and Priorities in Malaysia

Strategies to address the gaps in T&CM research have been previously documented in the T&CM Blueprint 2018 – 2027 (Health Care) as below:⁽¹⁷⁾

- Encourage participation in T&CM research by creating a conducive research environment;

- Develop a mechanism such as formation of a national research committee to determine research priorities in T&CM and propose recommendations on identified issues;
- Strengthen research in T&CM that contributes to evidence-based policy formulation;
- Promote and improve dissemination of research findings;
- Strengthen local research capabilities;
- Strengthen innovation and intellectual property (IP) protection of research findings;
- Strengthen efforts in preservation and conservation of traditional knowledge and resources;
- Encourage methodology development for herbal products;
- Encourage methodology development for procedure-based therapies; and
- Review of current regulations for herbal product development and registration.

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Section 2

General Considerations

for


T&CM Research

Section 2 : General Considerations for T&CM Research

2.1 Overview of Clinical Research and Evidence Level

This segment provides a basic overview of the types of clinical research and its general level of evidence. Different research designs will have different methodological requirements, can be utilised to answer different research questions, and provide meaningful contributions towards the understanding of T&CM practice and its impact. Some research designs have less technical, cost, and time requirements than others and may be relatively easier to conduct. Careful consideration of the impact, requirements, and suitability of each research design should be made prior to embarking on the clinical research journey. The overview on levels of evidence with their corresponding clinical research designs as well as the relative strength of evidence are presented in Table 1 and Figure 3.

Table 1: Levels of Evidence by Oxford Centre for Evidence-Based Medicine (March 2009)⁽¹⁹⁾

Level	Type of evidence	Strength of evidence
Ia	Evidence obtained from meta-analysis of randomised controlled trials (RCT)	
Ib	Evidence obtained from at least one RCT	
IIa	Evidence obtained from at least one well-designed controlled study without randomisation	
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study	
III	Evidence obtained from well-designed non-experimental description studies, such as comparative studies, correlation studies and case-control studies	
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities	

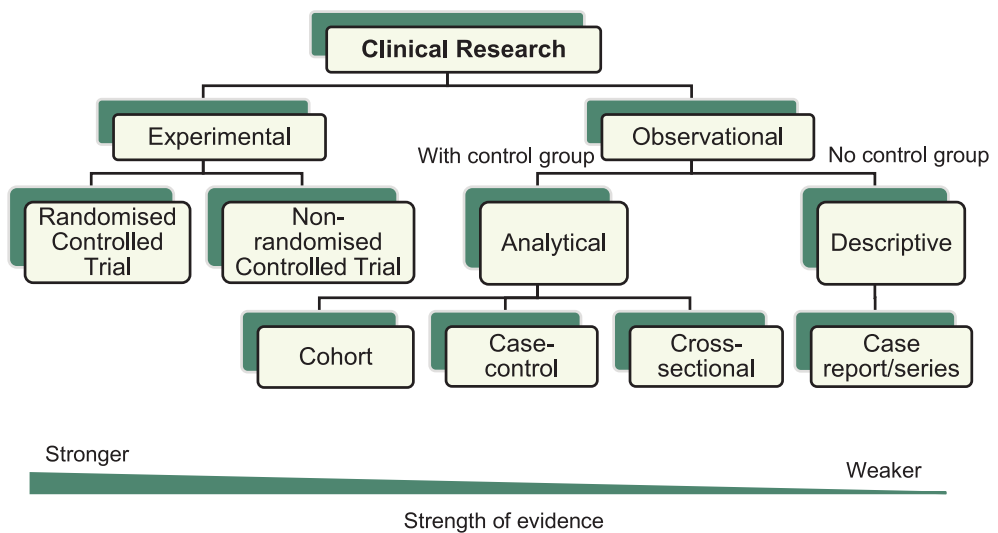


Figure 3. Common Types of Clinical Research Design and Strength of Evidence⁽²⁰⁾

2.1.1 Observational Studies^(21,22)

Observational studies involve assessment of health outcomes in selected populations or groups of participants with or without intervention. Observational studies may be prospective or retrospective. In prospective studies, investigators recruit participants and observe them prior to the occurrence of the outcome. In retrospective studies, investigators review the records of participants and interview participant after the outcome has occurred. In general, observational studies include (in ascending level of evidence):

- Descriptive studies with low level of evidence, such as:
 - **Case studies**
Case studies are a long-established research methodology in clinical practice which comprises a detailed narrative report of the diagnosis, treatment, response to treatment, and follow-up after treatment of an individual patient. The purpose of conducting a case study is to achieve a greater and in-depth understanding of a complex and rare disease or phenomenon in its real-life context.
 - **Case series**
A case series (also known as clinical series) is a collection of patients with common characteristics used to describe some clinical, pathophysiological, or operational aspects of a disease, treatment or

diagnostic procedures. It presents detailed information of the clinical experience of individual participants and evaluates large numbers of individuals to summarise the data using descriptive statistical measures.

- Analytical studies with intermediary level of evidence, such as:
 - **Cohort studies**

Cohort studies involve identifying study participants based on their exposure status and either following them through time to identify which participants develop the outcome(s) of interest, or look back at data that were created in the past, prior to the development of the outcome. They can be conducted in both prospective and retrospective manner.
 - **Case-control studies**

In case-control studies, study participants are identified based on their case status, i.e. diseased or not diseased. Participants are enrolled based on their outcome rather than based on their exposure. Quantification of the number of individuals among the cases and the controls who are exposed allow for statistical associations between exposure and outcomes to be established. Case-control studies are usually conducted either retrospectively or prospectively. The number of controls to case ratio selected usually involves 4 to 5 controls per case. Time matching is an important feature of this research design where controls are matched to cases such as age, date of entry into the cohort, length of time in the cohort, or combination of measures.
 - **Cross-sectional studies**

Cross-sectional studies can be both descriptive and analytical. In cross-sectional studies, the investigator measures the outcome and the exposures in the research participants at the same time. Unlike in case-control studies (participants selected based on the outcome status) or cohort studies (participants selected based on the exposure status), the participants in cross-sectional research are selected based on the inclusion and exclusion criteria set for the research.

2.1.2 Experimental/Interventional Research (Clinical Trials)

Clinical trials often involve application of an intervention and subsequently measuring the outcomes to test a hypothesis such as the relationship between the intervention and the outcomes measured. A single, large, well-conducted, and controlled clinical trial could provide sufficient evidence to establish an intervention/disease relationship. Clinical trials are considered studies with a high level of evidence. They can be divided into:

- **Randomised Controlled Trial (RCT)**

In a RCT, similar participants are randomly assigned either to receive the intervention or not to receive the intervention. RCTs are not an absolute requirement to demonstrate significant scientific agreement in all cases but are considered the most persuasive and given the most weight.

There are four phases of RCTs.^(23,24) This is briefly explained as:

- Phase I: Small scale clinical trial including first-in human trial that usually involve a small number of subjects (~20 subjects, usually healthy volunteers), mainly to assess the safety of an investigational product;
- Phase II: Small scale trial on homogenous patients that is usually conducted at one site to investigate the occurrence of possible clinical benefits and existence of side effects (generally ~100-200 subjects but it is advised that sample size is calculated for specific studies);
- Phase III: Large scale well-designed RCT to accommodate a larger sample size and a diversity of patients with greater power to test hypotheses and more precise estimation of population parameters; and
- Phase IV: Post marketing study undertaken to gain more safety data for newly registered products.

- **Non-randomised controlled trial (NRT)**

A NRT is an interventional research whereby the participants are assigned to different treatment or control products, using allocation methods that are non-randomised.

The NRT is done in these conditions:

- where randomisation could reduce the effectiveness of the intervention;
- when certain research using randomisation becomes unethical;
- when the randomisation of a certain research is impractical; or
- when legal or political hurdles surface.

The benefit of NRT is that participants get to be allocated into treatment groups that are appropriate for their condition.

Implementation of RCTs as a 'gold standard' in various methods of clinical trial can be used to answer questions about most clinical problems. Nevertheless, this approach is not always a practical and cost-effective solution. Pragmatic solutions that do not 'unpack' all the treatment options may therefore be required.⁽¹⁵⁾

- **Proof-of-concept studies**⁽²⁵⁾

Proof-of-concept studies, also known as proof-of-principle studies are early stage small and brief clinical studies predominantly conducted to substantiate future larger experimental clinical research. This research design plays an important role in developing novel treatments in health care settings.

2.2 General Considerations and Requirements for T&CM Research in Malaysia

2.2.1 Approval and Registration

All T&CM clinical research conducted in Malaysia must comply with the basic principles outlined by the Declaration of Helsinki. Additionally, all research conducted in Malaysia must be registered and comply with the relevant guidelines and local regulatory requirements.^(26,27)

To ensure safety and quality of the research, all T&CM research protocols must adhere to the relevant requirements by the authority bodies:

- All clinical research should comply with the Malaysian Guideline for Good Clinical Practice (GCP) and obtain ethical approval from the relevant Institutional Review Board (IRB)/Independent Ethics Committee (IEC).⁽²⁸⁾
- For research related to T&CM herbal products:
Application for CTIL/CTX is required for an unregistered traditional product imported or manufactured locally for the purpose of the clinical trial or a traditional product with a marketing authorisation with an indication for "traditionally used" when used for unapproved indication/therapeutic claims for clinical trial purpose.⁽²⁹⁾

The T&CM herbal products of interest should be collected, cultivated, harvested, manufactured, handled and stored in accordance with applicable Malaysia Standard on Good Agricultural Practice (GAP) and Good Manufacturing Practice (GMP).^(30,31) The latter follows the Pharmaceutical Inspection Cooperation Scheme - Guide to GMP for Medicinal Products guideline.⁽³²⁾

Non-clinical safety studies for therapeutic claims must be conducted in a facility which complies with the requirements of Good Scientific Practice (GSP) and Organisation for Economic Cooperation and Development (OECD) Good Laboratory Practice (GLP).^(33,34)

- For research involving the use of medical devices:
T&CM related medical devices described in the protocol should comply with the requirements set forth in the Medical Device Act 2012 and its subsidiary legislations, and any other relevant documents published by Medical Device Authority (MDA).^(35,36)

2.2.2 Design and Conduct

T&CM clinical research should be designed by taking the following key points into consideration:

- **Risk identification**
Foreseeable risks and discomforts and any anticipated benefit(s) for the individual clinical research participant and society should be identified.⁽³⁷⁾
- **Benefit-risk assessment**
The rights, safety and well-being of the T&CM clinical research participants are the most important considerations. Foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual clinical research participant and society.^(28,37)
- **Legal consideration**
The investigators should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission [as required by the applicable regulatory requirement(s)] to begin the clinical research.⁽²⁸⁾
- **Ethical consideration**
 - There are three basic ethical principles of equal importance, namely respect for persons, beneficence and justice, which permeate all other GCP principles.⁽³⁷⁾

- Research involving human and animal participants requires prior ethics review and approval by the relevant IRB/IEC (Refer to Appendix).
- A human participant (in the context of research) is “a living individual about whom an investigator obtains either data through intervention (e.g. clinical research) or interaction (e.g. questionnaire in health survey) with the individual, or investigator has access to identifiable private information (medical record or personal data)”.⁽²⁶⁾

2.2.2.1 Protocol and Compliance

Clinical research aimed at evaluating T&CM should incorporate the conventional concepts of research design, such as RCTs or other types of clinical studies, for example, observational studies. The choice of research design which are suitable for assessing T&CM, may be chosen from a whole spectrum of clinical research designs described in Section 2.1.

A T&CM research should be well designed, scientifically sound, and described in a clear, detailed protocol.⁽⁹⁾ This is to increase the transparency of the design and reporting which is critical for a replication in scientific research. Once a protocol has been approved, any changes of the protocol should be documented, and any form of protocol deviation thereafter should be explained.⁽²⁸⁾ The investigator must obtain approval from the relevant IRB/IEC prior to implementation of any amendments to the research.

2.2.2.2 Informed Consent

Freely given informed consent should be obtained from every participant prior to clinical research participation.^(28,37) Researchers must not initiate research involving humans without obtaining each participant’s individual informed consent or that of a legally authorised representative, unless researchers have received explicit approval to do so from the relevant IRB/IEC.⁽³⁸⁾

2.2.3 Assessment and Evaluation

2.2.3.1 Investigator Qualification and Training Background

Any individual with sufficient knowledge or interest in T&CM may design a protocol related to T&CM research. However, for T&CM clinical research, at least one investigator/sub-investigator must be from the T&CM system and

is required to have proper training in the related/respective speciality of T&CM. The practitioners' knowledge and skills need to be continuously upgraded to enable them to engage in clinical research within their own individual speciality.⁽⁹⁾

If the investigational products/procedure-based therapies of more than one system are used, then qualified investigator(s) from all respective systems should be included in the research as sub-investigator(s).⁽³⁹⁾

The investigator(s) should:

- have relevant qualifications by education and approved training or certifications including National Committee for Clinical Research (NCCR) approved GCP where applicable;
- have experience to assume responsibility for the proper conduct of the T&CM research;
- provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation; and
- be thoroughly familiar with the appropriate use of the T&CM investigational product(s) or T&CM procedure-based therapy(ies).⁽²⁸⁾

A qualified modern medicine physician (or dentist) must be part of the research team if the research is pertaining to integrative medicine. During and following an individual's participation in a T&CM clinical research, the investigator should ensure that adequate medical care is provided to the participant for any adverse events, including clinically significant laboratory values, related to the clinical research. The investigator should inform a participant when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.⁽²⁸⁾

It is recommended that the investigator informs the participant's primary physician about the participant's participation in a T&CM related clinical research if the participant has a primary physician and if the participant agrees to the primary physician being informed.⁽²⁸⁾

2.2.3.2 Staff Qualification

Each individual involved in conducting a T&CM clinical research should be qualified by education, training and experience to perform his or her respective task(s).^(28,37)

2.2.3.3 Record/Data Keeping

All research information should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification. All research data should be stored as per the requirements of the relevant authorities.^(28,37)

2.2.3.4 Confidentiality

The confidentiality of records that could identify participants should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).^(28,37)

2.2.3.5 Safety Monitoring System

A T&CM clinical research must be carried out under conditions which ensure adequate safety for the participants. The facility selected for T&CM clinical research must have adequate infrastructure, including laboratories and equipment, where necessary, and sufficient clerical, medical and allied health workers to support the research as required. Facilities should be available to meet any emergencies.⁽⁹⁾

Any Suspected Unexpected Serious Adverse Reaction (SUSAR) should be reported based on the Malaysian Guideline for Safety Reporting of Investigational Products.⁽⁴⁰⁾

Systems with procedures that assure the quality of every aspect of the T&CM clinical research should be implemented to ensure human participant protection and reliability of research results.^(28,37)

Monitoring, auditing and inspection by the appropriate regulatory authority(ies) could be performed to verify that:⁽²⁸⁾

- The rights and well-being of human participants are protected;
- The reported T&CM research data are accurate, complete and verifiable from source documents; and
- The conduct of the T&CM clinical research is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s) such as GMP.

2.2.3.6 Continuing Review/Ongoing Benefit-Risk Assessment

Research involving humans should be continued only if the benefit-risk profile remains favourable.⁽⁹⁾ Prompt written reports should be provided to the sponsor, relevant IRB/IEC or institution on any changes significantly affecting the conduct of the research, and/or increasing the risk to participants.⁽²⁸⁾

2.2.4 Reporting and Dissemination

Production of an accurate, transparent and complete report is an important part of a research process. Use of reporting guidelines assists researchers in reporting research methods and findings, which in turn, improves the quality of research.

The Enhancing the Quality and Transparency of Health Research (EQUATOR) network provides comprehensive information on the design, use and array of reporting guidelines.⁽⁴¹⁾ For example:

- Consolidated Standards of Reporting Trials (CONSORT) for RCTs;⁽⁴²⁾
- CONSORT Statement and Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT);^(43,44)
- SPIRIT 2013 Explanation and Elaboration: Guidance for Protocols of Clinical Trials;⁽⁴⁵⁾
- Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) for observational studies;⁽⁴⁶⁾
- Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for systematic reviews and meta-analyses;⁽⁴⁷⁾
- Standards for the Reporting of Diagnostic Accuracy Studies (STARD) for studies of diagnostic accuracy;⁽⁴⁸⁾ and
- Case Reports (CARE) guideline.⁽⁴⁹⁾

Any form of research result dissemination must obtain prior approval from the relevant authority(ies). Clinical research participants' identities should not be revealed without prior-expressed consent when publishing or presenting research results.

2.2.5 Document Requirements

The investigator should maintain documents which individually and collectively permit evaluation of the conduct of research and the quality of the data produced. These documents serve to demonstrate compliance of the research with the standards of GCP and all applicable regulatory requirements. The investigator should maintain a

record of the location(s) of their respective essential documents including source documents.⁽²⁸⁾

2.2.6 Intellectual Property (IP)

IP refers to creations of the mind, such as inventions; literary and artistic works; designs; and symbols, names and images used in commerce. Common types of IP include patents, copyright, trademarks, geographical indications, industrial designs and trade secrets.⁽⁵⁰⁾

In Malaysia, IP rights are monitored and governed by Intellectual Property Corporation of Malaysia (MyIPO).⁽⁵¹⁾

Calls for the protection of traditional medical knowledge are often based on a number of cases involving misappropriation by unauthorised third parties, who have patented compounds derived from traditional medicines without the prior consent of traditional medical knowledge holders and without fair compensation.⁽¹⁷⁾

Access to Biological Resources and Benefit Sharing 2017 (Act 795) was enacted to implement the Convention on Biological Diversity and any protocol to the Convention dealing with access to biological resources and traditional knowledge associated with biological resources and the sharing of benefits arising from their utilisation.⁽⁵²⁾

The application for access to biological resource is a compulsory requirement in Malaysia. Therefore, an application gateway for all relevant parties, especially researchers whom are interested to access to biological resources in Peninsular Malaysia can be accessed at <https://www.myabs.gov.my/>. The state of Sabah (<https://sabcapps.sabah.gov.my/>) and Sarawak (<https://soras.sarawak.gov.my/>) has its own law and system in accessing to its biological resource.

As a general principle, any local or foreign individual or corporation who intends to access biological resources or traditional knowledge for commercial, or potentially commercial or non-commercial purpose must obtain a permit. One of the accompanying documents required to be submitted along with an application for a permit is the Prior Informed Consent obtained from the indigenous and local communities where their resource or traditional knowledge is accessed. Another accompanying document required to be presented for the application of a permit is the Benefit Sharing Agreement, entered into with the resource provider who gave access to the biological resources or traditional knowledge. This is only if the purpose of the access is for commercial or potential commercial purposes. No such agreement is required if the access is purely for a non-commercial purpose.⁽⁵³⁾

2.2.7 Specific Requirements

2.2.7.1 Research and Development involving Biological Resources in Sarawak

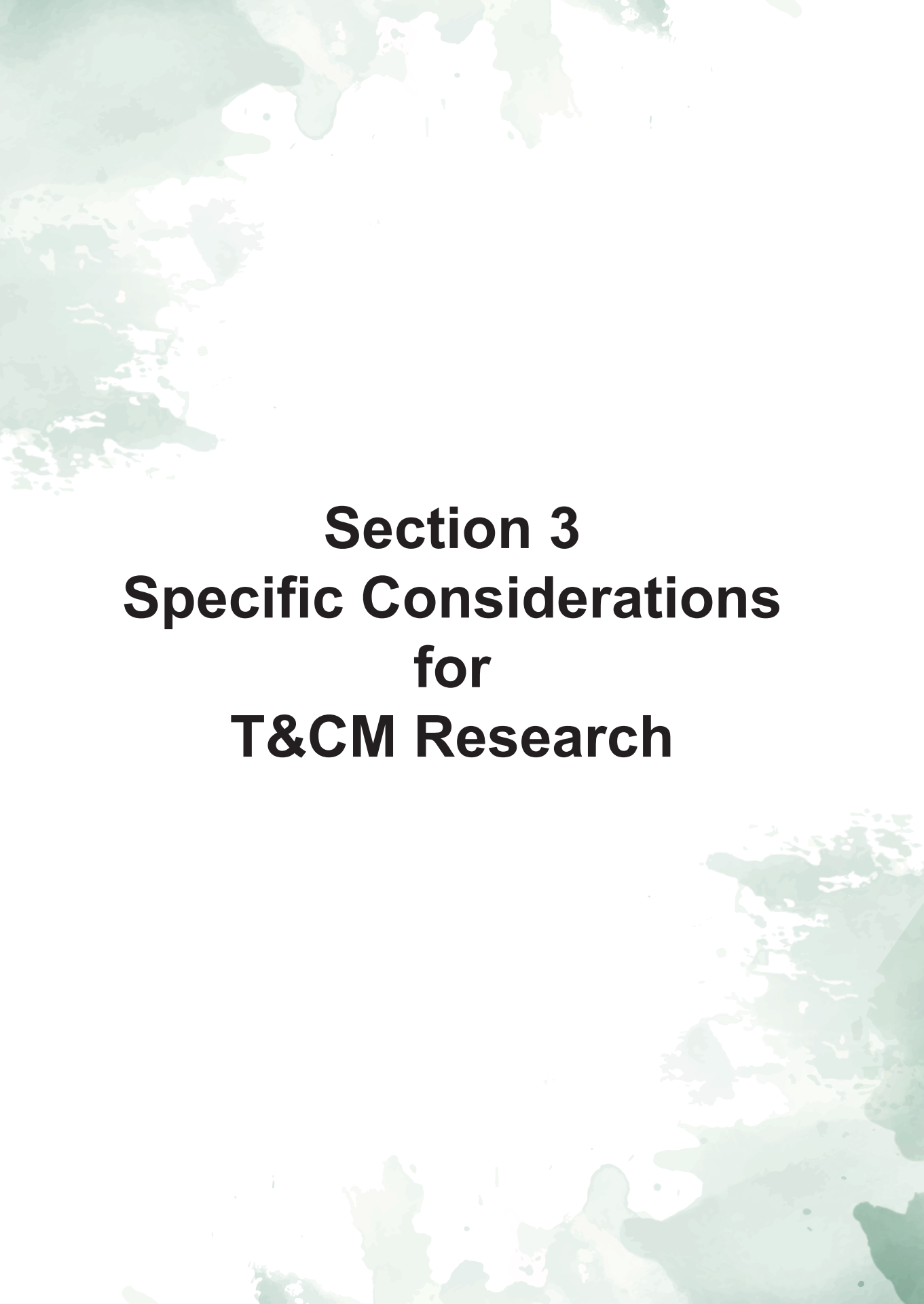
In order to access to biological resources in Sarawak for R&D purposes, the researcher is required to obtain R&D permit from the Sarawak Biodiversity Centre. Application must be made online via Sarawak Online Research Application System (SORAS) <https://soras.sarawak.gov.my/>.

2.2.7.2 Research and Development involving Biological Resources in Sabah

In order to access biological resources or associated relevant knowledge in Sabah, the researcher is required to apply Access Licence from the Sabah Biodiversity Centre. All applications should be submitted via online system <https://sabcapps.sabah.gov.my>. The guidelines on accessing biological resources or associated relevant knowledge in Sabah can be obtained from 'Procedure on Access and Export Licence Application for Non-Commercial Research 2022' at the website of Sabah Biodiversity Centre.

2.2.7.3 Research and Development involving Orang Asli (Aboriginal Peoples) in Peninsular Malaysia

Any research involving Orang Asli requires prior approval from the Department of Orang Asli Development (JAKOA). Research application form can be downloaded from www.jakoa.gov.my and shall be submitted to the State Director of JAKOA 14 days before commencement of the research. A copy of the research report must be submitted to the *Bahagian Perancangan dan Penyelidikan*, JAKOA.



Section 3
Specific Considerations
for
T&CM Research

Section 3 : Specific Considerations for T&CM Research

This section serves to provide specific considerations of the unique theoretical framework that form the characteristics of T&CM research.

Despite its long existence and popularity of use, T&CM has not been included as part of the mainstream health care system in many countries.⁽⁹⁾ Hence, 'modernising' T&CM through scientific research is regarded as one of the approaches to understand the benefits of T&CM for health care. Despite major improvements around T&CM research methodology recently, the infrastructure of research in T&CM is still significantly underdeveloped when compared to that of conventional medicine.⁽⁹⁾

As with any clinical research, special consideration is required when dealing with a heterogeneous population to ensure applicability of findings to clinical practice. Additionally, the need to eliminate bias; the influence on research participants introduced by the presence of other disease(s) and the use of other therapy(ies); drop out cases; missing data; ethical requirement constraints; and so forth makes T&CM research itself complex and challenging. Concerns on practitioner related issues such as intra-practitioner variability (a single practitioner) and inter-practitioner variability (group of practitioners) often pose challenges in research especially for procedure-based therapies.⁽⁹⁾ Nevertheless, one of the most challenging considerations is to reconcile the different philosophic concepts between conventional medicine and T&CM in terms of research methodology.

3.1. Overview of the Differences between Conventional Medicine and T&CM Research

The major difference between the research concepts of T&CM and conventional medicine reflect on the fundamentally dissimilar philosophies of each paradigm. T&CM is a formulation of concepts based upon empirical observation which provide a basis for clinical practice. T&CM differs from conventional medicine in the following regards:

- philosophical underpinnings;
- theories of pathology, physiology and aetiology of disease;

- theory of diagnosis and the diagnostic tools used; and
- therapeutic modalities applied.

Reconciliation of the differences between the two research concepts is a prerequisite for the future of T&CM research. Hence, there are urgent needs to implement standards for design of high quality T&CM research that reflects T&CM theoretical framework and practice concurrently whilst meeting the rigour of scientific methodologies.⁽⁹⁾

3.2. Principles in T&CM Research Design

The first step in the design of a T&CM research is to decide whether T&CM philosophies and theoretical framework such as individualisation should be considered, as it will likely affect research outcomes. These ‘confounding factors’ may be fully considered, partially considered or not considered at all. A statement on consideration of the confounding factors in the research design should be made in the protocol. Additionally, the purpose and scale of the research should also be considered. The general T&CM research framework is depicted in Figure 4.

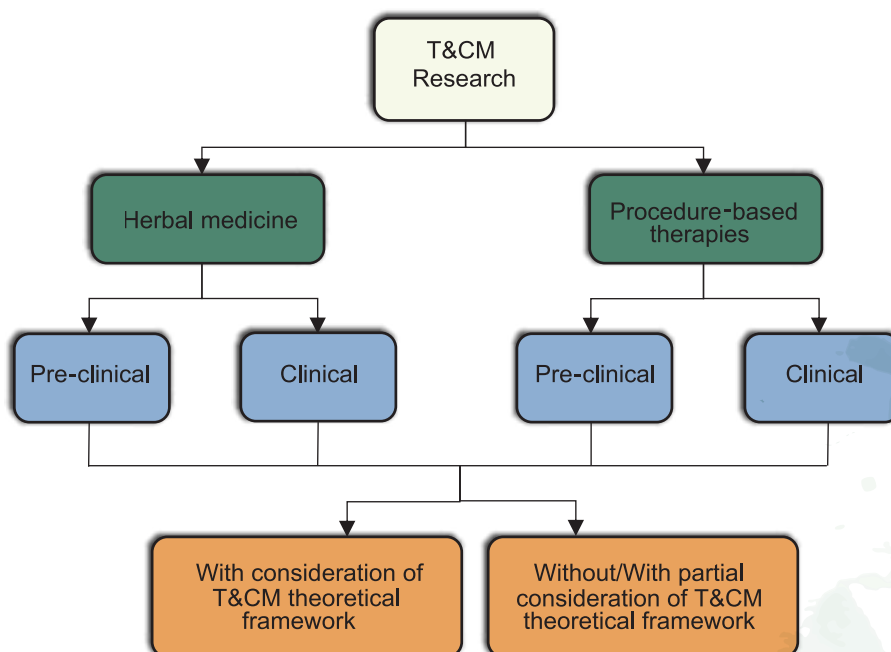


Figure 4: General T&CM Research Framework

There is a growing acceptance of the N-of-1 or single participant clinical trial in design that considers an individual patient as the sole unit of observation.^(54–56) It is a special type of crossover trial that involves rounds of intervention crossovers within a single participant.⁽⁵⁷⁾ In line with the unique theoretical framework of T&CM such as individualisation, within the N-of-1 trial, determining whether T&CM intervention A or B is more beneficial to the specific patient with a corresponding T&CM diagnostic defined population may be evaluated through quantified analysis of crossing outcome assessment. The N-of-1 design may be more consistent with the T&CM framework, which warrants further research.

A parallel, valuable research design is to compare between whole systems of T&CM and conventional medicine. The key is to reflect the real-world practice of the delivery in each paradigm. Pragmatic trials, add-on design, expertise-based trials, explanatory RCT, surveys of real-world clinical practice can help to form a more comprehensive understanding of the multiple components that contribute to the therapeutic effects of a defined T&CM therapy in a real-world setting. Qualitative methods can be used to explore patients' experience in terms of healing process and outcome influence. Combined qualitative and quantitative methods as an integrated research approach can be very informative.⁽⁵⁸⁾

Ultimately, when evaluating the safety and effectiveness of T&CM, emphasis should be given to the appropriate integration of T&CM unique theoretical framework with scientific research methods. Furthermore, more focus should be given to T&CM safety and effectiveness as it is directly related to health care service delivery, compared to addressing the mechanism of its therapeutic effect.

3.3. Key Components of T&CM Research Design

3.3.1. Research Title

The title should concisely identify the purpose of the research (intervention and population) and reflect the T&CM elements.

3.3.2. Introduction and Literature Review

The background and underlying rationale of the research design are important elements in the introduction. Whether the rationale is based on conventional medicine findings (e.g. conventional medicine-defined disease), T&CM theory (e.g. a Diagnostic Pattern in TCM), or both should be elucidated.⁽⁵⁹⁾ Consideration of T&CM theories in a proposed research should be stated for the purpose of clarity.

A thorough literature review with in-depth analysis should be a starting point for the evaluation of T&CM research. The literature search profile used should be recorded. Multi-lingual literature sources should be thoroughly searched where possible. The literature search may include indexed and non-indexed journal articles, books and reviews. Findings from laboratory and clinical studies should also be included if available. Publications that may not meet the stringent requirements of international peer-reviewed journals such as individual experiences recorded in reports from physicians, traditional health practitioners or treated patients, or findings from studies that may not be robustly conclusive due to the research's quality should still be considered as they may provide potentially useful observations and ideas for further research. Where little or no literature exists, the oral tradition and the source of this tradition need to be clearly stated.⁽⁹⁾

A review of the literature should identify the current level of evidence of effectiveness and safety for the proposed intervention based on the following:⁽⁹⁾

- The theories and concepts of T&CM systems
 - The theories and concepts of prevention, diagnosis, improvement and treatment of illness in T&CM historically rely on a holistic approach towards the sick individual, and disturbances are treated on the physical, emotional, mental, spiritual and environmental levels simultaneously. As a result, most systems of T&CM may use herbal medicines or procedure-based therapies along with certain behavioural rules in promoting healthy diets and habits.
 - When reviewing the literature on T&CM (both herbal medicines and procedure-based therapies), the theories and concepts of the individual practice of T&CM, as well as the cultural background of those involved, must be taken into account.

- Review of safety and effectiveness
 - Both safety and effectiveness are equally essential attributes of any herbal medicine or procedure-based therapy research and should be proven.
 - It is important that the proof of effectiveness to support the indicated claims is reported for single herbs, mixture of herbs and particularly for the formulation intended to be investigated specifically. The absence of any reported or documented side-effects is not an absolute assurance of safety for the studied T&CM practice or herbal medicines. Therefore, new clinical studies are necessary in cases where traditional use and experience of herbal medicine in humans have no established safety and effectiveness data.

- Safety and/or effectiveness data from *in vitro* and/or *in vivo* studies are not necessarily applicable to humans but may be viewed as scientific rationale.
- In certain cases, pre-clinical safety evaluation may not be a major requirement for T&CM clinical research if there is well-documented long history of use within the practice.
- Procedure-based therapies should be performed within accepted parameters, and the indications for a therapy should be evidence-based where possible.
- The effectiveness of most forms of procedure-based therapies depends heavily upon the proficiency of the practitioners, including their skills and experience. This may partly explain the disparity or inconsistency of results reported by different authors, even though the methodologies of the studies were equally sound.⁽⁹⁾

3.3.3. Research Objectives

The research objectives generally address how the study is going to answer a specific research question. Specific objectives may be set to state the outcome measures that are planned to be used in the study.⁽⁶⁰⁾

A research hypothesis is a specific, clear and testable proposition or predictive statement about the possible outcome of a scientific research study based on a particular property of a population, such as presumed differences between groups on a particular variable or relationships between variables.⁽⁶¹⁾

3.3.4. Research Methodology

3.3.4.1. Research Design

The level of evidence is varied depending on the types of research, and can be significantly increased by a well-designed research. The research design should indicate clearly whether a full consideration, partial consideration or no consideration of T&CM theoretical framework (theory, principles, individualisation, formulas/medicinal substances) is chosen; other factors such as numbers of experimental sites, research objectives and appropriate research methods will also form the structure of the research.

3.3.4.2. Participants/Treatment Conditions

It is ideal for a T&CM research to have a target population of participants that are T&CM theoretical framework considered. However, this is challenging because many treatment conditions defined in T&CM may be multifaceted in the paradigm of the conventional medicine; this will have an impact on research outcome. A statement should be made on whether participants with a specific T&CM Diagnostic Pattern are recruited. All criteria used should be well referenced. When unified diagnostic criteria are not available, the researcher should clearly explain how the criteria for the research are developed and applied in the recruitment, in which evidence of reliability and/or validity may be required to ensure appropriateness, authenticity and reduce potential errors that may occur.

3.3.4.3. Interventions

An intervention is defined as a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioural processes and/or endpoints.⁽⁶²⁾ The interventions that are commonly considered in T&CM research can be procedural or herbal-based, or a combination of both. Refer to Section 4, 5 and 6 for further details.

3.3.4.4. Outcomes and Outcome Measurements

It is essential that the outcomes and measurements chosen be appropriate to the research question. Appropriate general outcomes and measurements may be quantitative and/or qualitative; primary and/or secondary; generic and/or highly specific; and finally, specific outcomes and measurements associated with T&CM theoretical framework should be included to reflect relevance to T&CM research.⁽⁹⁾

3.3.4.5. Follow-up

A follow-up should be included for the usefulness of longitudinal data, both in terms of the validity and the generalisability of the findings of the research. A lack of adequate follow-up in T&CM research may either underestimate potential benefits or fail to detect adverse effects of intervention investigated, which may take much longer to emerge. The duration of follow-up should be clearly stated and appropriate to the intervention.⁽⁹⁾

3.3.4.6. Sample Size

Sample size calculation is an essential part of clinical trial, as it provides adequate power to allow investigators to detect clinically and statistically meaningful differences between the experimental and the control intervention or among the alternative treatments studied.

The variability of the outcomes is directly related to the sample size. Generally, a larger sample size minimises type I errors (falsely rejecting a potential promising treatment) and type II errors (accepting an ineffective treatment).⁽⁶³⁾ Additional factors that may be considered when estimating sample size include:⁽⁶⁴⁾

- objective and design of the study;
- pool of potentially eligible subjects;
- research inclusion and exclusion criteria; and
- estimated recruitment and dropout rate.

3.3.4.7. Randomisation

Two elements are included for sequence generation:

- method used to generate the random application sequence; and
- type of randomisation and details of any restriction.⁽⁴²⁾

Researchers should be aware of the differences between true randomisation and quasi randomisation.

3.3.4.8. Allocation Concealment

Allocation concealment should be described in detail. Implementation of allocation generation, participation enrolment and intervention assignment should be explained.⁽⁴²⁾

3.3.4.9. Blind Assessment

Blinding should be reported with clear indication on participants, intervention provider, assessor of outcomes, and/or statistical analysis. If it is not possible, descriptions of any attempts to limit bias is required.⁽⁴²⁾

3.3.4.10. Statistical Analysis

Statistical methods used to compare groups and methods for additional analysis should be described.⁽⁴²⁾

3.3.5. Reporting

Discussion on how the T&CM intervention works on different or specific T&CM Patterns or a defined conventional medicine disease should be made if there is full or partial consideration of T&CM theoretical framework in the research.

There are several reporting guidelines that are valuable resources not only for reporting but also designing T&CM research. This includes the CONSORT Extension for Reporting Herbal Medicines, CONSORT Extension for Chinese Herbal Medicine (CHM) Formulas 2017, CONSORT Statement for Randomised Trials of Nonpharmacologic Treatment, and Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): Extending the CONSORT Statement and CONSORT Extension for Acupuncture Checklist. Recently, CONSORT Extension for Reporting N-of-1 Trials for Traditional Chinese Medicine (CENT for TCM) was developed.^(59,65–69) The Template for Intervention Description and Replication (TIDieR)⁽⁷⁰⁾ may also be used for non-pharmacological interventions as a tool for improving the design and reporting of the interventions.

The aforementioned guidelines acknowledge unique issues in blinding, standardising delivery, training or allocating investigators or practitioners, and reporting on intervention adherence.



Section 4
Clinical Research
on
Herbal Medicine

Section 4 : Clinical Research on Herbal Medicine

There are many forms of herbal medicine, definitions such as crude plant materials in forms of entire, fragmented or powdered; herbal preparations as extract, fraction, purified fraction, concentrate; and finished herbal products. All these could be one or more herbs as a formulation. Refer to Glossary for definitions.

Outcomes from clinical research in herbal medicine may guide patients in making an informed decision on preferred treatment; health care providers in determining their choice of treatment; and health care policymakers in making a wise decision during decision making process.

4.1. Clinical Research on Herbal Medicine in Malaysia

In general, there are two clinical research pathways for herbal medicine in Malaysia that can be considered depending on its intended human use; either as traditional preparation of medicinal materials or as natural products with therapeutic claim.^(71,72)

The designs of clinical research that are applicable in herbal medicine research has been described in Section 2.1. Research designs for traditional preparation of medicinal materials should consider T&CM theoretical framework while research for natural products with therapeutic claims may or may not consider T&CM theoretical framework, depending on the intended therapeutic indication and targeted research population.

4.2. With Consideration of T&CM Theoretical Framework

Figure 5 summarises T&CM clinical research on herbal medicine with consideration of T&CM theoretical framework.

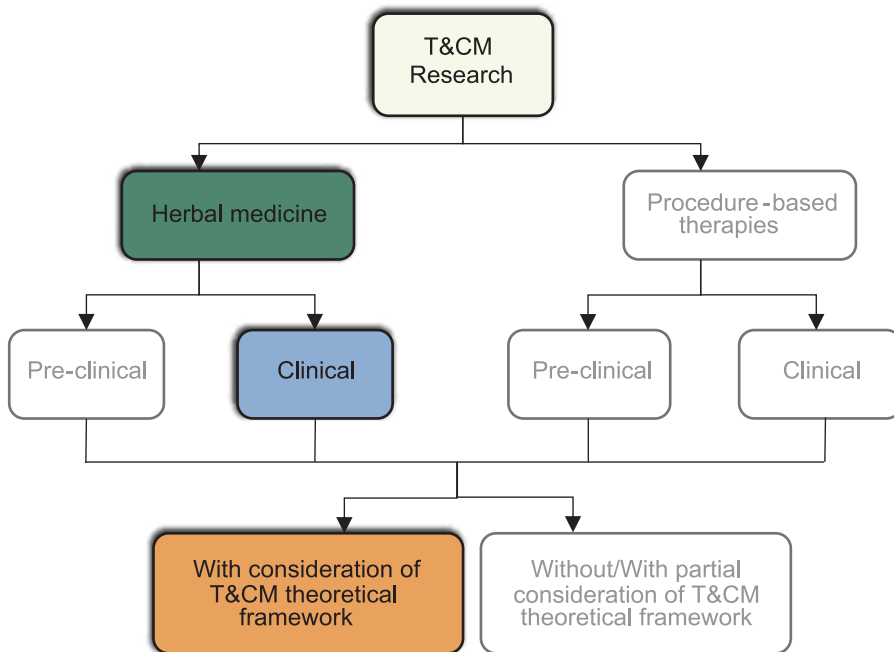


Figure 5: T&CM Clinical Research on Herbal Medicine With Consideration of T&CM Theoretical Framework

4.2.1. Research Design

It is recommended that research on traditional preparation of medicinal materials is designed based on principles of T&CM (full or partial consideration of T&CM theoretical framework) as it will be more relevant to the practice. Indications that may be considered appropriate for investigations in this category should take into account the following factors:

- indication being similar to or based on what has been used within the T&CM practice;
- reasonable records on safe human use;
- low risk of harm e.g. safe for self-medication; and
- does not involve therapeutic claims on diseases, disorders or conditions that require medical supervision such as cancer, psychiatric diseases, infectious diseases such as hepatitis or influenza, cardiovascular diseases such as heart failure and metabolic diseases such as diabetes.

If the T&CM principles used are not derived from pharmacological models, terms directly implying or transposing conventional medicine concepts should be avoided, unless there are supporting evidence or data available to guarantee that both have identical meanings.⁽⁷³⁾

As indicated, conventional concepts of clinical research design may be difficult to apply in the evaluation of safety and effectiveness of herbal medicine. For example, when diagnosis is based on T&CM theoretical framework, there may be a lack of internationally recognised diagnostic criteria to identify eligible research participants as well as outcome measures.

Box 1 shows an example of research with full consideration of T&CM theoretical framework.

Box 1: Example of Herbal Medicine Research with Full Consideration of T&CM Theoretical Framework

With full consideration of T&CM theoretical framework

If liquorice root is studied based on TCM framework, the selected population should be defined by TCM Pattern Diagnosis which would be suitable for the use of liquorice from TCM viewpoint.

Note: It is worth noting that Pattern Diagnosis may vary during the course of intervention leading to possible variation of intervention. This may create difficulty in the integration of scientific research methods with T&CM approach.

4.2.2. Interventions

Precise description of both experimental intervention and comparator should be provided. The following information is based on CHM as research in this area is more developed compared to other modalities of herbal medicine (Box 2).⁽⁵⁹⁾ It is recommended that similar data is provided for any herbal medicine research.

Box 2: Descriptions for Different Types of CHM Formula in Research

For fixed herbal medicine formulas

- Name, source, and dosage;
- Name, source, processing methods, and amount of each ingredient;
- Authentication of each ingredient: where, when, how and by whom produced;
- Principles, rationale, and interpretation of forming the formula;
Reference as to the effectiveness of the formula;
- Pharmacologic study results;
- Production methods, if any;
- Quality control and safety assessment, if any;
- Safety assessment; and
- Administration route, regimen and dosage.

Box 2: Descriptions for Different Types of CHM Formula in Research (cont.)

For individualised herbal medicine formulas

- Same as fixed formulas; and
- Additional information on how, when and by whom the formula is modified.

For patent proprietary herbal medicine formulas

- Reference to publicly available materials, such as pharmacopoeia, for the details about the composition, dosage, effectiveness, safety and quality control of the formula
- Illustration of the details of the formula, namely
 - the proprietary product name (i.e., brand name);
 - name of manufacturer;
 - lot number;
 - production date and expiry date;
 - name and percentage of added material; and
 - whether any additional quality control measures were conducted.
- Statement of whether the patent proprietary formula used in the research is for a condition that is identical to the publicly available reference.

4.2.3. Controls

Different controls can be used in clinical research to answer different questions. However, the use of a placebo, when possible, is desirable because it generates better quality evidence.⁽⁹⁾

Detailed description of placebo control should be provided as follows:

- Name and amount of each ingredient;
- Description of the similarity of placebo with the intervention (e.g. colour, smell, taste, appearance and packaging);
- Quality control and safety assessment;
- Administration route, regimen and dosage; and
- Production information.

Active control may be used if placebo-controlled research is not possible. The active control may be a traditional medicinal formula; or a pharmaceutical drug. Synergistic effects of herbal medicine may be investigated if it is not ethically possible to withdraw the conventional treatment. In this case, the rationale of potential herb-drug interactions and adverse effects that may occur should be well described.⁽⁹⁾

4.2.4. Blind Assessment

It may be impossible to keep the treatment blinded if the herbal medicine cannot be administered in a predetermined standardised formulation. Therefore, introduction of a blinded assessment of the primary outcomes is essential.⁽⁹⁾

4.2.5. Quality

For safety, quality control, clinical trial and registration requirements of natural products, refer to guidelines such as:

- Malaysian Standard on GAP;⁽³⁰⁾
- GMP;⁽³¹⁾
- DRGD;⁽¹²⁾
- Malaysian Guideline for Application of CTIL and CTX;⁽²⁹⁾ and
- Guideline for Natural Products with Therapeutic Claim.⁽¹⁴⁾

In particular, packaging, labelling and testing data on specific ingredient, heavy metals, microbial contamination and certificate of analysis (active ingredient and finished products) where appropriate should be taken into account.

4.3. Without/With Partial Consideration of T&CM Theoretical Framework

Figure 6 summarises T&CM clinical research on herbal medicine without/with partial consideration of T&CM theoretical framework.

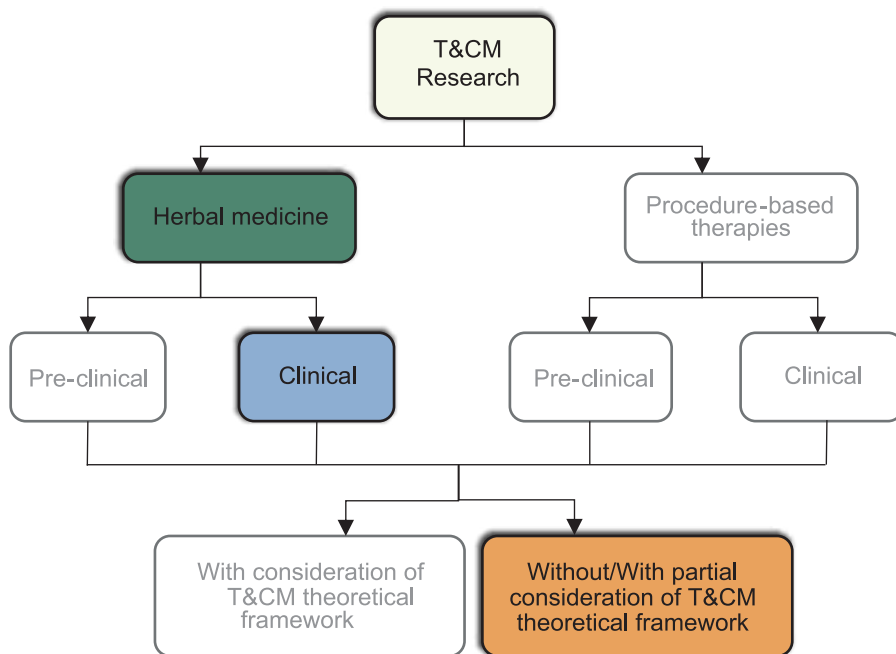


Figure 6: T&CM Clinical Research on Herbal Medicine Without/With Partial Consideration of T&CM Theoretical Framework

In conventional clinical research design, it may be difficult to consider T&CM theoretical framework in the evaluation of safety and effectiveness of herbal medicine. Furthermore, the findings may not be relevant to T&CM practice.

To substantiate therapeutic claims for diseases defined by or diagnosis made according to conventional medicine principles, evidence from different phases of RCT will be needed, as discussed in Section 2.1.2.

Following conventional clinical research design, for natural products with therapeutic claim, the application process for approval to conduct clinical research in Malaysia is depicted in Figure 7. In order to conduct a clinical research investigating therapeutic indications of herbal products, it is required to send an application for CTIL/CTX to the NPRA. The research stages for Natural Products with Therapeutic Claim mirrors the conventional drug development pathway including the conduct of pre-clinical and clinical research to obtain data on quality, safety, and efficacy. Following this pathway, for research that involves herbal medicine products in MOH facilities, recommendation or opinion of National Committee for Research and Development of Herbal Medicine (NRDHM) on the safety of products to be used in the research is a requisite for application of ethics approval from Medical Research and Ethics Committee (MREC). The checklist for NRDHM provides guidance on required information for Investigator’s Brochure on herbal medicine. This checklist covers both

clinical and non-clinical research. Aspects of pre-clinical research in herbal medicine are briefly discussed in Section 6. Detailed guidance on conducting herbal medicine research (from pre-clinical to clinical research) in Malaysia will be addressed in the Guideline for Herbal Medicine Research (guideline in development).

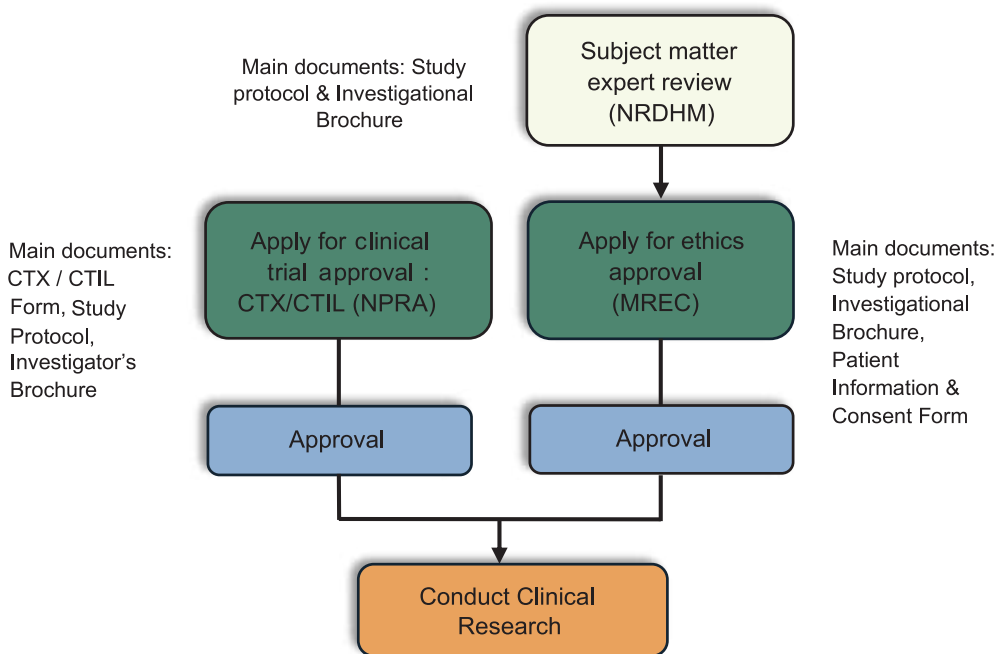


Figure 7: Application Process for Approval to Conduct Clinical Research on Herbal Medicine Products

At present, herbal medicine research is mainly conducted without consideration of T&CM theoretical framework. This research approach may be more suited for investigating indications based on conventional medicine. However, this approach is less relevant to T&CM practice and it may not be appropriate to relate the findings from such research to the specific principles of T&CM.

Examples of research without/with partial consideration of T&CM theoretical framework are depicted in Box 3.

**Box 3: Examples of Herbal Medicine Research
Without/With Partial Consideration of T&CM Theoretical
Framework**


Without consideration of T&CM theoretical framework

- In Ayurvedic medicine framework, if research on the effects of liquorice root do not address its therapeutic effect from the 'doshas'^a viewpoint, it is a T&CM research design without consideration of T&CM theoretical framework.
- In TCM framework, if pharmacological effects of liquorice root are researched in a clinical trial without consideration of participants' body constitution, then it is also a T&CM research design without consideration of T&CM theoretical framework. If evaluating T&CM is mainly based on conventional medicine, the findings of the research may not completely reflect the T&CM practice.

With partial consideration of T&CM theoretical framework

In TCM framework, if effects of the combination of liquorice root and ginseng is studied based on TCM formulation theory without consideration of the body constitution in a group of heart failure patients diagnosed by conventional medicine, then it is a research with partial consideration of T&CM theoretical framework (i.e. formulation theory).

^a In Ayurvedic medicine, the backbone of this ancient medicine is the philosophies employed in its theory and practice, it is believed that every person is made of five basic elements found in the universe which combine in the human body to form three life forces or energies, called 'doshas'.



Section 5
Clinical Research
on
T&CM Procedure-Based
Therapies

Section 5 : Clinical Research on T&CM Procedure-based Therapies

5.1. General Considerations

There are many forms of T&CM procedure-based therapies, for example, acupuncture and related techniques, Qigong, Tai Chi, traditional massage, Shirodhara and Basti therapy, chiropractic, osteopathy, and other physical, mental, spiritual, mind-body therapies. It is challenging to develop a research framework that defines the important elements and attributes across such a diverse and ever evolving field of knowledge on T&CM procedure-based therapies.

Outcomes of clinical research in T&CM procedure-based therapies may guide patients in making an informed decision on preferred treatment; health care providers in determining their choice of treatment; and health care policymakers in making a wise decision during decision making process.

T&CM procedure-based therapies comprise several components interacting with each other as well as influence of outside factors that result in changes to outcomes.⁽⁷⁴⁾ T&CM procedure-based therapies often involve complex behavioural treatments such as Qigong compared to passive treatment such as medication and surgery in conventional medicine.⁽⁶³⁾ T&CM procedure-based therapies are often delivered face to face and inter-personal relationships play an important role in influencing not only patient's engagement but also outcomes.⁽⁷⁵⁾

Conducting research on T&CM procedure-based therapies raises specific methodological issues related to the complexity of the intervention, the expertise of T&CM practitioners, quality control of therapy equipment and the difficulties of blinding.⁽⁶⁶⁾

To date, no specific guidelines are available for research on many T&CM procedure-based therapies. However, research in acupuncture has been more developed recently and would be described in Section 5.2 as an example. The TIDierR checklist and guidelines for research on manipulative therapies such as rehabilitation and physiotherapy; as well as surgery may also be referenced when designing research on T&CM procedure-based therapies.

5.1.1. Quality

The proficiency of T&CM practitioners and quality of therapy equipment can contribute to treatment effectiveness, leading to potential disparity or inconsistency of results reported by different researchers despite sound methodologies of research.⁽⁹⁾ Hence, description on the quality control measures of T&CM practitioner and/or the manufacture of T&CM related equipment used should be documented such as addressing intra-practitioner variability (a single practitioner) and inter-practitioner variability (group of practitioners).

It is recommended that research involving skills dependent techniques should be conducted by more than one practitioner in order to increase generalisability of results.⁽⁶⁾ Determination of criteria on the allocation and proficiency of T&CM practitioners involved in the research will help to minimise bias.^(63,67,76)

5.1.2. Control

Setting up an appropriate control in T&CM procedure-based therapy research is challenging. Although the introduction of a placebo allows for double-blinding, it is almost impossible to create a true placebo effect for research in procedure-based therapies as light touch may also deliver a therapeutic effect.⁽⁷⁷⁾

Compared to the group receiving the intervention, no therapy or usual care (or treatment-as-usual) is often used as the control. This may be followed by a cross-over phase, so that every participant has the chance to receive every type of treatment, especially with the concern regarding the therapeutic impact from light touch.

The main limitations for usual care are that there may not exist any usual care for the studied problem, or the usual care may be too variable. These may be managed by creating a standardised version of typical care for the condition that is being researched.⁽⁷⁸⁾ For T&CM procedure-based therapies, standard regime for control group are typically rehabilitation therapies as most indications are for musculoskeletal conditions.

In principle, all groups (intervention vs control) should be presented as equally credible to manage bias.

5.1.3. Blinding

It can be difficult, or impossible for the practitioner to be kept blinded on the types of intervention the participants are receiving. Hence, a blinded assessment of the primary outcomes of the research should be considered to reduce bias.⁽⁹⁾ This type of blinding is not difficult to attain in procedure-based therapy research as it only requires setting up a mechanism to keep assessors/evaluators and treatment providers from revealing information to one another. Instructions should also be provided to participants to prevent them from revealing treatment allocation information to assessors/evaluators. Outcome assessments that depend on observer ratings may be amendable to additional blinding methods, for example, using audio or videotaping the outcome sessions and keeping the assessors/evaluators blind to the timing of sessions.⁽⁶³⁾

5.1.4. Dose

The dose, frequency and duration of an intervention must be described in detail. In the case of procedure-based therapies, it refers to a variety of attributes related to each episode of the intervention. The 'dose' adapted in a research should be based on the relevant literature and experience of T&CM practice.⁽⁹⁾

5.1.5. Reporting

Incomplete reporting could compromise internal and external validity of results. In addition to the standard guidelines mentioned in Section 2.2.4, modified guidelines addressing theoretical framework of some T&CM procedure-based therapies may be further referred, such as:

- General guidance:
 - PRISMA checklist;⁽⁴⁷⁾ and
 - CONSORT Statement for Randomised Trials of Nonpharmacologic Treatment.⁽⁶⁶⁾
- Specific guidance:
 - Manual therapies - TIDieR checklist;⁽⁷⁰⁾
 - Acupuncture research - Revised STRICTA: Extending the CONSORT Statement and CONSORT Extension for Acupuncture Checklist;⁽⁶⁷⁾ and
 - Cupping - STandards for Reporting Interventions in Clinical Trials of Cupping (STRICTOC): extending the CONSORT Statement.⁽⁷⁹⁾

5.2. With Consideration of T&CM Theoretical Framework

Figure 8 summarises T&CM clinical research on procedure-based therapies with consideration of T&CM theoretical framework.

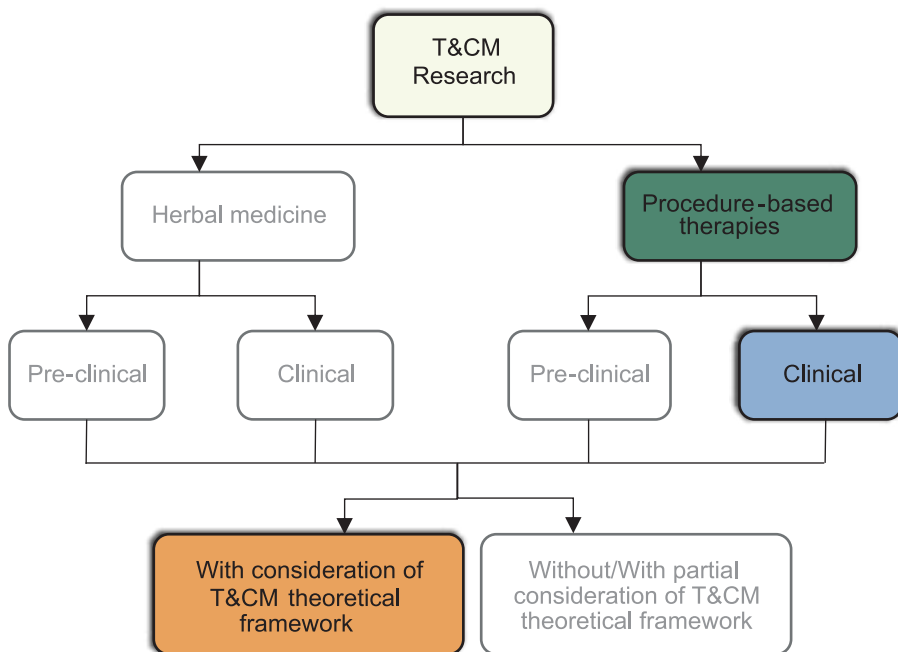


Figure 8: T&CM Clinical Research on Procedure-based Therapies With Consideration of T&CM Theoretical Framework

As clinical research in acupuncture has developed rapidly over the past 50 years, it will be used as an example in this Section (Box 4). In general, research on other T&CM procedure-based therapies may refer to similar considerations.

Box 4: Key Elements in Acupuncture Research

It is critical to have clear definitions in acupuncture as a number of terms have created confusion which impacts on the design of the research.⁽⁵⁸⁾

- Definition of acupuncture
Acupuncture involves the act of insertion and manipulation of fine needles at specific points of the body.⁽⁸⁰⁾ Points may be selected according to traditional medical systems; symptoms; based on scientific relationships of point function; and point prescription based on clinical experience or literature.⁽¹⁵⁾ There are also other non-invasive techniques for acupuncture point stimulation such as laser and transcutaneous electrical nerve stimulation (TENS).
- Dry needling may not necessary be equivalent to acupuncture as the former has been recently adopted whilst the latter has been used for thousands of years. In TCM, acupuncture includes insertion of a needle and a complex intervention with the traditional acupuncture characteristics, see the components of acupuncture as below.
- Components of acupuncture treatment
Each of the following components of acupuncture treatment may contribute to therapeutic effects;⁽⁸¹⁾
 - Needling components (location, insertion depth, stimulation, needles sizes, and numbers);
 - Specific non-needling components (psychological, physiological and characteristic of traditional acupuncture practice including Pattern Diagnosis process, palpation and the meridians theory); and
 - Generic, non-specific, non-needling components (time, attention, credibility and expectation).
- Acupuncture points
There is significant variability in the precise location of points, either across practitioners or in a lack of precise description.

5.2.1. Research Design

The rationale for the use of a T&CM procedure-based therapy should be adequately considered in a clinical research design as it may involve complex multicomponent interventions. This is one of the commonalities amongst many T&CM procedure-based therapies. Therefore, application of conventional clinical research design may be difficult when evaluating its safety and effectiveness. For example, non-needling specific effects may provide substantial therapeutic effects in an acupuncture clinical research.

The research should be well-designed to include information such as full, partial or no consideration of T&CM theoretical framework (theory, principles, individualisation, selection of intervention points based on T&CM theory), because this forms the structure of the research.

For acupuncture research with full or partial consideration of T&CM theoretical framework (Box 5), it is worth noting that Pattern Diagnosis may vary during the course of intervention leading to possible variation of intervention. This may create difficulty in the integration of scientific research methods with T&CM approach.

Box 5: Acupuncture Research Design

Acupuncture rationale may be based on:

- Style of acupuncture
 - Traditional (TCM, Japanese, Korean etc.); and
 - Non -traditional (based on anatomy and physiology).
- Justification for treatment provided
 - Historical context;
 - Literature sources; and
 - Consensus methods.⁽⁶⁷⁾

Details of needling procedure

- Number of needle insertions per participant per session;
- Acupuncture points used;
- Depth of insertion;
- Intended response;
- Needle stimulation;
- Needle retention time; and
- Needle type (diameter, length, and manufacturer or material).⁽⁶⁷⁾

Box 5: Acupuncture Research Design (cont.)

Intervention regimen

- Number of intervention sessions; and
- Frequency and duration of intervention sessions.⁽⁶⁷⁾

Other components of intervention

- Other intervention administered with acupuncture (e.g. moxibustion, herbs, cupping, exercise, lifestyle advice); and
- Setting and context of treatment (instructions to practitioners, information and explanation to participants).⁽⁶⁷⁾

Practitioner background

- Description of participating acupuncturists (qualification or professional affiliation, years in acupuncture practice, other relevant experience);⁽⁶⁷⁾
- T&CM practitioners with relevant expertise and experience should be part of the research team in order to fully understand applied philosophies, principles and techniques of intervention.^(66,82)

5.2.2. Interventions

Precise description of both experimental intervention and comparator should be provided. The following information is based on acupuncture as research in this area is more developed compared to other T&CM procedure-based therapies (Box 6).

Box 6: Control or Comparator Interventions in Acupuncture RCTs

Acupuncture RCTs require one or more control groups as comparison. The type of control may be as follows:⁽⁸²⁾

- Sham acupuncture;
- Minimal acupuncture;
- Real acupuncture with different acupuncture points;
- Non-treatment ; or
- Mock TENS.

Box 6: Control or Comparator Interventions in Acupuncture RCTs (cont.)

Precise description and rationale for the control or comparator in the context of the research question, with sources that justify this choice is required. Other information defined in the experimental group should be provided where appropriate.⁽⁶⁷⁾

Acupuncture treatment is complex with multi-components effects. Using sham acupuncture as a control may elicit a 'limbic touch' response which results in emotional and hormonal reactions,⁽⁸³⁾ giving rise to potential therapeutic effect and thus rendering the control invalid. A better understanding of potential differences in therapeutic effect elicited at acupuncture points and non-acupuncture points will help with the inclusion of sham control in clinical research design.

A well -designed pragmatic design^b may produce results that can be generalised and applied in routine practice settings.⁽⁸⁴⁾ Acupuncture research may be designed as a pragmatic RCT that compares real acupuncture to a wait-list group; participants are assigned to either acupuncture intervention group or wait-list control group, where the observation period is employed as the control. Wait-list control design is more ethical than no-treatment control and may lead to more eligible participants recruited into a research. This pragmatic design balances the risk of participants having unfair opportunity to benefit and their risk of exposure to adverse events.⁽⁸⁵⁾

5.2.3. Participants

Determining recruitment criteria for eligible participants is an integral part of the research design. Consideration of T&CM theoretical framework (full, partial or no consideration) in the research design will determine the inclusion or exclusion of a participant accordingly.

^b Pragmatic trial is a trial designed to test the effectiveness of the intervention in a broad routine clinical practice.

5.3. Without/With Partial Consideration of T&CM Theoretical Framework

Figure 9 summarises T&CM clinical research on procedure-based therapies without/with partial consideration of T&CM theoretical framework.

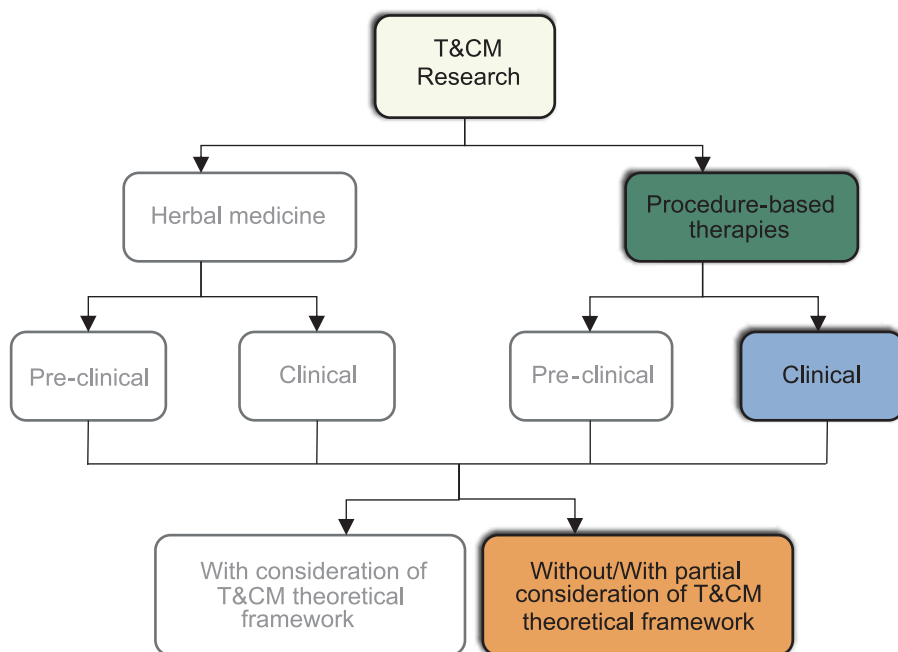


Figure 9: T&CM Clinical Research on Procedure-based Therapies Without/With Partial Consideration of T&CM Theoretical Framework

Box 7 describes the examples of procedure-based therapy research without/with partial consideration of T&CM theoretical framework.

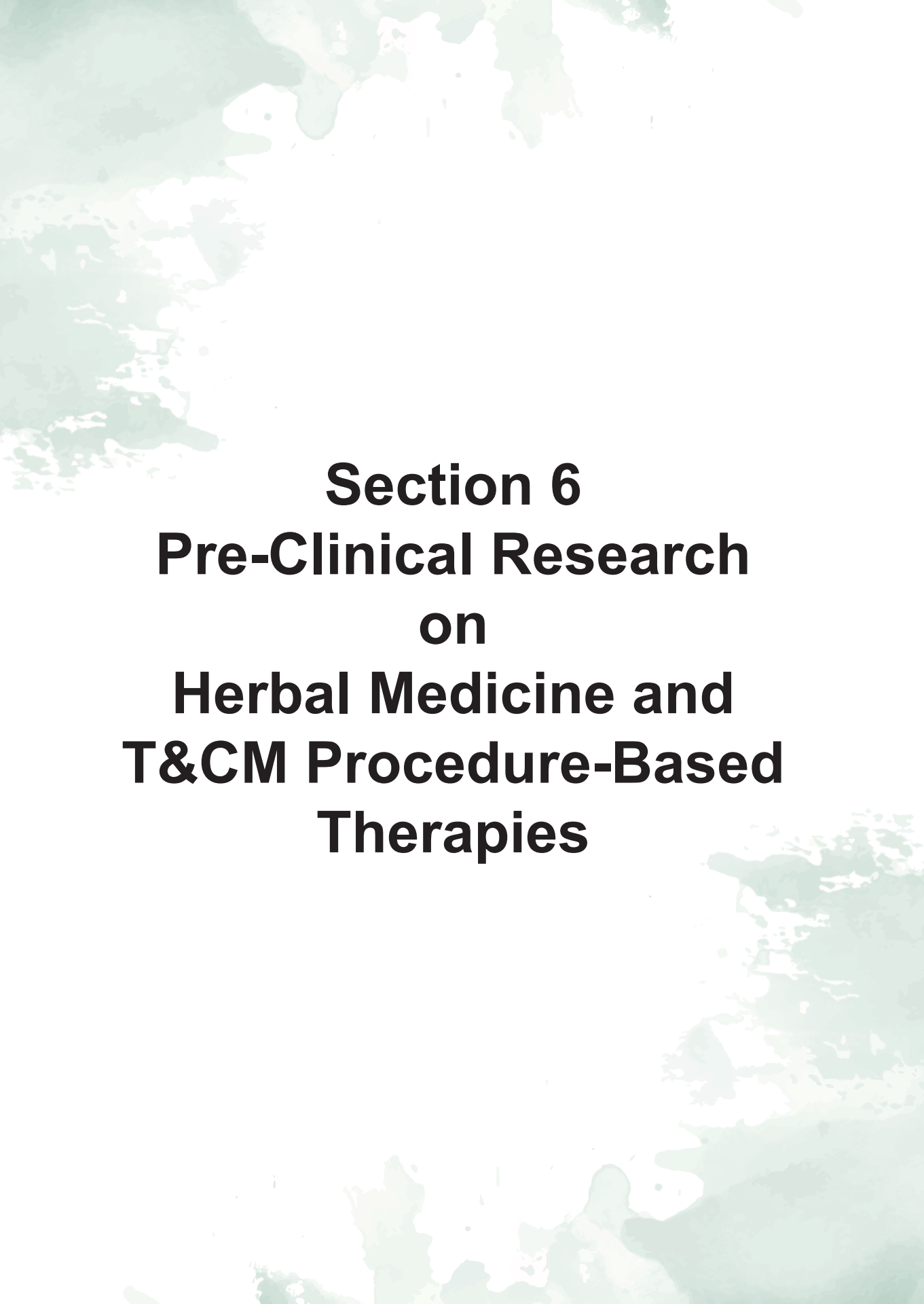
Box 7: Examples of Procedure-based Therapy Research Without/With Partial Consideration of T&CM Theoretical Framework

Without consideration of T&CM theoretical framework

When acupuncture is investigated for its effectiveness on Bell's Palsy, the population is defined based on a 'disease' instead of Pattern Diagnosis. It is critical to note that findings of research on procedure-based therapies that are conducted without consideration of T&CM theoretical framework should be interpreted with caution in terms of its relevance and generalisation to T&CM practice.

With partial consideration of T&CM theoretical framework

In Ayurvedic medicine framework, if the effects of Shirodhara treatment is studied based on Ayurvedic treatment regime without consideration of the doshas in a group of insomnia patients diagnosed by conventional medicine, then it is a research with partial consideration of T&CM theoretical framework.



Section 6
Pre-Clinical Research
on
Herbal Medicine and
T&CM Procedure-Based
Therapies

Section 6 : Pre-clinical Research on Herbal Medicine and Procedure-based Therapies

Pre-clinical research or basic science research is performed to obtain basic information about the mechanism of safety and biological effectiveness of intervention before proceeding to human clinical trial. Models of pre-clinical research include *in silico*, *in vitro*, *ex vivo* and *in vivo* studies.

In Malaysia, pre-clinical research on herbal products with therapeutic claims, particularly toxicity studies, must be conducted in compliance with GLP requirements to ensure reliability and reproducibility of results.^(14,86) Other safety pharmacology studies may be used to further support the overall safety profile of a test item under investigation.⁽⁸⁷⁾

Researchers should work closely with their clinical counterparts in designing pre-clinical research projects. 'Bedside to Bench' instead of 'Bench to Bedside' is the approach to be encouraged. Results of pre-clinical research alone may not be considered as sufficient evidence to support a scientific indication. However, they may be used to provide secondary support to human data.⁽¹³⁾

For safety and effectiveness, a pharmacological effect observed in *in vitro* or *in vivo* models may not be necessarily applicable to humans.⁽⁹⁾

At present, there are no widely acceptable guidelines for pre-clinical research on T&CM procedure-based therapies. Hence, future guidelines for pre-clinical research on T&CM procedure-based therapies should address several key challenges in research design and reporting such as epistemic instability due to the difficult mixture of traditional framework and biomedical rationales, as well as the reproducibility of methods using animal models.

Commonly, pre-clinical research is conducted in the areas of herbal medicine and acupuncture, and these examples in pre-clinical research are given as below. Nevertheless, conducting pre-clinical research for T&CM procedure-based therapies, prior to undertaking clinical research, may not be a mandatory requirement due to challenges in reproducibility and translating pre-clinical findings into clinical research.

6.1. Herbal Medicine

Herbal medicine is a complex system, and the quality is largely influenced by the significant diversity of phytochemical components. Hence, quality control and standardisation for herbal medicines, herbal preparations, and finished herbal products are extremely challenging. Furthermore, the unique features of synergistic reactions among different components and mechanisms of effect may be difficult to explore in conventional research design that is usually a model of 'single component and single target'. Reconciliation between the underlying theory of T&CM and conventional medicine makes it more challenging.⁽⁵⁷⁾ Figure 10 summarises T&CM pre-clinical research on herbal medicine with/without/partial consideration of T&CM theoretical framework.

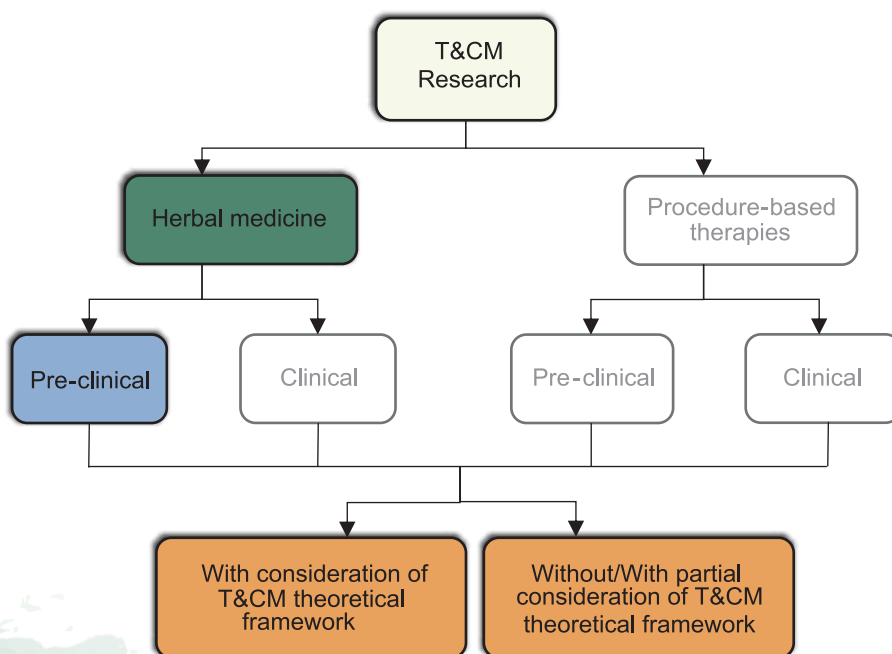


Figure 10: T&CM Pre-clinical Research on Herbal Medicine With/Without/Partial Consideration of T&CM Theoretical Framework

In light of the guidelines published by WHO^(9,10,13) and Malaysia regulatory bodies⁽⁸⁸⁾ the areas of basic research in herbal medicine are included but not limited to:

- Quality:
 - Botanical verification (authentication of the botanical identity of natural products);
 - Quality control and bioactivity [active ingredients, extraction, isolation and quantification of natural product characterising compounds (chemical profiling and chemo markers) or biomarkers];

- Method development for quality assurance of complex natural products and stability research (standard methods are usually employed, however, the use of novel technologies and methods resulting from scientific progress should be encouraged); and
 - For further details on quality specifications for natural materials; starting and packaging materials; intermediate and bulk products; and finished products for traditional medicines, please refer to Guidelines on Good Manufacturing Practice for Traditional Medicines and Health Supplements, Malaysia (1st Edition, 2008).
- Safety
 - Intrinsic toxicity assessments (general toxicity, specific toxicity and safety pharmacology studies);
 - Extrinsic toxicity assessments (e.g. microbial, heavy metal, adulteration analysis, pesticide contamination, radioactivity, aflatoxin and any treatment used to reduce fungal/microbial contamination or other infestation); and
 - Herb-drug interactions
 - Effectiveness
 - Effectiveness and pharmacology related studies; and
 - Pharmacokinetics and pharmacodynamics

It is very important to understand that the current technology and/or methodology may neither be adequate nor possible to explain some of the traditional theories of traditional medicines (e.g. the properties and characteristics of herbs) in biomedical terms.

In vitro studies as well as *in vivo* are intended to generate the non-clinical data. When data from *in vivo* and *in vitro* studies are submitted as substantiation of claims, an explanation on its relevance to humans should be included.⁽¹⁴⁾ The Guideline also sets out the requirements on non-clinical document in herbal medicine.

Detailed guidance on conducting herbal medicine research (from pre-clinical to clinical research) in Malaysia will be addressed in the upcoming Guideline for Herbal Medicine Research.

6.2. T&CM Procedure-based Therapies

Pre-clinical research on T&CM procedure-based therapies are still at the infancy stages. Figure 11 summarises T&CM pre-clinical research on procedure-based therapies with/without/partial consideration of T&CM theoretical framework. There is limited data available on pre-clinical research for many T&CM procedure-based therapies except acupuncture. Hence, pre-clinical research on acupuncture is described in Box 8 for reference.

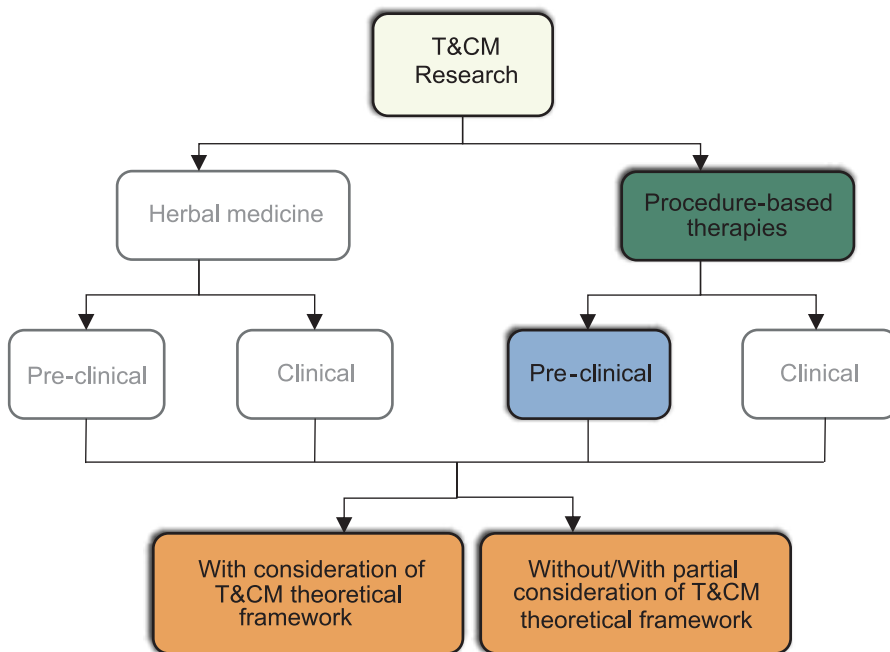


Figure 11: T&CM Pre-Clinical Research on Procedure-based Therapies With/Without/Partial Consideration of T&CM Theoretical Framework

Box 8: Pre-clinical Research on Acupuncture

In the past 50 years, there has been major development in the area of pre-clinical and translational acupuncture research. This has led to important findings which have become essential to understanding the underlying mechanisms and clinical applications of acupuncture.

Many pre-clinical acupuncture studies focus on biomarkers that are related to a defined pathological condition that may improve with acupuncture treatment. It is important to ensure that the chosen biomarkers are reliable and clinical outcomes are measured in both immediate and delayed response to needling. Moreover, biomarkers should be associated with the traditional acupuncture philosophies which may potentially expand the understanding of human physiology and pathophysiology.⁽⁵⁸⁾ It is important to emphasise that pre-clinical research on acupuncture is designed with consideration of the traditional meridian system and its framework.

There are no specific guidelines for pre-clinical research in acupuncture. Therefore, guidelines for the design and reporting of animal studies, such as Animals in Research: Reporting In Vivo Experiments (ARRIVE) guideline, have been used to improve reporting of pre-clinical research in acupuncture.⁽⁸⁹⁾

Reproducibility, clinical translation and general scientific acceptance of prior pre-clinical research on acupuncture have been impeded by the following limitations:⁽⁹⁰⁾

- Lack of a clear rationale on choice of acupoints to address the experimental objective;
- Lack of detailed and sufficient description of acupuncture needling procedures for reproducibility; and
- Lack of consistent adherence to the ARRIVE guideline.

If there is a global initiative in developing a STandards for Reporting Interventions in Acupuncture Using Animal Models (STRIAAM), it would greatly improve the design of new pre-clinical research and lead to better execution and reporting of acupuncture animal studies.⁽⁹⁰⁾

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Section 7

Way Forward

Section 7 : Way Forward

There is a need to create a conducive research environment and support for the development of T&CM research as part of the T&CM Blueprint 2018-2027 (Health Care) strategy. To achieve that strategy, key priority areas include advancing methodology with a holistic approach for the design of research; quality control of both interventions and practitioners; and evaluating clinical research outcomes by leveraging on real-world data.

Guidelines related to T&CM research should encompass innovation of operational procedures; advancement in science and technology; and multi-disciplinary collaborations. The goals are to improve efficiency of the evaluation and approval process, deliver safe and quality therapies to patients and improve patient outcomes.

This framework was developed in an attempt to bridge the gaps and challenges faced by various stakeholders in conducting T&CM research and become a precursor to creating a more conducive research environment for this field in Malaysia. Based on this framework, more specific guidelines related to T&CM research in Malaysia could be developed in the future such as Guideline for Herbal Medicine Research. As a complement to NRDHM, a T&CM Research Advisory Committee shall be established to evaluate T&CM practice related research protocols. With this, it is hoped that it can be an impetus to enhance T&CM research capacity in Malaysia.

Appendix

This framework should be read in conjunction with the current laws and regulations, as well as other relevant legislation, in particular the guidelines for clinical trials in Malaysia and those published by World Health Organization (WHO) as follows:

Document name	Document source (Link)	Organisation in charge	Notes
A. National Traditional and Complementary Medicine (T&CM) Blueprints and Policy			
1. T&CM Blueprint 2018-2027 (Health Care), Malaysia	https://itcm.moh.gov.my/ms/upload/Blueprintprint.pdf	T&CM Division	
2. National Policy on Traditional and Complementary Medicine, Malaysia 2007	https://itcm.moh.gov.my/en/index.php/policy/national	T&CM Division	
B. General Research and Registration Guidelines			
(i) National			
1. Medical Research and Ethics Committee (MREC) for human subjects	https://www.nih.gov.my/mrec/	MREC	

Document name	Document source (Link)	Organisation in charge	Notes
2. Institutional Review Board (IRB) or Independent Ethics Committee (IEC)	List of ethics committee registered with Drug Control Authority (DCA) https://www.npra.gov.my/index.php/e/n/component/sppagebuilder/733-clinical-trials.html	DCA	
3. National Institutes of Health (NIH) Guidelines for Conducting Research in MOH Institutions and Facilities	https://www.nih.gov/my/images/media/publication/guidelines/NIH_Guideline_2021.pdf	NIH Malaysia	
4. Animal Welfare Act 2015 (Act 772)	https://lom.agc.gov.my/act-detail.php?type=principal&lang=BI&act=772		Principal legislations that govern the care and use of laboratory animals in Malaysia.
5. Wildlife Conservation Act 2010 (Act 716)	https://lom.agc.gov.my/act-detail.php?type=principal&lang=BI&act=716		
6. Malaysian Guideline for Good Clinical Practice (GCP) 4 th Edition	http://www.nccr.gov.my/index.cfm?menuid=17	National Committee for Clinical Research (NCCR)	
7. Malaysian Guidelines for GCP Inspection, Edition 2.1	https://www.npra.gov.my/index.php/en/guideline-for-the-submission-of-product-samples-for-laboratory-testing/clinical-trial/clinical-trial-guidelines.html	National Pharmaceutical Regulatory Agency (NPRA)	
8. Malaysian Guideline for Application of Clinical Trial Import Licence (CTIL) and Clinical Trial Exemption (CTX), 7.1 th Edition	https://www.npra.gov.my/index.php/en/guideline-for-the-submission-of-product-samples-for-laboratory-testing/clinical-trial/clinical-trial-guidelines.html	NPRA	

Document name	Document source (Link)	Organisation in charge	Notes
9. Good Laboratory Practice (GLP)	https://www.npra.gov.my/index.php/en/glp-main-page.html (Malaysia) https://www.oecd.org/chemicalsafety/testing/good-laboratory-practiceglp.htm [International Organisation for Economic Co-operation and Development (OECD) Guidelines]	NPRA	Pre-clinical safety research (required for clinical testing) required to be conducted in a facility that complies to OECD GLP principles
10. Malaysian Good Agriculture Practices (MyGAP)	https://www.mafi.gov.my/documents/20182/361765/Garis+Panduan+MyGAP.P.pdf/1d3c05ea-9c45-4407-b068-8bd969cc62e0	Ministry of Agriculture and Food Security	
11. Malaysian Guideline for Phase I Unit Inspection and Accreditation Programme	https://www.npra.gov.my/index.php/en/guideline-for-the-submission-of-product-samples-for-laboratory-testing/clinical-trial/clinical-trial-guidelines.html	NPRA	
12. ASEAN Guideline for the Conduct of Bioequivalence (BE) Studies	https://www.npra.gov.my/images/reg-info/BE/BE_Guideline_FinalMarch2015_endorsed_22PPWG.pdf	NPRA	BE research made for the purpose of registering a product in Malaysia must be carried out in a BE research centre.
13. Malaysian Guideline for Safety Reporting of Investigational Products, 1 st Edition	https://www.npra.gov.my/index.php/en/guideline-for-the-submission-of-product-samples-for-laboratory-testing/clinical-trial/clinical-trial-guidelines.html	NPRA	

Document name	Document source (Link)	Organisation in charge	Notes
14. Drug Registration Guidance Document (DRGD) 3 rd Edition	https://www.npra.gov.my/index.php/en/component/spagebuilder/925-drug-registration-guidance-document-drgd.html	NPRA	
15. Medical Device Authority (MDA) regulatory documents	<p>Legislative Documents</p> <p>https://www.mda.gov.my/documents/regulation/685-medical-device-act-2012-eng/file.html</p> <p>https://www.mda.gov.my/documents/regulation/688-medical-device-regulations-2012/file.html</p> <p>https://www.mda.gov.my/documents/regulation/1313-medical-device-regulations-duties-and-obligations-of-establishments-2019/file.html</p> <p>https://www.mda.gov.my/documents/regulation/683-medical-device-exemption-order-2016-1/file.html</p> <p>Circular Letter</p> <p>https://www.mda.gov.my/doc-list/circular-letter.html</p> <p>Guidance Documents</p> <p>https://www.mda.gov.my/doc-list/guidance-document.html</p> <p>Guidelines</p> <p>https://www.mda.gov.my/doc-list/guideline.html</p>	MDA	Medical Devices

Document name	Document source (Link)	Organisation in charge	Notes
16. National Medical Research Register	http://www.nmrr.gov.my/	NIH Malaysia and MREC	
17. Access to Biological Resources and Benefit Sharing Act 2017 (Act 795)	https://www.mybis.gov.my/pb/3567		
18. Sarawak Biodiversity Centre Ordinance 1997 with Amendments 2003 and Amendments 2014	https://www.sbc.org.my/research-regulations-permit/ordinance-and-regulations/4-the-sarawak-biodiversity-ordinance-1997	Sarawak Biodiversity Centre (SBC) SBC	
19. Sarawak Biodiversity Regulations 2016 with Amendments 2018	https://www.sbc.org.my/research-regulations-permit/ordinance-and-regulations/409-sarawak-biodiversity-regulations-2016		
20. Sarawak Online Research Application System (SORAS)	https://soras.sarawak.gov.my/soras/welcome		
21. Sabah Biodiversity Enactment 2000	https://sabc.sabah.gov.my/content/sabah-biodiversity-enactment-2000	Sabah Biodiversity Centre (SabC)	
22. Sabah Biodiversity Access & Export Licence Online Application	https://sabcapps.sabah.gov.my/		
23. Application for Research in <i>Perkampungan Orang Asli</i> or JAKOA facilities	https://www.jakoa.gov.my/lumum/bermohonan-penyelidikan/	Department of Orang Asli Development (JAKOA)	
(ii) International			
1. WHO Handbook for Good Clinical Research Practice	https://www.who.int/medicines/areas/quality_safety/safety_effectiveness/gcp1.pdf	WHO	

Document name	Document source (Link)	Organisation in charge	Notes
2. International Ethical Guidelines for Biomedical Research Involving Human Subjects	https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf	Council for International Organizations of Medical Sciences (CIOMS) & WHO	General Clinical Research
3. WHO Operational Guidelines for Ethics Committees That Review Biomedical Research	http://www.nccr.gov.my/index.cfm?menuid=24&parentid=17	WHO	General Clinical Research
C. T&CM based Research and Registration Guideline			
(i) National			
1. Guideline of Natural Products with Therapeutic Claim	https://www.npra.gov.my/index.php/en/component/sppagebuilder/925-drug-registration-guidance-document.html	NPRA	Herbal Medicine (This guideline is part of the DRGD)
2. Guideline on Registration of Natural Products	https://www.npra.gov.my/index.php/en/component/sppagebuilder/925-drug-registration-guidance-document.html	NPRA	Natural Products (This guideline is part of the DRGD)
3. Checklist for National Committee for Research and Development of Herbal Medicine (NRDHM)	https://www.nih.gov.nih.gov/images/media/publication/guidelines/NIH_Guideline_2021.pdf	NRDHM	Herbal Medicine The NRDHM checklist is part of the NIH Guideline for Conducting Research in MOH Institutions and Facilities, 2021

Document name	Document source (Link)	Organisation in charge	Notes
4. Good Manufacturing Practice (GMP) (in accordance with Pharmaceutical Inspection Co-Operation Scheme-Guide to GMP for Medicinal Products)	https://npra.gov.my/index.php/en/abou/ut/recognition-international-membership/pic-s.html https://picscheme.org/	NPRA	Herbal Medicine
(ii) International			
1. WHO General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine	https://www.who.int/publications/item/9789241506090	WHO	General Traditional Medicine
2. Set of ASEAN Guiding Principles on Traditional Medicines and Health Supplements developed by the Traditional Medicines and Health Supplements Product Working Group	https://www.hsa.gov.sg/international-collaboration-complementary-health-products/asean	The Product Working Group for Traditional Medicines and Health Supplements (TMHSPWG)	General Traditional Medicine
3. WHO Research Guidelines for Evaluating the Safety and Effectiveness of Herbal Medicines, 1993	https://apps.who.int/iris/handle/10665/207008	WHO	Herbal Medicine
4. WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems, 2004	https://apps.who.int/iris/handle/10665/43034	WHO	Herbal Medicine
5. WHO Quality Control Methods for Medicinal Plant Materials. World Health Organization, 1998	https://apps.who.int/iris/handle/10665/41986	WHO	Herbal Medicine

Document name	Document source (Link)	Organisation in charge	Notes
6. European Medicines Agency (EMA) Guideline: Assessment of Clinical Safety and Effectiveness in the Preparation of EU Herbal Monographs for Well-established and Traditional Herbal Medicinal Products	https://www.ema.europa.eu/en/assessment-clinical-safety-effectiveness-preparation-eu-herbal-monographs-well-established-traditional	EMA	Herbal Medicine
7. EMA Guideline: Clinical Assessment of Fixed Combinations of Herbal Substances/Herbal Preparations	https://www.ema.europa.eu/en/assessment-clinical-safety-effectiveness-preparation-eu-herbal-monographs-well-established-traditional	EMA	Herbal Medicine
8. EMA Guideline: Specifications; Test Procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products/Traditional Herbal Medicinal Products	https://www.ema.europa.eu/en/specifications-test-procedures-acceptance-criteria-herbal-substances-herbal-preparations-herbal	EMA	Herbal Medicine
9. EMA Guideline: Quality of Herbal Medicinal Products/Traditional Herbal Medicinal Products	https://www.ema.europa.eu/en/quality-herbal-medicinal-products-traditional-herbal-medicinal-products	EMA	Herbal Medicine
10. India General Guidelines for Clinical Evaluation of Ayurvedic Interventions	https://www.ayush.gov.in/docs/clinical_evaluation.pdf	Ministry of AYUSH, Government of India	Ayurveda
11. India General Guidelines for Drug Development of Ayurvedic Formulations	https://www.ayush.gov.in/docs/guideline-drug-development.pdf	Ministry of AYUSH, Government of India	Ayurveda

Document name	Document source (Link)	Organisation in charge	Notes
12. India General Guidelines for Safety Toxicity Evaluation of Ayurvedic Formulations	https://www.ayush.gov.in/docs/guideline_safety_toxicity.pdf	Ministry of AYUSH, Government of India	Ayurveda
13. Hong Kong GCP for Proprietary Chinese Medicines	https://www.cmchk.org.hk/pcm/pdf/gcp_e.pdf	Chinese Medicine Council of Hong Kong	Proprietary Chinese Medicine
14. WHO Guidelines for Clinical Research on Acupuncture, 1995	https://apps.who.int/iris/handle/10665/207013	WHO	Acupuncture
15. WHO Meeting on Revision of Guidelines for Clinical Research on Acupuncture, 2005	https://iris.wpro.who.int/handle/10665.1/6160	WHO	To be read with WHO Guidelines for Clinical Research on Acupuncture 1995
D. Reporting guidelines			
1. The Enhancing the Quality and Transparency of Health Research (EQUATOR) Network	https://www.equator-network.org/		Reporting guidelines
2. Consolidated Standards of Reporting Trial (CONSORT) Extension for Reporting Herbal Medicines	http://www.consort-statement.org/extensions/overview/herbal-medicinal/interventions	CONSORT	Herbal Medicine
3. CONSORT Extension for CHM Formulas 2017	http://www.consort-statement.org/extensions/overview/chineseherbalmeds	CONSORT	Chinese Herbal Medicine

Document name	Document source (Link)	Organisation in charge	Notes
4. CONSORT Statement for Randomised Trials of Nonpharmacologic Treatment	http://www.consort-statement.org/extensions/overview/non-pharmacologic-treatment-interventions	CONSORT	Nonpharmacological Intervention
5. Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): Extending the CONSORT Statement and the CONSORT Extension for Acupuncture Checklist	http://www.consort-statement.org/extensions/overview/acupuncture-interventions	CONSORT	Acupuncture
6. CONSORT Extension of Reporting N-of-1 trials (CENT) 2015	http://www.consort-statement.org/extensions/overview/n-of-1	CONSORT	N-of-1 trial
7. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)	https://www.spirit-statement.org/publications-downloads/	SPIRIT	Study protocols
8. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)	https://www.strobe-statement.org/checklists/	STROBE	Observational studies
9. Animal Research: Reporting of In Vivo Experiments (ARRIVE) guideline	https://arriveguidelines.org/	ARRIVE	Pre-clinical

Document name	Document source (Link)	Organisation in charge	Notes
E. Others			
1. WHO Guidelines on Basic Training and Safety in Acupuncture, 1999	https://apps.who.int/iris/handle/10665/66007	WHO	Acupuncture
2. WHO Guidelines on Basic Training and Safety in Chiropractic, 2005	https://apps.who.int/iris/handle/10665/43352	WHO	Chiropractic
3. WHO Benchmarks for Training in Osteopathy, 2010	https://apps.who.int/iris/handle/10665/44356	WHO	Osteopathy
4. WHO Benchmarks for Training in Ayurveda, 2010	https://apps.who.int/iris/handle/10665/44352	WHO	Ayurveda
5. WHO Regulatory Situation of Herbal Medicines: A Worldwide Review, 1998	https://apps.who.int/iris/handle/10665/63801	WHO	Herbal Medicine

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