Ethical Guidelines for Health Research in Ayurveda

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Government Of Nepal
Ministry Of Health and Population
National Ayurveda Research and Training Center
Kirtipur , Kathmandu

Foreword

National Ayurveda Research and Training Center (NARTC) is a premier institution for research and development in the field of Ayurveda and indigenous medicines. Research is the back bone of any system to develop and adopt globally. Basically, research includes fundamental drug research and clinical research. Various types of research should be carried out to develop and adopt Ayurveda nationally and internationally.

There is a need of comprehensive guidelines to conduct research at different levels. Hope this guideline will pave the way in drug development (standardization and quality assurance), safety, toxicity and clinical evaluation.

This guideline will be helpful for investigators, researchers, organizations and academic institutions for making research proposal and planning. In addition to this, it is helpful for seeking grant from different agencies. I would like to thank Prof. Dr. Dhanik Lal Bharkher, Chairman of Nepal Ayuvedic Medical Council (NAMC) and also Co-ordinator of Guideline Committee, who devoted his valuable time in drafting and finalizing the guideline. I would also like to thank Prof. Dr. Pradeep Vaidya, Dr. Pramod Bhatta, Dr. Puneshwor Keshari, Dr. Bishun Dayal Prasad Patel and Mr. Man Bahadur Basnet for their valuable time in drafting and finalizing the guideline. I would also like to thank Dr. Amit Man Joshi for his contribution in preparation and edition of the guideline.

At last, this ethical guideline certainly helps the researcher while designing the research proposal and will be a milestone for the research in Ayurveda.

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LIST OF ABBREVATIONS

Abbreviation	Full Form
AAM	Ayurveda and Alternative Medicines
ADR	Adverse Reactions
AE	Adverse Events
CIOMS	Council of International Organization of Medical Sciences
CoI	Conflict of Interest
CTR	Clinical Trial Registration

DSMB	Data Safety Monitoring Board
ERB	Ethical Review Board
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIV	Human Immuno-deficiency Virus
IAEC	Institutional Animal Ethics Committee
ICD	Informed Consent Documents
ICF	Informed Consent Form
ICH	International Council of Harmonization
ICMJE	International Committee of Medical Journal Editors
IEGBR	International Ethical Guidelines for Biomedical Research
IP	Investigational Product
IPR	Intellectual Property Rights
IRC	Institutional Review Committee
LAR	Legally Authorized Representative
MoU	Memorandum of Understanding
MTA	Material Transfer Agreement
NARTC	National Ayurveda Research and Training Center
NSAIDs	Non-Steroid Anti-inflammatory Drugs
OECD	Organization for Economic Co-operation and Development

PI	Principal Investigator
PIS	Patient/Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
RCR	Responsible Conduct of Research
RCT	Randomized controlled trial
RP	Reverse Pharmacology
SAE	Side Adverse Event
SHR	Spontaneously Hypertensive Rat
SOP	Standard Operating Procedure
STZ	Streptozotocin or Streptozocin
TB	Tuberculosis
TK	Traditional knowledge
WHO	World Health Organization
WMA	World Medical Association

Section 1: INTRODUCTION

1.1 Background

Nepal is a sovereign nation enriched with diversities in geography, culture, religion, ethnicity, linguistic and indigenous medical knowledge. Since the time immemorial, the country has been practicing ancient Veda based traditional medicinal practices such as Ayurveda. Other practices based on indigenous medical wisdom like Folklore medicine, Sowa-rigpa, traditional healing, ethno-medicine etc. are also being practiced according to the culture, race, religion and geography. These traditional medical practices are primarily preferred by majority of Nepalese population in rural as well as in urban area because of its time tested and ancestral belief. Even in this age of evidence based medical practice, these complementary medicines are gaining paramount significance for prevention, curative and rehabilitation of both communicable and non-communicable diseases. The positive results of these in the communities have indirectly enforced the scientific communities to conduct medical research in these fields. Most of the countries are in agreement to conduct evidence based practices of traditional medicines and has agreed to generate scientific evidences for their rational uses.

In this challenging global scenario, Nepal should also practice these traditional medicines, based on scientific evidences, and have to produce such evidences by the means of scientific studies and research. Hence for conducting the scientific researches National Ayurveda Research and Training Center (NARTC) was established in 2011 A.D. In addition to this, National Health Policy 2076 B.S. also supports to promote research activities in Ayurveda. To maintain, promote and

conduct different research studies and to keep up with the newer developments, NARTC has currently revised "Ethical Guidelines for Health Research in Ayurveda" published in 2013 A.D.

1.2 Historical background

Ayurveda is said to be an eternal science that first existed in the universal consciousness before it was passed from the creator to the ancient Acharyas. The origins of Ayurveda stretch deep into antiquity, and is known as one of the ancient medical systems in the world. When human being started suffering from various diseases, the wise men like Bharadwaja learnt from God Indra, and used the knowledge of the Ayurveda medical science to treat the illness. Several such references of illness, cures and other health-related issues were mentioned in Vedas, the oldest recorded compendium of wisdom on the earth at 3000 B.C. The knowledge of this medical science was further elaborated with adding new concepts, methods, interventions, approaches and drugs right from Ancients scholars in Vedas; Rig-veda (3000 B.C.), Atharvaveda (1500 B.C.), Yajurveda (1200 to 1000 B.C.), and Samhitas; major authoritative compendia namely Charaka Samhita (1000 B.C.), Sushruta Samhita (600 B.C.), Sharangadhara Samhita (1300 A.D.) and the latest Samhita such as Bhavaprakash Samhita (1600 A.D.). These medieval and current literatures enriched into the Ayurvedic Pharmacopiea and Pharmaco-therapeutics.

Ayurveda conceives life as a four dimensional entity. *Ayu*, the living entity is the sum total of physical body, the senses, the psyche and the soul. The human mind has three components i.e. *Sattva*, *Raja* and *Tama*, which interact with the biological components *Vata*, *Pitta* and *Kapha* which decides the psychosomatic constitution of an individual (*Prakriti*).

Hence, Ayurveda defines health as a state resulting from the balance of the three doshas, seven *dhatus* and three *malas*, as well as the sensorial, mental, emotional and spiritual well being (*Prasanna*). Ayurveda, the science of life lays great emphasis on preservation and promotion of health, thereby preventing diseases. The main purposes of Ayurveda are preservation and promotion of the health of a healthy person and restoration of health in the diseased one.

The universe, according to Ayurveda is composed of *Pancha-mahabhootas* (Five basic elements) namely *Prithvi* (Earth), *Jala* (water), *Agni* (Fire), *Vayu* (Air) and *Akasha* (Space). As the human body is similarly constituted, there is a fundamental similarity between universe and man. A healthy balance between the microcosm (Human being) and macrocosm (Universe) is the basis of good health.

In other word, Ayurveda is based on the theory of three doshas (*Tridosha* theory; humours) namely *Vata, Pitta* and *Kapha*, seven *Dhatus* (Saptadhatu; body tissues) namely *Rasa* (Fluid components of the body), *Rakta* (Blood and Blood components), *Mamsa* (Muscle tissue), *Medas* (Adipose tissue), *Asthi* (Bone tissue), *Majja* (Bone marrow) and *Sukra* (Reproductive elements) and three *Malas* (*Trimalas*; Bio-wastes) such as *Mootra* (Urine), *Pureesha* (Faeces) and *Sweda* (Sweat). The essence of *saptadhatu* called *Ojas* is responsible for immunity and strength.

In Ayurveda, the process of learning, research and clinical practice are experimental and passed from generations to generations. Like other systems of ancient learning, Ayurveda has been discovered through most recognized schools of acquiring knowledge and producing evidence (*Pramanas*) from direct perception through sense organs (*Pratyaksa*), inference (*Anumana*), verbal sharing with many of the trustworthy persons, who knows truth and can communicate correctly (*Aptopadesha*) and has logical/rational interpretation (*Yukti*), etc.

Every individual has a peculiar body and mind constitution, which is responsible for the health or disease pattern of an individual. Ayurvedic concept of examination of constitution (*Prakriti-pareeksha*) is to find out of physical and mental constitution for selecting diet and medicine or treatment regimen.

On the other hand, the diagnosis in Ayurveda is based on a two-fold approaches namely examination of the patient (*Rogi-pareeksha)*; and examination of the disease (*Roga-pareeksha)*. Ideal treatment according to Ayurveda is one, which cures the disease without causing adverse effect. Three classical therapeutic streams advocated by Ayurveda are namely therapies with inexplicable mode of action (*Daivavyapasraya-chikitsa),* rationale treatment (*Yuktivyapasraya-chikitsa*) and preventive and remedial measures to Psychic disorders (*Satwavajaya-chikitsa*). The rational use of Ayurveda treatment is carried out in four parts namely *Dosha* pacifying therapy (*Samsamana*), Bio-cleansing therapy (*Samsodhana* or *Panchakarma*), avoiding causative factors (*Nidana Parivarjana*) and Dietetics (*Pathya Vyavastha*).

Ayurvedic treatments rely heavily on plant materials. Sometimes, herbs are mixed with metals, minerals or other naturally occurring substances and the formulae are prepared according to specific Ayurvedic text procedures; and such preparations involve several precise treatments to detoxify and potentiate the medicines. Specific diet (*Pathya*) is prescribed along with the drugs and treatment. The diet regimen is as important as remedies since the former helps to restore the balance as much as the later.

Description on personal hygiene is sufficiently elaborated in classical literatures, which includes diet and regimen during day (*Dinacharya*), during night (*Ratricharya*), seasonal routine (*Ritucharya*), behavioural and ethical practices (*Sadvritta*). Observance of certain rules regarding suppressible and non-suppressible natural urges

also paves the way towards positive health.

Ethics related to new entity development and clinical practices, an important concept are clearly mentioned in Ayurveda. Charaka Samhita has laid down the principle that every patient has right to get remedies by qualified and competent *Bheshaka* (Physician). A non-qualified and incompetent physician may be subjected to punishments. Many examples of experiments have been described in Sushruta Samhita, since it was noted that ants were attracted to urine of diabetic patients which confirmed diabetes in the patients. Similarly, new entity was first tested on animals (Dogs, Crows, Cats, Rats, etc.) to evaluate toxicity/safety before its use in human being. The drug was considered safe if no harm was observed on the experimental animals, and then was prescribed to the very important persons and his family members. Similarly, in Sushruta Samhita there had been mentioned many surgical procedures which were first practiced on cadavers and artificial models by the scholars to acquire proficiency in surgical procedure before performing surgery independently. These are some evidences of ethics used for research and practices in Ayurveda at the ancient times.

Codes of medical ethics can be found as far back as period of Charaka Samhita (1000 B.C.). There has been several references of ethics regarding evaluation of new entity, conduct and behavior, knowledge and skill of *Bheshaka* (Physician), quality of drugs and assisting staffs. It was thought that Hippocrates (600 B.C.) was follower of Charaka which was reflected in his scriptures, and his Oath regarding medical ethics is famous worldwide. Babylon (1790 B.C.) with Hammurabi's "Code of Law", are recorded writings on medical ethics, however there were mentions of this even earlier in the ancient writings of Egyptian, Arabic and Greek scientists and philosophers.

In the west, the concept of moral priority in medical humanism was proposed by John

Gregory in the 18th century. Thomas Percival came up with the concept of bio-ethics and legislatives aspects of ethics related behavior.

As the lead agency responsible for health within the structure of United Nations, the World Health Organization (WHO) endorses the Universal Bill of Human Rights which includes Universal Declaration of Human Rights promulgated in 1948, the International Covenant of Economic, Social and Cultural Rights (1966, ratified in 1976), and the International Covenant on Civil and Political Rights (1966). These three instruments define and describe basic human rights and fundamental freedom. They form the nucleus of an interlocking set of international conventions, resolutions and declarations intent on promoting the rights and freedoms of persons through law. The Universal Declaration on Human Rights is supported and promoted by Nepal in all its activities.

The first international document on this subject is the Nuremberg Code in 1947. This was followed by series of international declarations, conventions and covenants related to ethics in health, health care and research. The most prominent of these documents are the World Medical Association (WMA), Declaration of Helsinki, the Council of International Organization of Medical Sciences (CIOMS), International Ethical Guidelines for Biomedical Research (IEGBR) Involving Human Subjects, the WHO and International Council of Harmonization (ICH) Guidelines for Good Clinical Practice (GCP).

The ethical framework for the protection of human participants in research has its origins in the ancient Charaka Samhita and Hippocratic Oath, which specified a prime duty of a physician to avoid harming the patient. However, this oath was not much respected in human experimentation and most human abuses occurred in the World War II experiments.

In 1964 at Helsinki, the WMA articulated general principles and specific guidelines on use of human subjects in medical research, known as the Helsinki Declaration. The Helsinki Declaration has been undergoing changes every few years the last one being in 2008.

In 1966, the International Covenant on Civil and Political Rights specifically stated, 'No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment'. In particular, no one shall be subjected without his consent to medical or scientific treatment. Dr. Henry Beecher's 1966 study of abuses and the discovery of human exploitation of Tuskegee study in the 1972 reinforced the call for tighter regulation of government funded human research. The U.S. National Research Act of 1974 and Belmont Report of 1979 were major efforts in shaping ethics of human experimentation. In 1996, International Conference on Harmonization published GCP, which has become the universal standard for ethical conduct of clinical trials.

Ethical Guidelines for Health Research in Ayurveda are cognizant of these declarations, code and guidelines and has followed the spirit in which they are written.

1.3 Scope of the guidelines

These guidelines serve for researchers, sponsors, manufacturers, health service providers, traders, health authorities and agencies for doing any kinds of Ayurveda research in Nepal.

1.4 Purpose of the guidelines

1.4.1 To provide the guidance for the researchers for Ayurveda research.

1.4.2 To improve quality of Ayurveda research.

1.4.3 To improvise in generating evidence on Ayurveda treatment.

Section 2: Ethical Principles

The ethical principles should be considered as an important human value. The ethical principles of the health research in Ayurveda account for the principles of respect for autonomy of an individual, beneficence, non-maleficence, justice and environment. While conducting research at a community level or hospitals involving humans in groups, all these principles are applied in a composite way. The principle of respect for the environment aims to ensure cultural respect and benefit of community members, their environment, and do not harming them, and ensuring the justice to them.

2.1 Basic ethical principles

The following are the four basic ethical principles:

(a) respect for the autonomy of an individual,

(b) beneficence and non-maleficence,

(c) justice

(d) respect for the environment

They form the basis for the ethical evaluation of Ayurveda research proposals in Nepal.

2.1.1 Respect for the autonomy of an individual (participant): The obligation to respect the dignity of participating individuals in all activities of the research is the cornerstone of the ethics. This principle is based on the foundation that an individual when informed of all aspects of the research activities can individually

decide a correct course of action for participation or rejection, and withdrawal at any time. This requires specific attention to the following.

2.1.2 An individual's right to decide what is the best for his/her which cannot be over ruled by researchers.

2.1.3 Researchers must safeguard the interests of individuals with impaired or diminished autonomy and ensure that the vulnerable people are secured against any harm, abuse or exploitation.

No research should take precedence over respect for human right, fundamental freedom and human dignity, and practices contrary to human dignity should be prohibited. The provisions of respect for autonomy of the human participants in health research in Ayurveda are implemented primarily through the instrument of "Informed Consent" process.

2.1.4 Beneficence and non-maleficence: Beneficence is the obligation to maximize possible benefits and to minimize the harms of individuals. This requires that all health research projects be preceded by careful assessment of the potential risks and burdens, in comparison to the potential benefits to the prospective research participants and their communities. This does not prevent the participation of healthy volunteers in research. However, in all cases the research should promote the health of the population represented. Non-maleficence means do no harm, and requires not to cause deliberate harm to the study participants.

2.1.5 Justice: Justice requires individuals in similar circumstances be treated alike, and the differences between persons due to circumstances be acknowledged and addressed. For example, individuals with similar health complaints should be treated equally. Further, Justice requires an equitable distribution of the burdens and benefits in research. Differences should be in such distribution are justifiable

only if they are based on morally relevant distinctions between individuals for examples, in case, where it is essential to ensure the protection of the rights and welfare of vulnerable persons. The protection of persons in vulnerable situations is important. People in such situations include those who are unable to express or protect their interest fully or partially. Such impediments lack of capacity to consent adequately, an inability to obtain alternative means of medical care and or other health care necessities. These individuals could also be juniors or subordinate members of a hierarchical group, and legally incompetent. Thus, special provision is mandatory for the protection of the rights and welfare of all the people in vulnerable situation.

2.1.6 Respect for the environment: This principle requires that research in Ayurveda should be undertaken with respect for the social, cultural, and natural environment and historical heritage of a society. Every researcher is accountable for moral engagement of protection of social, cultural and natural environment and historical heritage of communities and societies, as well as biodiversity. This responsibility includes commitments: to ensure proper and safe disposal of any hazardous waste from laboratory/clinical/field research; to safeguard the cultural, linguistic and religious heritage of communities, individuals and biodiversity; to treat the biologic and genetic heritage of the people with respect and these take outmost caution.

These four basic ethical principles have been extended into 12 general principles.

2.2 General ethical guidelines

2.2.1 Principle of essentiality: With due consideration of all the options within the existing knowledge, the use of human participants is considered to be essential for the proposed research in Ayurveda.

2.2.2 Principle of voluntariness: The right of the human participants should be respected in terms of their agreement to participate or not to participate in health research in Ayurveda at any time. Informed consent guarantees that the rights of participants are protected. An Ethical Review Board (ERB) should assess the proposed research.

2.2.3 Principle of non-exploitation: The human participants should not be exploited and discriminated. During equitable selection process in Ayurveda research, benefits and risks should be distributed fairly. Appropriate precautions should be taken to safeguard vulnerable populations to guarantee this aspect and outmost.

2.2.4 Principle of social responsibility: Ayurveda Research needs to be planned and conducted in such a way that it should not disturb social harmony in community relationships, and should avoid creation or deepening of social and historic divisions. The research outcome must benefit the society as a whole.

2.2.5 Principle of ensuring privacy and confidentiality: Researchers are required to maintain privacy of the participants. Identity and records of the participants should be kept confidential and access of such information should be limited to authorized individuals. However, privacy of certain information such as suicidal ideation, homicidal tendency, positive status of Aupasargic roga (Infectious diseases: Human Immunodeficiency Virus (HIV), Tuberculosis (TB), Leprosy, Bird Flu, Swine Flu, Sexually transmitted diseases, etc.) can be breached in consultation with the ERB and judicial bodies, if necessary, for valid scientific or legal explanations as the right to life of other individual overtakes the right to privacy of the research participants.

2.2.6 Principle of risk minimization: All the stakeholders (researchers, ERB members, regulators and sponsors) should take precaution during research process to ensure that the risks are minimized and suitable care and compensation is given if any harm happens.

2.2.7 Principle of benefit maximization: Researchers must be careful during research process in such a way that the benefits (direct or indirect) are maximized to the research participants and society.

2.2.8 Principle of professional competence: Individuals, who are capable, experienced and have the suitable qualification and training, should plan, conduct, evaluate and monitor research process in Ayurveda.

2.2.9 Principle of institutional arrangements: Institutions where the Ayurveda research is being planned and conducted must have policies for suitable research governance and take the responsibility to expedite research by creating and enabling environment through delivering essential infrastructure, human resources, funds and opportunities for training.

2.2.10 Principle of transparency and accountability: Transparency and accountability are two important elements of good governance, wherein the research plan and results arising from the research are brought into the domain of public through data base, reports and publications while protecting the privacy of the participant's right. Stakeholders (researchers, ERB members, regulators and sponsors) involved in the particular research should disclose any existing Conflict of Interest (CoI) and manage them properly. Ayurveda Research should be conducted in an unbiased, honest, justifiable and transparent way to assure accountability. Research related data including records and notes should be preserved for the specified period of time for any possible external inspection/audit and other reasons.

2.2.11 Principle of totality of responsibility: All the stakeholders involved in Ayurveda Research are accountable for their engagements and bound directly or indirectly with the ethical guidelines for research in Ayurveda/National ethical guidelines and related protocols, Standard Operating Procedure (SOP) and directive standards for their professional, social and moral responsibilities.

2.2.12 Principle of environmental protection: Researchers are accountable for ensuring environment protection and resources during research process and bound with existing guidelines and related protocols, SOP and directive standards.

All the investigating team members should take accountability and responsibility to abide and maintaining the above outlined principles while conducting the research in health or research for health involving human participants.

Section 3: Responsible Conduct of Ayurveda Research

Researchers have a significant role and responsibility to prevent scientific fraud and research misconduct. Researchers are guided by the standard ethical norm, value and relevant law. Research teams are expected to maintain high ethical standards and fundamental values of research. The Responsible Conduct of Research (RCR) has following major components: research values, norms and standard; policies and priorities that influence health research in Ayurveda; issues during research planning and conduction including standardization of tools and calibration of instruments to be used in research; professional, legal and moral responsibilities of researchers, sponsors and institutions; research monitoring, reviewing and reporting; authorships in research publications; handling research misconduct, clinical trials registration, and collaboration & networking in research.

Ayurveda research and academic institutions must establish a research office within their institution to facilitate and manage research grants, and all aspects of RCR. Health researches to be conducted by such institution must take prior ethical approval from ERB of NARTC of from Institutional Review Committee (IRC) existing in their own institutions. Such institution must follow guidelines developed by NARTC and prevailing law of the country. Such institutions should develop SOPs to address all aspect of RCR.

3.1 Research values, norms and standard

Research is guided by research values, norms and highest ethical standard which include objectivity, accountability, accuracy, social justice, efficiency, transparency, personal integrity, best research practices, and relevant policies related to RCR. For

maintaining RCR, following points must be taken into consideration by the investigators:

3.1.1 Accountability for people/society/community

3.1.2 Mentoring of Ayurveda researchers

3.1.3 Contemporary ethical issues for conduction of health research must be tackled

3.1.4 Sensitivity to Nepali socio-cultural/religion/caste/ethnicity and their values and norms in Ayurveda research

3.2 Policies and priorities that Influences Ayurveda research

Ayurveda research must be guided by relevant health and related policies and priorities adopted by the country. Researcher must protect his/her study participants, and research institution should develop SOPs based on national guidelines published by NARTC and relevant policies for the protection of human participants. For animal research, researchers must follow all the existing policies and guidelines for the care and use of animals in Ayurveda research.

3.3 Specific issues during research planning and conduction

CoI may occur while designing the study, selection of participants, interpretation of data, ethical review of research and research publication. Hence, there is a need to develop and follow policies and procedures to identify, mitigate and manage such CoI from different levels such as researchers, reviewers, institutions and ethics committees.

3.4 Identifying, mitigating and managing CoI

3.4.1 At the level of researchers*:* Researchers must declare CoI (financial and non-financial) during research process and also ensure investigators' commitment, time and devotion.

3.4.2 At the level of reviewers: Reviewers should declare CoI during review process if any of his/her close friends, family members and/or students has submitted the research proposals for obtaining research grants and approval. Reviewers should declare CoI if they are directly or indirectly involved in the research study.

3.4.3 At the level of research institutions*:* Institution must declare CoI during research process and develop SOP to mitigate CoI issues if any. Such issues should be communicated in a transparent way.

3.4.4 At the level of ERB*:* ERB members must declare their CoI (if any) and take appropriate actions to recuse themselves from the review and decision-making process on the protocol(s) related to their CoI; and make suitable advices for its execution. ERB must evaluate the study in light of any disclosed CoI and ensure that an appropriate action has been taken to mitigate this.

3.5 Data acquisition, management, sharing and ownership

Researchers should be sensitive to research participants and their related environment and use best practices during data collection process. Investigators should be responsible for knowing when and from where the permission is needed to collect the data. Data collectors must have suitable qualification and training for collecting reliable and valid data.

3.5.1 Collected data should be entered and analyzed in appropriate data management software and findings should be shared to right people at right places. Data should be archived in proper place.

3.5.2 Data ownership matters, publication rights, and accountability should cautiously be worked out well before data collection and investigators should ensure such clarity. Memorandum of Understanding (MoU), if needed, should be made between investigators and institutions or sponsors in advance.

3.5.3 Proper attention should be given while developing the protocol, its tools and SOPs. All the research results should accurately be recorded, interpreted and reported. Research must be conducted by using suitable method to provide reliable data. Implementation of poorly designed research study should be avoided as far as possible.

3.5.4 For biological samples, researchers should maintain the ownership of such sample and it should be mentioned in the informed consent document.

3.5.5 Institutes executing the research must protect the data, and biological samples (if any).

Data protection and archiving is an important and it may be required at a later stage to confirm research findings, establish priority, or be validated by other researchers. Liable data handling starts with proper storage and protection from damage, loss or theft. Appropriate care should be made to reduce the risk of damage, loss or theft, fire, flood and other disastrous events. Data files should properly be archived and these must be saved and outmost in a secure place including back-up system. Data governance mechanism should be in place.

Data for the following study types cannot be collected without having prior permission from the ERB:

- Human participants in Ayurveda research
- Animals use in Ayurveda research

- Biological specimen collection
- Use of data sets from the bio-samples stored in the Bio-bank for future research
- Data from hospital/clinic/medical/police records, some institutions/library, databases and archives
- Photographs, recorded messages and notes
- Other copyrighted or patented processes or materials

Data sharing plan (when, and with whom) should be mentioned in research proposal. After completing of the study, it is expected that the final data sets might have freely been available for other researchers for cross-check and future research. Data can be placed in a public domain must be in an anonymized form unless prior permission.

3.6 Professional, legal and moral responsibilities of researchers, sponsors and institutions

3.6.1 Study team that conduct the research, sponsor that funds the research and institution where the research is conducted, should take respective professional, legal and moral responsibility to follow all the principles, guidelines and directives of the ERB.

3.6.2 Researchers from collaborating sites should adequately be represented throughout the study period including from proposal developing stage. Same study protocol and SOPs should be followed in each site unless prior permission.

3.6.3 Sponsor should be responsible for unbiased contract negotiation during collaborative research partnership for benefit sharing and avoid unauthorized use of bio-samples, data and human resources.

3.6.4 Sponsor/lead institution should offer some opportunities for capacity building.

Obligations/duties of researcher

- Identify the vulnerability of the human participants and ensure their protection.
- Select the participants based on inclusion and exclusion criteria of the study as specified in the protocol.
- Researchers should not coerce the research participants.
- Mechanism of early identification and prevent misconduct of research.
- CoI issues must be declared.
- Follow the SOPs.
- Ensure a balanced risk-benefit ratio.
- Ensure competency of the prospective research participants to provide informed consent.
- When a prospective participant lacks the capacity to consent, take proxy informed consent from Legally Authorized Representative (LAR).
- Respect disagreement from the study participant.
- Seek permission from relevant authorities (admitted patients in the hospital, students in the school, orphans in the orphanage, geriatric population in old age home, tribal communities, etc.) if required.
- Follow existing relevant guidelines/regulations during research process.
- Obtain approval if any changes are required in the original approved protocol.
- Inform to ERB if any miss-happening/adverse events (if relevant) occur during research implementation process.

Obligations/duties of sponsor

- Justify the inclusion of vulnerable groups in the proposal and make provisions for safeguarding them.
- Justification for excluding some specific participants (if any) who meet the inclusion criteria.
- Facilitate monitoring and guarantee that procedures are in place for Quality Assurance (QA) and Quality Control (QC).
- Ensure that research participants and study team are well protected especially when the study is on sensitive topics.
- Select appropriate investigator/s, ensure availability of study site/s (according to research protocol), and assure relevant qualification of study team to conduct the study.
- Develop, maintain, modify and ensure the availability of research support systems and tools.
- No undue influence on research design, data collection, data analysis and publication of research findings.

Responsibility of researchers

- Submit the proposal in the prescribed format of ERB.
- Use ERB approved version of the questionnaires and consent form including its Nepali translation or in local language of the participants.
- Communicate essential information adequately for informed consent in an understandable language by prospective research participants.

- Use appropriate method in case of differently abled prospective research participants to enhance the participant's understanding (Braille for visually impaired participant).
- Provide an opportunity to ask questions related to the study and also provide enough time to come for a decision after participants' discussion with their family members and friends.
- Should not influence or threaten or pressurize and must not provide unjustifiable assurances to a prospective participant.
- Ensure that the participant has understood all aspects of the research and that the consent is given voluntarily. If prospective participant and/or the LAR are illiterate, a witness who is not connected to the study (impartial witness) should be present throughout the consent process.
- Apply a test of understanding tool whenever possible for sensitive studies. The test may be repeated until the prospective research participant has actually understood the contents of the research.
- When a prospective participant is ready to participate but not willing to sign or give a thumb impression or cannot do so, then verbal/oral consent may be taken in the presence of an impartial witness who should sign and date the consent document, but this has to receive prior approval from ERB. This whole process can be documented through video recording process, wherein the participant, the investigator, and the impartial witness should have to be seen and voice should clearly be heard in the recorded frame.

Note: *Verbal/oral consent should only be taken in exceptional conditions and for precise, reasonable explanations, only with ERB/IRC approval*

- Take fresh informed consent or re-consent of each participant.

- Assure prospective participants that their decision whether or not to participate in the study will not affect their rights, or any other benefits to which they are entitled.
- Reimburse participant's travel and incidental expenses occurred while participating in the study, but this has to receive prior approval from ERB/IRC.
- Ensure free treatment for research related injury and if required, provide payment of compensation as per recommendation of the relevant authority.
- Ensure that the participants can continue to access regular treatment and care even after their withdrawal from the study.

3.7. Research reporting

3.7.1. A copy of completed research report should be submitted to NARTC.

3.7.2. Researchers should acknowledge all the contributors of the research study in the report.

3.7.3. Any changes/modification in the protocol should be reported IRC/ERB.

3.7.4. Mid-term reporting must be submitted to IRC/ERB.

3.7.5. Investigators may provide research based data in the public domain after necessary approval from the NARTC or relevant authority.

3.8 Authorships in research publications

3.8.1 Research institution should follow the authorship policies and guidelines of International Committee of Medical Journal Editors (ICMJE).

3.8.2 The authorship should be reflected at the time of beginning of the study and should not be accepted the gifted and 'ghost' authors.

3.8.3 The principal author should do the most of the research work related to the manuscript submitted for the publication. For academic thesis research, the student should be candidate as the principal author. For fulfillment criteria of authorship, all efforts should be made to provide the candidate an opportunity for authorship based on guideline of ICMJE.

Criteria for authorship in research publication according to ICMJE

- Substantial contributions to the idea or the work design, or the acquisition, analysis, or interpretation of finding for the work.
- Drafting the work or modifying it for key intellectual content.
- Final approval of the version to be published.
- Authors must avoid plagiarism.
- Agreement to be responsible for all phase of the work and confirming that questions related to the correctness are properly examined and undertaken.
- The authors should be signed in Authorship consent letter.

3.9 Handling research misconduct

Research misconduct may occur due to fabrication, distortion and plagiarism of data.

3.9.1 IRC/ERB must examine all claims of misconduct as present or future participants' career may be jeopardized, if evidences are not presented timely and precisely. Such investigation must be done timely and fairly manner and its findings should be made public after completing the investigation.

3.9.2 NARTC addresses research misconduct in line with the prevailing laws of the country.

3.10 Clinical trials registration

All clinical trials involving human participants including any interventions/trial such as vaccines, drugs, herbal products, complementary medicine, device, surgical/para-surgical procedures and public health intervention using clinical procedures related to Ayurveda should be registered in the accredited clinical trial registry. Researcher should provide its registration number to the IRC/ERB of NARTC during submission of the clinical trial proposal for ethical approval.

3.11 Collaboration and networking in research

Collaboration and networking could be done with colleagues / experts / sponsor / institution to conduct individual research. This could be inter/intra departmental/ institutional or provincial/national/international, and also multi-center involving public and or private research institutions and agencies.

The main issues related to collaborations concern sharing tools & techniques, representation of sample, follow same SOP, ownership of materials and data, Intellectual Property Rights (IPR), joint publication, handling research data, managing CoI, commercializing study results, etc. Relevant agreements related to these issues should be mentioned in the MoU, and IRC/ERB needs to review and approve the MoU.

Investigators must be aware of all above mentioned aspects including provincial, national and international requirements for research collaboration and its necessary approval and agreement processes.

Researcher should be cautious enough to judge whether such collaboration create the impression of exploitation by other countries experimenting on Nepalese population

or not. Researcher needs to play a smart role in such aspect including IPR and equitable sharing of research benefits.

Collaboration with international agencies (public or private) may include either execution of various components of the research or even a single component like laboratory testing. Before the sponsor agency/province/country initiates collaboration, relevant regulatory requirements including ethical guidelines to be followed.

Externally sponsored research

The following conditions must be considered before externally sponsored research can take place in Nepal;

- The research should be based on needs and priorities of the Nation as well as being sensitive to the existing socio-environmental contexts including socio-cultural, religious and social norms and value.
- The research protocol should be approved from the sponsor country.
- The sponsor should consider means in which the research capacity of Nepal can be strengthened and other means of appropriately compensating the community.
- The research process should be transparent and be of the highest ethical standard.
- External sponsors should provide insurance/compensation to research participants as well as study team members in health research that involves more than minimal risks.
- If it is necessary to transfer biological specimens abroad, a MoU has to be signed by the sponsor/collaborating institute and researcher/research implementing institute defining clearly the purpose for the bio-sample transfer, its justification, Material Transfer Agreement (MTA), ownership of IPR, and provisions for privacy protection. The transferring of biological samples based on existing national guidelines should be followed.

- The research proposal has to be approved by ERB.

Inter-institutional research arrangements

The collaborative research activity should be carried out only after making required institutional arrangements to conduct the research. Such institutional arrangements should include involvement of competent researchers and support staff, organizational set up conducive to research, SOP, ensuring safety to the research participants and confidentiality of data and disseminating the research findings. Institutional arrangements for preservation and archiving of research materials, data and reports must be kept in secured place. Sponsor/institution/researchers should ensure whether such arrangements for the research study are in place or not. The collaborative institutions should follow the same standard of the protocol and procedures. The research conducted in any institution should obtain no objection letter from the institution.

Special considerations in collaborative research

- There should be good communication among collaborative partners. In case of any conflict or unfavorable events or any change made between the partners, these should be notified to the ERB/IRC, and decision will be made as per existing policies/ guidelines / relevant laws.
- The context, magnitude and probability of all possible harm resulting from involving in the study should be mentioned in the collaborative research proposal.
- The possible harms and benefits should equally be distributed amongst the research participants/institutions to be recruited by all collaborative centers.
- All collaborative research involving human participants should have access to the best standard care and treatments available in Nepal.

- For International collaborative research, there should be additional one Nepalese Principal Investigator (PI) relevant to the study subject, and Nepalese PI must be responsible for proposal submission and its related communication and correspondences.

International collaborative partners should strengthen Nepalese capacity in terms of developing knowledge, testing of specimens, providing appropriate technical support and capacity building trainings.

SECTION 4: Ethical Review Board

The investigator should seek the opinion of an ERB regarding suitability of the protocol, methods and documents to be used in recruitment of participants and obtaining their Informed Consent including adequacy of the information being provided to the participants. The ERB is entrusted not only with the initial review of the proposed research protocols prior to initiation of the projects but also have a continuing responsibility of regular monitoring for the compliance of the Ethics of the approved programs till the same are completed. Such an ongoing review is in accordance with the "Ethical guidelines for Research in Ayurveda" 2020, as amended from time to time by NARTC, Kathmandu, Nepal.

4.1 Basic Responsibilities

The basic responsibility of the ERB is to ensure a competent review of all ethical aspects of the project proposals received and execute the same free from any bias and influence that could affect their objectivity.

4.2 Composition of ERB

a.ERB should be multidisciplinary and multi-sectorial in composition. Independence, attendance and competence are the three hallmarks of it.

b.The number of persons in the board to be kept fairly small (7 members). It is generally accepted that above fifty percentages is required to compose a quorum. There is no specific recommendation for a widely acceptable maximum number of persons but it should be kept in mind that too large a committee will make it difficult in reaching consensus opinion. If required, experts can be invited temporarily to review any research proposal.

c.The Chairperson of the board should preferably be from outside the Institution and not head of the same Institution to maintain the independence of the board. The Member Secretary who generally belongs to the same Institution should conduct the functioning of the board. Other members should be a combination of medical/non-medical, scientific and non-scientific persons including lay person to reflect the differed viewpoints. The composition may be as follows:-

1.Chairperson- Ayurveda academician with research background

2.Member secretary

3.Clinicians -1-2 Ayurvedic clinicians/allopathic clinician from different Institutions

4.Basic medical scientists- 1-2 basic medical scientists (one pharmacologist and one preferably from Dravyaguna / Rasa shastra / Bhaishajya Kalpana).

5.Legal Expert- One Legal expert

6.One Social Scientist / philosopher / ethicist /representative of Non-Governmental Voluntary Agency

7.Statiscian

4.3 Functions and duties of ERB

4.3.1 To support and coordinate with affiliated IRCs.

4.3.2 To review research proposals according to the Ethical Guidelines for Health Research in Ayurveda with a view to approve, amend or reject the proposal.

4.3.3 To supervise or monitor Ayurveda research projects, approved by ERB.

4.3.4 To resolve ethical issues arising out of reviewing, approving, supervising, monitoring and disseminating the research findings.

4.3.5 To review, implement, supervise, monitor research and disseminate findings of research.

4.4 Membership of ERB

4.4.1 Development Committee of NARTC will appoint the members and Chairperson of the ERB. In case of absence of above mentioned committee, Executive director will appoint the chairperson and members of the ERB.

4.4.2 Executive Director of NARTC will prepare a list of potential candidates for the ERB membership and submit these names to the Chairperson of NARTC who in consultation with Development Committee of NARTC will make the appointments.

4.4.3 While making the appointment, at least 33% of the members of the existing ERB will be retained in order to ensure continuity of experience.

4.4.4 Executive Director of NARTC will act as the member secretary of the ERB.

4.5 Term of appointment to the ERB members

4.5.1 The ERB member will be appointed for the duration of a three-year term.

4.5.2 Policy for renewal: in order to maintain continuity of experience at least 33 % of the member will retained in a new ERB.

4.5.3 Disqualification procedure: A member who was found upon an investigation conducted by ERB acting contrary to the interests of NARTC, breaching the conditions of the appointment will be disqualified from continuing in the ERB. This disqualification would be made by the Development Committee of NARTC. Legal prosecution and mentally ill will also lead to disqualification.

4.5.4 Resignation: a member who does not want to continue in on the ERB can submit his or her resignation to Executive director of NARTC.

4.6 Conditions of appointment to the ERB Members

4.6.1 Member accepting to serve on the ERB should agree that his or her name, professional qualification, experience and affiliations would be publicized through the reports of NARTC.

4.6.2 Member accepting to serve in the ERB should agree that the remunerations paid to him or her in course of ERB work will be recorded and will be made available to the public on request.

4.6.3 Member accepting to serve in the ERB will have to sign a confidentiality agreement regarding meeting deliberations, applications information on research participants and related matters.

4.6.4 All administrative staff working for ERB will also have to sign a confidentiality agreement regarding meeting deliberations, applications information on research participants and related matters.

4.7 Office of the ERB

4.7.1 NARTC will assign space within the premises of NARTC for the exclusive use by Chairperson of the ERB and administrative staff.

4.7.2 ERB of NARTC will have its own phone, fax, photocopy cupboard and administrative staff.

4.8 Meetings

4.8.1 Member Secretary of the ERB will prepare the agenda for the meeting in consultation with the Chairperson of ERB. The Member Secretary will also keep minutes of the meeting and notify decisions to the researcher. The member Secretary will be assisted in his or her tasks by an administrative staffs.

4.8.2 ERB will prepare a regular annual report which will be published after its approval by ERB of NARTC.

4.9 Quorum requirements for ERB

4.9.1 ERB will have 7 members.

4.9.2 At least 4 members must be present to compose a quorum.

4.9.3 At least one member present should have expertise in other than the subject under discussion. Preferably, a member from outside of the Ayurveda since background must be present.

4.10 Independent consultant(s) of ERB

4.10.1 Ethical Review Board will prepare a list of independent consultants to provide expert opinion on proposed research proposals.

4.10.2 Independent consultants who agree to help the ERB will have to sign a confidentiality agreement regarding their assignment, meeting deliberations, applications, information on research participants and related matters.

4.10.3 Independent consultants will be paid remuneration as per NARTC regulations.

4.11 Ongoing education of ERB members

4.11.1 All new ERB members will be provided with orientation training.

4.11.2 ERB will conduct regular training programs for ERB members at least two times in a year. Such training programs will provide opportunities for hands on

experience of reviewing the research proposal as well as problems faced while reviewing, implementing or disseminating of research.

4.11.3 ERB will forward request from ERB members for participation in national, regional or international training programs on ethics in Ayurveda Research.

4.12 Submitting the application

Individuals or institutions desire to conduct Research in Ayurveda throughout in Nepal are required to submit their Research proposal to ERB of NARTC.

4.13 Application submission

The PI and/or the one responsible for the Research will submit the Research proposal for review.

4.14 Application requirement

4.14.1 Application: Application should be addressing to the Member Secretary of ERB.

4.14.2 Format for Application: Application should be submitted format provided by NARTC. The prescribed format can accessed from the NARTC office or website of NARTC.

4.14.3 Language of Applications: All Applications should be submitted in English/Nepali language.

4.14.4 Application should include one hard copy and an electronic copy of the proposal.

4.14.5 Only those applications fulfilling the requirements will be accepted for review. Deficits in the application shall be informed to the applicants within a week of submission. Incomplete applications will have to be resubmitted.

4.14.6 A receipt of the accepted application will be provided to the researchers.

4.14.7 Application Fee: Applications should be submitted along with processing fee as per NARTC rule/decision.

4.14.8 Additional documents or changes: ERB can request the applicant for supplementary documents/or changes to the proposal during the review which will be communicated to the applicant and the application will be considered in the subsequent meeting after those changes are made by the researcher.

4.14.9 Amendments: If any amendments are made in the proposal already submitted and approved, the researcher must submit in writing the changes made with reasoning. The proposal will be reviewed again in the ERB, considering the amendments during the re-approval process.

4.14.10 Informed consent: Application should include the Informed Consent Form as a separate copy, which is to be used while undertaking the research. In addition, this can include a translation copy, in a local language if that is applicable.

4.15 Documentation requirement for the application

All the documents that are required by the ERB for a process of review and approval should be submitted along with the application. If any additional documents are required during the review process, the researcher will be notified by ERB secretariat.

4.15.1 The application form should be submitted with the signature and date of submission using the NARTC format.

4.15.2 Application must include the most current version of the curriculum vitae of the Principal Investigator and co-investigator with special mention of academic qualification and research experiences with passport size photos.

4.15.3 Application must include protocol of the proposed research project in the provided format together with the supporting documents. (A copy of research tools, questionnaires, etc.).

4.15.4 A copy of informed consent form should be included in the application. This should include a detailed description of the process of giving the information to the research participant and its content, process of obtaining the consent, the person responsible for obtaining the informed consent and documentation of the signature of the researcher/research participant and/witness if applicable.

4.15.5 Any compensation is given to the research participant/s should be clearly mentioned (e.g. any transportation costs, food, free health care or insurance coverage etc. that is borne by the researcher).

4.15.6 In case of clinical trials, description about the study design, the trial phase, and a detail description of the safety of the product or procedures must be mentioned. It should include the Ayurvedic pharmacology, pharmaceutical, and toxicological data available and also include the protocol and investigators brochure of the trial.

4.15.7 A signed statement by researcher stating that he or she will abide by the ethical principles of research.

4.15.8 Information about any previous submission of this application to ERB and the result of such submission in the past will have to be provided along with the application.

4.15.9 A declaration of the conflict of interest, if applicable, should be mentioned in the application.

4.16 Ethical review process

The ERB will review the entire submitted Research proposal in a timely manner and in accordance with the set review process.

4.16.1 Meeting of the ERB: The meetings of the ERB will be held on a regularly scheduled dates that will be announced in advance. The Member Secretary of ERB with the permission of the Chairperson of the ERB will call the meeting. The following are considered as applicable for the ERB meeting:

4.16.1.1 The meeting of ERB will be planned in accordance with the workloads and number of proposals received for review. Normally, ERB will meet once a month.

4.16.1.2 ERB members will be informed about the meeting at least 24 hours prior to the scheduled date.

4.16.1.3 If the ERB felt necessary, the applicant researcher or sponsor of the research can be invited to present the proposal. Similarly, if necessary, experts can also be invited to the meeting for expert opinion about the research.

4.16.1.4 Minutes will be kept of all decisions and procedures of the meeting.

4.16.1.5 All the members and invitees present in the meeting should sign the minutes to indicate their presence.

4.16.2 Elements of the review process technical review by the reviewers: Once the application is submitted and screened for completeness of documents, technical review of the proposal is done by the internal reviewers for the scientific and technical

contents. The application received after internal review is then subjected for review by the external reviewers, if necessary.

4.16.3 Ethical review: Those applications that qualify are then submitted to the Member-Secretary of the ERB and then discussed in ERB meeting for ethical review.

4.16.4 Scientific design of research proposal and conduct of research in Ayurveda

4.16.4.1 The appropriateness of the study design in relation to the objectives of the study**.**

4.16.4.2 Statistical methods**:** sampling method, sample size and analysis of data

4.16.4.3 Justification of predictable risks and inconveniencies against the anticipated benefits for the research participants and community by the proposed study

4.16.4.4 Justification of the use of control arm (if relevant for the study)

4.16.4.5 Criteria for prematurely withdrawing research participants

4.16.4.6 Criteria for suspending or terminating the research

4.16.4.7 Provisions for Data Safety Monitoring Board (DSMB)

4.16.4.8 Plan for dissemination or publication of research results

4.16.4.9 Infrastructure and other facilities in the institutions conducting the research

4.16.4.10 Sustainability of researcher's qualification and experiences for the proposed research

4.16.4.11 Description of the population from which the research participants will be drawn

4.16.4.12 Inclusion criteria for the research participants

4.16.4.13 Exclusion criteria for the research participants

4.16.4.14 Measures to ensure the confidentiality of the research participants

4.16.4.15 Description about who has access to data and biological samples

4.16.4.16 The compensation provide to the participants in case of adverse reaction and or adverse events

4.16.4.17 Description of the process of reporting any adverse drug reaction and/or adverse event

4.16.4.18 Description about the provision of availability of the research product for the participants after completion of the research project

4.17 Informed consent process

4.17.1 A full description of the process for obtaining informed consent including the description about who is responsible for obtaining the informed consent

4.17.2 Process of communication with the research participants about the objectives, method, risks and benefit of the research

4.17.3 Description about obtaining consent from the vulnerable research participant (e.g. children, elderly, disabled, prison population, people in uniform services, etc.)

4.17.4 Description about the provision for the participants to queries and complaints during the course of research

4.18 Community considerations

4.18.1 The relevance of the research for the community from where research participants are drawn.

4.18.2 The process taken for the consultation and communication with the community

4.18.3 Description about how the research result will be available for the community

4.19 Expedited review

In the following situations, the Ethical Review Board will allow the Chairperson or Member Secretary to expedite the review of the proposal.

4.19.1 If the research is non-interventional, based on secondary data, leading to thesis or has received approval from the Institutional Review Committee/Board

4.19.2 If the research is carried out under the circumstances of outbreak, disaster and other emergency conditions

4.19.3 If the proposal is found technically and scientifically sound after reviewing by internal reviewer of NARTC

4.19.4 The Member Secretary should inform to NARTC Chairperson and in the ERB meeting about the proposals expedited

4.20 Decision making

The ERB will consider the following while making decision about the research proposal

4.20.1 The ERB will make the decision only if the meeting has met required quorum

4.20.2 Normally the decision will be taken by consensus (if consensus is not possible then a vote will be taken).

4.20.3 The ERB member should withdraw from the decision process when conflict of interest arises; the member should declare the conflict of interest

4.20.4 The ERB may approve the proposal conditionally with specific suggestion to the researcher

4.21 Communicating a decision

On behalf of the ERB, the Member Secretary will communicate his decision to the applicant in writing within one week after the meeting. The communication of the decision will include, but is not limited to the following information:

4.21.1 The exact title of the research proposal reviewed;

4.21.2 The clear identification of the protocol of the proposed Research or amendment date and version number (if applicable) on which the decision is based;

4.21.3 The names and (where possible) specific identification number (version number/dates) of the documents reviewed, including the potential research participant information sheet/material and informed consent form;

4.21.4 The name and title of the applicant;

4.21.5 The name of the research site(s);

4.21.6 The date and place of the decision;

4.21.7 Any advice by the ERB;

4.21.8 In the case of a conditional decision, any requirements by the ERB, including suggestions for revision and the procedure for having the application re-reviewed;

4.21.9 In case of a positive decision the following is required:

4.21.10 A statement of the responsibilities of the applicant;

4.21.11 Confirmation of the acceptance of any requirements imposed by the ERB;

4.21.12 Deadlines for the submission of the progress report(s);

4.21.13 The need to notify the ERB in case of protocol amendments (other than amendments involving only logistical or administrative aspects of the study);

4.21.14 The need to identify the ERB in the case of amendments to the recruitment, the potential research participant information, or the informed consent form;

4.21.15 The need to report serious and unexpected adverse event related to the conduct of the study;

4.21.16 The need to report unforeseen circumstances, the termination of the study, or significant decisions by other Ethical Committees;

4.21.17 The information of ERB expects to receive in order to perform ongoing review and deadlines for the submission of final report;

4.21.18 The schedule/plan of ongoing monitoring by the ERB;

4.21.19 In case of a negative decision, clearly stated reason(s) for the negative decision; and

4.21.20 Signature (dated) of the Member Secretary (or other Authorized person) of the ERB.

4.22 Follow up of the ERB

ERB will establish a follow-up procedure for following the progress of all studies for which a positive decision has been reached, from the time the decision was taken until the termination of the research.

4.22.1 The follow-up review intervals will be determined by the nature and the events of research projects, through each protocol should undergo a follow-up review once at a year.

4.22.2 The following instances or events require the follow-up review of a study

4.22.2.1 Any protocol amendment

4.22.2.2 Serious and unexpected adverse event related to the conduct of the study, pre-study product and the response taken by investigators, sponsors and regulatory agencies

4.22.2.3 Any event or new information that may affect the benefit/risk ratio of the study

4.22.2.4 A decision of a follow-up review will be issued and communicate to the applicant, indicating a modification, suspension or termination of the ERB original decision or confirmation that the decision is still valid.

4.22.2.5 In case of the premature suspension/termination of a study, the applicant should notify the ERB with the reasons for suspension/termination; a summary of result obtained in a study. Prematurely suspended/terminated should be submitted to the ERB.

4.22.2.6 The applicant will inform the ERB at the time of the completion of the study.

4.22.2.7 The applicant will submit to the ERB a copy of the final summary or final report of a study (both hard and soft copy).

4.22.2.8 The ERB can issue an approval letter for publication as per need.

4.23 Documentation and archiving

All documentation and communication of ERB will be dated, filed and archived according to written procedures. A statement is required defining the access and retrieval procedures (including authorized persons) for the various documents, files and archives. The document will be archived for a minimum period of 5 years following the completion of a study.

Documents that should be field and archived include:

- The Guidelines, written in the ERB , and regular (annual) reports
- The curriculum vitae all the ERB members

- A record of all income and expenses of the ERB, including allowances and reimbursements made to the secretariat and ERB members
- The published guidelines for submission established by the ERB
- The agenda of the ERB meetings
- The minutes of the ERB meetings
- All materials submitted by an applicant
- The correspondence by ERB members with applicants or concerned parties regarding application, decision, and follow-up.
- A copy of the decision and any advice or requirements sent to an applicant
- All written documentation received during the follow-up
- The notification of the completion, premature suspension, or premature termination of a study.
- The final summary or final report of the study should be submitted to ERB within the allocated time period of the study.

Section 5: Informed Consent Process

The information should be given to the participants and / or their legal representatives or guardians in a language and at a level of complexity that is understandable to the participant(s) in both written and oral form, whenever possible. The Informed Consent Documents (ICD) has two parts - (i) Patient/Participant Information Sheet (PIS) and (ii) the Informed Consent Form (ICF). Information on known facts about the research, which has relevance to participation, is included in the PIS. This is followed by the ICF in which the participant acknowledges that she/he has understood the information given in the PIS and is volunteering to be included in that research.

5.1 Patient /Participant information sheet (PIS)

Before requesting an individual's consent to participate in research, the investigator must provide the individual with the following information in the language he or she is able to understand which should not only be scientifically accurate but should also be sensitive to their social and cultural context:

- The aims and methods of the research;
- The expected duration of the participant participation;
- The benefits that might reasonably be expected as an outcome of research to the participant or to others;
- Any alternative procedures or courses of treatment that might be as advantageous to the participant as the procedure or treatment to which she/he is being subjected;

• Any foreseeable risk or discomfort to the participant resulting from participation in the study;

• The extent to which confidentiality of records could be able to safeguard, confidentiality and the anticipated consequences of breach of confidentiality;

• Free treatment for research related injury by the investigator / institution;

• Compensation of participants for disability or death resulting from such injury;

• Freedom of individual/family to participate and to withdraw from research any time without penalty or loss of benefits which the participant would otherwise be entitled to;

• The identity of the research teams and contact persons with address and phone numbers;

• Foreseeable extent of information on possible current and future uses of the biological material and of the data to be generated from the research and if the material is likely to be used for secondary purposes or would be shared with others, clear mention of the same;

• Risk of discovery of biologically sensitive information;

• Publication, if any, including photographs and pedigree charts;

• Information on standard of care (including modem medicine);

The quality of the consent of certain social groups requires careful consideration as their agreement to volunteer may be unduly influenced by the Investigator.

5.2 Informed consent form

5.2.1 Informed consent of participant: Prior to the beginning of the Study the Investigator(s) must obtain the Ethics Committee's approval for the written informed consent form and all information being provided to the Participants and/or their legal

representatives or guardians or an impartial witness in case participant /LAR is illiterate. None of the oral and written information concerning the Study, including the written informed consent form, should contain any language that causes the Participant(s) or their legal representatives or guardians to waive or to appear to waive their legal rights, or that releases or appears to release the Investigator, the Institution, the Sponsor or their representatives from their liabilities for any negligence.

This requirement is based on the principle that competent individuals are entitled to choose freely whether or not to participate or continue to participate in the research. Informed consent is a continuous process involving three main components - providing relevant information to potential participants, ensuring competence of the individual, ensuring the information is easily comprehended by the participants and assuring voluntariness of participation.

Informed voluntary consent protects the individual's freedom of choice and respects the individual's autonomy.

Requisites

The participant must have the capacity to understand the proposed research, be able to make an informed decision on whether or not to be enrolled and convey her/his decision to the researcher in order to give consent.

The consent should be given voluntarily and not be obtained under duress or coercion of any sort or by offering any undue inducements.

In the case of an individual who is not capable of giving voluntary informed consent, the consent of LAR must be obtained.

It is necessary to maintain privacy and confidentiality of participants at all stages

5.2.2 Informed consent in non-therapeutic study: In case of a Non-Therapeutic study the consent must always be given by the participant. Non Therapeutic Studies

may be conducted in participants with consent of a legal representative or guardian provided all of the following conditions are fulfilled:

- The objective of the study cannot be met by means of a trial in Participants) who can personally give the informed consent
- The foreseeable risks to the Participant(s) are low
- Ethics Committee's written approval is expressly sought on the inclusion of such Participant(s)

5.2.3 Community consent: In certain populations, the community plays an important role in the consent process. Some participants may not participate in the research unless the community's consent is available. There may be situations when individual consent cannot be obtained as it will change the behaviour of the individual. In such situations community consent is required. When permission is obtained from an organization that represents the community, the quorum required for such a committee must be met. For example, in a village, Panchayat the number of members ordinarily required to conduct a meeting must be present while giving consent. Individual consent is important and required even if the community gives permission.

5.2.4 Documentation of informed consent process:

- Each prospective participant should sign the informed consent form after going through the informed consent process of receiving information, understanding it and voluntarily agreeing to participate in the research.
- In case the participant is incompetent (medically or legally) to give consent, the LAR's consent must be documented.
- The process of consent for an illiterate participant/LAR should be witnessed by an impartial literate witness who is not a relative of the participant and is in no way

connected to the conduct of research, such as other patients in the ward who are not in the study, staff from the social service department and counsellors. The witness should be a literate person who can read the participant information sheet and consent form and understand the language of the participant.

- If the participant cannot sign then a thumb impression must be obtained.
- The researcher who administers the consent must also sign and date the consent form.
- In the case of institutionalized individuals, in addition to individual/LAR consent, permission for conducting the research should be obtained from the head of that institution.
- In some types of research, the partner/spouse may be required to give additional consent.
- In genetic research, other member of a family may become involved as secondary participants if their details are recorded as a part of the family history. If information about the secondary participants is identifiable then their informed consent will also be required.
- Online consent may be obtained, for example, in research involving sensitive data such as unsafe sex, high risk behaviour, use of contraceptives (condoms, oral pills), or emergency contraceptive pills among unmarried females in India etc. Investigators must ensure that privacy of the participant and confidentiality of related data is maintained.

5.2.5 Procedures after the consent process

• After consent is obtained, the participant should be given a copy of the PIS and signed ICF unless the participant is unwilling to take these documents. Such reluctance should be recorded.

• The researcher has an obligation to convey details of how confidentiality will be maintained to the participant.

• The original PIS and ICF should be archived as per the requirements given in the guidelines and regulations.

5.3 Waiver of consent

The researcher can apply to the IRC for a waiver of consent if the research involves less than minimal risk to participants and the waiver will not adversely affect the rights and welfare of the participants.

Conditions for granting waiver of consent

The IRC may grant consent waiver in the following situations:

• Research cannot practically be carried out without the waiver and the waiver is scientifically justified;

• Retrospective studies, where the participants are de-identified or cannot be contacted;

• Research on anonymized biological samples/data;

• Certain types of public health studies/surveillance programmes/programme evaluation studies;

• Research on data available in the public domain; or

• Research during humanitarian emergencies and disasters, when the participant may not be in a position to give consent. Attempt should be made to obtain the participant's consent at the earliest.

Section-6: Ayurveda Research and Methodology

Ayurveda has been long history of medical practice in the societies since time immemorial and well documented in their classical literature. For those standard Ayurveda treatment modalities that have been in practice since antiquity, all the pre-clinical steps may not be required and only steps of evaluating efficacy of the drugs can be done. For those treatment modalities which have not been in practice since long time in traditional or folklore medicines, or in cases of new drugs, or in those with unavailability of sufficient data, all the stages of pre-clinical and clinical research need to be followed. For those Ayurveda treatment modalities which have well-documented history of long use, the following procedures for conducting research and evaluating safety and efficacy may be followed.

6.1 Literature review and references of the study

The literature survey should include reference books, review articles, systematic surveillance of primary sources, and/or database searches. If the reference is not even available in classical texts then the folkloric beliefs can be considered as reference. A literary survey helps to find gap of the existing studies and to set the problem, the objectives (General and Specific), methods of the study, etc. The relevant information should be cited in the report or publication. If sufficient secondary data regarding safety and/or efficacy are available, the similar studies should not be designed to conduct the study. The ERB must review and approved the reliability of classical, scientific or folkloric reference of the study before approving the research proposal.

6.1.1 Understanding the theories and concepts: While reviewing the literature on Ayurveda, the classical as well as scientific theories and concepts of the medical

system; and the involved cultural background of those must be taken into account.

6.1.2 Review of safety and efficacy in literature: A review of the literature should identify the current level of evidence for the safe and effective use of herbs, herbo-minerals preparations, therapies, etc.

6.1.3 Safety: If a literature clearly indicates the toxicological effects in raw form but the methods of purification is also mentioned, then for the product/s from purified raw materials full range of toxicological investigation may not be necessary. Only when there is no documentation of long historical use of a herb, herbo-mineral preparations, herbal medicine, etc., or probably herbs or new product/s or when doubts exist about its safety, should additional toxicity studies be performed.

6.1.4 Toxicological studies: When toxicological investigation is essential, in vitro study should be carried out first. It can reduce/avoid the number of animals' in vivo studies. If in vivo studies are needed, they are to be conducted humanely, with respect for the animals' welfare and rights. Toxicity studies should be conducted in accordance with generally accepted principles or Organization for Economic Co-operation and Development (OECD) guidelines.

6.1.5 Efficacy: Efficacy of all drugs and procedures/therapies of Ayurveda need to be evaluated against their indicated claims through clinical research. Selection of clinical research depends on the nature and level of the indications. For the treatment of minor disorders, for nonspecific indications, or for prophylaxis uses, less rigorous requirements such as observational studies may be adequate to evaluate efficacy. For specific use of Ayurveda, well-established randomized controlled clinical trials are conducted to generate the highest level of confidence for efficacy.

6.1.6 New formulation: In case of a new Ayurveda product, a new indication for an existing medicine, or a significantly different dosage form or route of drug

administration, the general principles and requirements for clinical trials should be similar to those which apply to standard drugs.

6.2 Research in procedure based therapies

Non-pharmacological therapies or traditional procedure-based therapies are therapies that use various techniques, tools and methods primarily without the use of medication, to provide health care. They include dietetics, faith healing, fasting, life style medicine, meditation, and yoga, etc.

6.2.1 Evaluation of safety and efficacy of procedure based therapies:

6.2.1.1 Theories and concepts: The research project should explain the related theories and concepts of study procedure/s or the therapies. It is very important to evaluate Ayurveda and traditional procedure-based therapies.

6.2.1.2 Safety: In general, non-pharmacological procedure-based therapies are relatively safe, if they are performed properly by well-trained practitioners. But accidents do occasionally occur, most probably when practitioners are not fully trained. Another problem in ensuring safety of a therapy is with the manufacturing defect of equipments. Therefore, to ensure the safety of the equipment used in therapies, it should meet the international standards of quality, as well as ensuring that the practitioners who use it have sound and well supervised theoretical and practical training on its use. Therapies should be performed within accepted parameters, and the indications for a therapy should be evidence based when possible. It should also ensure that the practitioner knows how to deal with accidents when they do occur, and knows how to refer the patient to hospital if the patient does not respond to therapy or if there is a medical emergency.

6.2.1.3 Efficacy: The efficacy of many non-pharmacological procedure-based

therapies mostly depends upon the proficiency of the practitioners, including their skills and experience. There may partly explain the disparity or inconsistency of results reported by different authors, even though the methodologies of the studies were similar and equally sound. Non-specific effects of the therapy can also contribute to efficacy, but these are difficult to measure or quantify. Therefore, clinical trials and other research methodologies are extremely important in the evaluation of the efficacy of Ayurveda procedure-based therapies.

6.3 Protocol preparation: A carefully well designed protocol is a prerequisite for any successful research project. A protocol is prepared to achieve the objectives of the study in the way forwards.

- A research committee and ERB should minutely review the protocol to be followed during the implementation of proposed study.
- If the proposed protocol is not comprehensive or against the ethical norms the ERB rejects the protocol or suggest for alternative one.

6.3.1 Preclinical studies: Pre-clinical study is a stage of research that begins before clinical research (testing in humans) and during which drug safety and efficacy data are collected. In case of procedures based therapies preclinical studies are conducted in healthy volunteers for evaluating the physiological changes after the application of the procedures. The primary objectives of pre-clinical studies are;

- To determine whether such studies supports the clinical use of Ayurveda.
- To characterize the range of physiological and pharmacological actions of the Ayurveda.
- To define the chemical characteristics of pharmacologically active natural products and elucidate their action.

- Pharmacodynamic investigations are conducted in the light of the expected therapeutic effects of the herbs, minerals and animal derived medicinal products using non-human subjects.
- General pharmacological investigations are conducted to elucidate various pharmacological activities other than the main pharmacodynamic action. Such investigations usually covers the investigations on nervous system, cardiovascular system, respiratory system and if necessary other, and should be performed on conscious and anesthetized animal using adequate dose and proper route of drug administration.
- Toxicological investigations are required to supplement human experiences in defining possible toxicity from short term use, but they are particularly important in detecting toxicity that may occur either after prolong exposure or years after the exposure have been discontinued. Generally the longer the anticipated human use, the longer the toxicity test in animals is carried out.
- In case of procedure based Ayurveda treatments modalities, the physiological studies are conducted in healthy human volunteers, sometime even in animals in the lights of expected therapeutic effects (Effect of music in lactation).

6.3.2 Methods of preclinical studies: While conducting the preclinical research on herbal medicines, standard methods are usually employed. Moreover the use of recent technologies and methods resulting from scientific progress should be encouraged.

Pharmacodynamic and general pharmacological activities are carried out utilizing animal models or bioassay that closely relates to human disease.

6.3.2.1 Toxicological methods: Toxicological studies are conducted according to principles generally referred to collectively as Good Laboratory Practice (GLP).

6.3.2.2 Systemic toxicity tests: Systemic toxicity tests refers to alterations of either

physiological, anatomical (either gross or microscopic), or biochemical (including hematology) that result from pathological changes in any organ distant from the site of drug administration. Systemic toxicity further classified into acute and long term toxicity.

- Acute toxicity tests aims to determine toxic manifestations of the test substances that occurs when animals are exposed to one or more dose of the test substances within 24 hours of periods and observed for 14 days.
- Long term toxicity tests aim to determine toxic reactions when animal are exposed to the test drug for sub-chronic and chronic toxicity tests. In such test, the animals are observed for behavioral changes as well as anatomical, physiological and biochemical manifestation of tissue damage.

6.3.2.3 Local toxicity tests: Local toxicity tests are done to determine the local irritation and the systemic absorption of drug used for local application (e.g. respiratory inhalants, drug applied to skin or mucosa).

6.3.2.4 Special toxicity tests: The special test like carcinogenicity test, mutagenicity test, teratogenicity, reproduction and developmental toxicity test, specific tissue toxicity test, endocrine disruption test, organ specific toxicity like hepatotoxic, neurotoxic, nephrotoxic, cardiotoxic tests are considered as special toxicity tests. If any deviation from traditional use is contemplated, additional toxicity tests such as carcinogenicity, mutagenicity, teratogenicity, development and reproduction toxicity endocrine disruption studies may be recommended.

Section 7: Pre-requisite for Ayurveda Clinical Research

Ayurveda is getting paramount significance in every corner of the globe. Lots of people are utilizing these medicines since the time immemorial and popularity is increasing in recent decades. This popularity of Ayurveda in global market makes the stakeholders enthusiastic but lack of supportive data of efficacy, quality control and standardization creates ambiguities and abates the faith on it. In this context, evidences of drug efficacy should be generated by clinical trials. In order to achieve them, precise research methodology for Ayurveda treatment modalities is needed.

Research protocol preparation:

Research protocol is the plan of the study to achieve the research aim. The protocol directs the appropriate direction to accomplish the research work. It should be as per the format mentioned in Annex I.

7.1 Abstract

An abstract summarizes, usually in one paragraph of 300 words or less, the major aspects of the entire paper in a prescribed sequence that includes: 1) the overall purpose of the study and the research problem(s) you investigated; 2) the basic design of the study; 3) major findings or trends found as a result of your analysis; and, 4) a brief summary of your interpretations and conclusions.

7.2 Coining a Research Title

The title should reflect the main idea of the study. A good title contains the fewest possible words that adequately describe the contents, purpose of the research as well as the type of the clinical trial, and if it is possible it also incorporates the outcome of the

study.

7.3 Background information and Scientific Rationale

This section should address background of both research question and/or interventions**.**

7.4 Research question/Hypothesis

The description of the importance of the selected disease/condition in the context of current scenario should be presented appropriately *i.e.* existing disease prevalence, burden of disease. Sometime, there is a gap in the result of previous study(s) or the explanation in the study which need a good explanation. The review and discussion of important literature and data that are relevant to the trial is important before starting research to know whether others have investigated similar/ variables/ parameters/ methods/ results/ populations or geographic regions, etc. to avoid replication. It will provide the background in the context of the study.

7.5 Rational/Justification of the study

Description and justification for the population to be studied. The justification for the population to be taken should be described in detail.

7.6 Aim of the research

The aim means the overall purpose of the study and it should be clearly and concisely defined. The aim is the broad statements of desired outcomes, or the general intentions of the research.

7.7 Objectives of the research

A research objective is a clear, concise, narrative statement, which provides direction to

investigate the variables under the study. A clearly defined objective directs a researcher in the right direction. The researcher should clearly mention the primary or the general objectives as well as secondary or specific objectives of a research. Primary objective is the ultimate question one wants to answer and secondary objectives are the things one needs to do to fulfill primary objective.

7.8 Outcome measures

The primary outcome (principal effects) measure is the most important and desired outcome of the research. Secondary outcomes (additional effects) are additional outcomes which are not included in the primary outcome measure. These both outcome measures are needed to be defined at the time when the study is designed. The researcher should mention the outcome measures as well as the method by which this outcome will be determined.

An outcome is an observation variable or changes recorded in the study at one or more time points from the baseline after enrollment of the participant in the study. It is the end point or measurements required in line of the objectives.

7.8.1 Primary outcome measures: The end point of the primary objective is called primary outcome measure. Generally, there should be just one primary variable, with evidence that it will provide a clinically relevant, valid, and reliable measure of the primary objective (e.g., laboratory procedures, changes in the signs & symptoms, safety assays, etc).

7.8.2 Secondary outcome measures: The endpoints of additional or secondary objectives are called secondary outcome measures. But any other results found at the time of data analysis and interpretation of study results are also the secondary outcome measures.

Secondary outcome measures should be included, whether or not they add information about the primary objective or address secondary objectives. Discuss their importance and role in the analysis and interpretation of study results.

For example- I f in a study, the effect of Medohara Guggulu on Sthaulya (obesity) is to be assessed and the primary objective is weight loss, then "To see the changes in the weight from the baseline at the end of 1st or 2nd or 3rd months of the treatment" [according to the interval (continuous, binary, event times) when the expected changes by the effect of the intervention to be observed] "will be the primary outcome measure. Changes in the lipid profile, changes in the quality of life, etc. may be considered as the secondary outcome measure.

7.9 Results

Result section is just a presentation of the data. There should not be any discussion in the results section (that goes in the discussion section). The results need to be presented in enough detail for someone not familiar with the scientific paper to understand them.

7.10 Discussion

Discussion unrolls the main results, explain their meanings. The new questions, perspectives the most interesting points for the entire field are described under discussion. The possible answers and the researcher's suggestions are put under discussion section.

7.11 Conclusion

Conclusion is a summary of the discussion or the whole work. The main points and results, their factual meaning for the field and a possible further direction are written under this.

7.12 Acknowledgements

A page of acknowledgements is usually included at the beginning of research paper, immediately after the table of contents. Acknowledgements enable the author to thank all those who have helped in carrying out the research.

7.13 Expected research population

A research population is the well-defined collection of individuals or objects known to have similar characteristics. Researcher who is going to select the study population for clinical trial should define the size of the population of same age, sex, race, ethnicity, geographic location, socioeconomic as well as general health status of the research participants before starting the research.

7.14 Phase of the study

While developing a drug through clinical trials, the researcher generally conducts the phase wise experiments. The phases of clinical trials are the steps in which scientists do experiments with a health intervention in an attempt to find enough evidence for a process which would be useful as a medical treatment. The drug discovery process begins from preclinical phase followed by Phase-0, Phase-I, Phase-II, Phase-III and Phase-IV (Wherever is necessary). In the protocol of the research project the researcher should mentioned the phase of the study.

7.15 Number of the sites

Research studies could be conducted in a single or multiple sites. The research protocol should be notified the site of the studies.

7.16 Clinical study design

It is the formulation of appropriate clinical trials or interventions, as well as observational studies in clinical study. The protocol should also include the appropriate clinical study design. A good study design helps to prevent possible bias in the study.

7.17 Sampling method

When research is conducted about a group of people, it's rarely possible to collect data from every person in that group. Instead, a sample group is selected. The sample is the group of individuals who will actually participate in the research. To draw valid conclusions from the results, the researcher has to carefully decide how the researcher will select a sample that is representative of the group as a whole. There are two types of sampling methods:

- Probability sampling involves random selection, allowing the researcher to make statistical inferences about the whole group.
- Non-probability sampling involves non-random selection based on convenience or other criteria, allowing the researcher to easily collect initial data.

7.18 Sample size considerations

The number of participants in a study needs to be adequate, in order to be able to determine any clinically important differences (outcome measures) between the study groups. For this purpose provide all information needed to validate the calculations for sample size, and also to judge the feasibility of enrolling and following the necessary numbers of participants. In particular, specify all of the following:

- Outcome measure used for calculations (almost always the primary variable)
- Test statistic
- Null and alternate hypotheses
- Type I error rate
- Type II error rate
- Assumed event rate for dichotomous outcome (or mean or variance of continuous outcome) for each study arm, justified and referenced by historical data as much as possible
- Assumed dropout rates, withdrawal, cross-over to other study arms, missing data, etc., also justified
- Approach to handling withdrawals and protocol violations, i.e., whether participants will be included in the "intent-to-treat" population
- Statistical method used to calculate the sample size, with a reference for it and for any software utilized

7.19 Study duration

The protocol should also speak about the duration of the study along with the important milestones.

7.20 Duration of subjects' participation

The time duration of the study that will be taken to conduct the study involving every individual or participant.

7.21 Description of study intervention

The protocol should include the name of the intervention along with reference, dose, dosage form, adjuvant, route of drug administration and references along with the name of the intervention.

7.22 Estimated time to complete the enrollment

The protocol should provide the estimated time from enrollment into study of the first subject to the enrollment into study of the last subject.

7.23 Utility of the study outcome

Researcher should extrapolate the possible utilization of the study outcome.

7.24 Conduction of clinical trials

A clinical trial is designed to evaluate efficacy of drug/s which has specific, innovative and clear hypothesis mentioned in Annex 4.

7.24.1 Prior to clinical research: Intervention Details: Researcher should gather the detail of the intervention agents. Intervention agent could be drug, surgical intervention, procedures and application of devices.

7.24.2 Intervention details of a drug:

7.24.2.1 Quality assurance & standardization of the trial drugs: Only the standardized drugs as per Bhaishajya Samhitas (as per pharmacopoeial standard)

should be taken for the trial. The physical characteristics along with analytical data of raw drugs, standard operating procedures for preparation, certification of drug analysis of both raw materials and finished product should be properly documented.

7.24.2.2 Safety/ toxicity studies & biological activity: To assure the safety and biological activity of the trial drug, researcher should have the data of the toxicological studies. If there is no data regarding the toxicological studies then one should generate safety data of the drug by conducting pre-clinical studies.

7.24.2.3 Therapy/ Procedure: Following factors may be considered while designing efficacy studies or validation of the therapy or procedures.

General consideration for procedure based modalities:

- Inclusion and exclusion criteria of the subjects for the therapy/procedures/diseases.
- To generate baseline data (Pre-therapeutic procedures) that is useful to compare with data taken after post therapeutic procedures.
- Ideal Desh/Kala/Ritu (season/periods/time), etc.
- Possible errors by the performers/participant and their prevention
- Duration of each procedure based on individual constitution/severity of disease condition**.**
- Possible complications/adverse events and their management.
- Dietary life style guidelines before, during and after performing therapy or procedures**.**
- Quality of medicine
- Subjective and objective parameters of evaluation

7.25 Study design

The scientific integrity of the study and the credibility of the data from the study depend substantially on the study design. A description of the study design should include:

- A description of the type/design of study to be conducted (e.g., placebo-controlled, double mask, parallel design, open-label, dose-escalation, dose-ranging)
- A description of the study population (e.g., healthy/sick, in-patient/out-patient)
- Rationale for study design
- Phase of trial
- Single or multicenter
- The number of study groups/arms
- Prospective or Retrospective or Cross-sectional study
- Description of study groups/arms including sample size (including a table, if appropriate)
- Approximate time to complete the study
- The expected duration of the subject participation
- Identification of the test agent and specifies of administration of other agents (e.g., placebo)
- A description of the sequence and duration of all trial periods, including follow-up (specify individual participants vs. entire trial)
- Changes in scheduling, such as dose escalation
- Any stratification

7.26 Phases of clinical trials

A clinical trial is only done when a new entity or treatment or therapy may improve the care of patients. Before clinical trials, tests and treatments are assessed in preclinical research. After preclinical study, an entity has to investigate through a series of clinical trials. Clinical trials have the following five phases.

Phase 0: Phase 0 trials are the first clinical trials done among people. They aim to learn how a drug is processed in the body and how it affects the body. In these trials, micro-dosing (a very small dose) of a candidate drug is given to few subjects.

Phase I: Phase I trials aim to find the best dose of a new drug with the fewest side effects. The drug will be tested in a small group of 20 to 80 patients. Doctors start by giving very low doses of the candidate drug to a few patients. Higher doses are given to other patients until side effects become too severe or the desired effect is seen. The drug may help patients, but Phase I trials are to test a drug's safety. If a drug is found to be safe enough, it can be tested in a phase II clinical trial.

Phase II: Phase II trials further assess safety as well as efficacy of test drug. Phase II trials are done in larger groups of patients (100 to 500 subjects) compared to Phase I trials. Often, new combinations of drugs are tested. Patients are closely observed to assess, if the drug works. However, the new drug is rarely compared to the current (standard-of-care) drug that is used. If a test drug is found to be effective, it can be tested in a phase III clinical trial.

Phase III: Phase III trials compare a new test drug to the standard-of-care drug. These trials assess the side effects of each drug and which drug works better. Phase III trials enroll 500 to 3000 or more subjects. Often, these trials are randomized. This means that patients are put into a treatment group, called trial arms, by chance. Randomization is needed to make sure that the subjects in all trial arms are alike. This lets researchers know that the results of the clinical trial are due to the treatment and not by any other

confounding factors. A computer program is often used to randomly assign subjects to the trial arms.

Phase III clinical trials are often needed approval from authorized government's agencies before commencing the use of a new test drug for the general public.

Phase IV: Phase IV trials investigate new candidate drugs which is authorized government's agencies. The drug is tested in several thousands of patients. This study allows broader information regarding efficacy, acceptability and adverse effects among the patients for long time use in the market. This helps to identify rare adverse or side effects due to use of new drug in very large groups of people.

NOTE:

- *For classical uses of drugs mentioned in Ayurveda with clear indications, directly phase III/IV trial may be conducted.*
- *For classical uses of drugs mentioned in Ayurveda but study is designed for new indications/patent or proprietary, then directly phase II trial may be conducted.*
- *Patent or proprietary medicines with authorized government's agencies, Phase I trials may be conducted as appropriate.*

7.27 Clinical studies in Ayurveda

Clinical trials are usually well-controlled studies that prospectively assign human participation to evaluate the effects on health outcomes.

They use a design that allows comparison of the groups treated with an intervention and control so that the effect of the intervention can be determined and differentiated from effects of other influences, such as spontaneous change, placebo effect, concomitant treatment, etc.

7.28 Objectives of Ayurveda research

The prime objectives of all kinds of clinical trials are to ensure safety and efficacy of drug/s or therapies or procedures, and it should be conducted according to Ethical guideline of Health Research in Ayurveda, WHO guidelines or GCP and the Declaration of Helsinki. The objectives of scientific study in Ayurveda could be different and unique than conventional medicine, and apart from the safety and efficacy. Some of the objectives may be specific to the assessment of Ayurveda through clinical trials which are as follows;

- Evaluation of Ayurveda in its own theoretical framework.
- Evaluation of Ayurveda in the theoretical framework of conventional medicine.
- Comparison of the efficacy of different Ayurveda with conventional Medicine.
- Compare the efficacy of different practices within a system of Ayurveda.

7.29 General consideration

All clinical research should be scientifically and ethically acceptable and sound. ERB need to focus on the details of the ethical concerns involved with the study. The sponsor of the study, the researcher, institution, ERB, and regulatory authorities are responsible for ethics of the study.

1. Ayurveda clinical research must be designed, conducted, evaluated and reported in such a manner that should ensure the protection of dignity, rights, safety and well-being of the subjects.
2. Before an Ayurveda clinical research is initiated, foreseen risks and inconvenience should be weighed against the anticipated benefit for the individual subject and/or society involved in the study. A research should be initiated and continued only if the anticipated benefits justify the risks.

3. All Ayurveda clinical research must be conducted in accordance with the International GCP guidelines, the Declaration of Helsinki, Ethical guidelines of Research in Ayurveda, with the use of pharmaceutical products and other relevant regulations and guidelines, wherever applicable.
4. The right of the participant to accept or decline the consent to take part in a clinical research must be respected and his/her refusal should not affect routine care.
5. All Ayurveda clinical research must protect the privacy and confidentiality of every participant. Any information gathered from the participant should be kept strictly confidential.
6. Any misconception regarding Ayurveda clinical research among potential participants must be avoided.
7. Applicable/Relevant regulatory approvals must be taken for all Ayurveda clinical research.
8. Ayurveda clinical research should be conducted with Clinical Trial Registration (CTR) from authorized agencies.
9. Written informed consent must be obtained from each participant before any research related procedure is performed.
10. If the Ayurveda clinical research is planned in a vulnerable population, ERB must approve the arrangement of protective measures for possible adverse events in research place.
11. Procedures assuring the quality of every aspect of the Ayurveda clinical research should be implemented.
12. If any serious adverse event (SAE) happens during the conduction of Ayurveda clinical research it must be reported to the ERB within 24 hrs.
13. Compensation must be given to the participants if the SAE is proven to be related to

Ayurveda clinical research.

14. If needed, ancillary care may be provided to the participants of the Ayurveda clinical research.
15. Institutional mechanisms must be established to allow for insurance coverage for compensating research related illnesses, injury, adverse events wherever deemed necessary by the ERB.

7.30 Procedures of clinical trial

7.30.1 Literature review: A literature review is a process of gathering information found in the previous literatures related to the hypothesis under research which may include the traditional use of the proposed practice and existing scientific research in the same. The literature review should identify the current level of evidences regarding safety and efficacy for the proposed intervention. If little or no literature exists, the oral tradition and the source of this tradition need to be clearly stated as a literature review.

7.30.2 Selection of study design: Selection of study design mainly depends on the question of research hypothesis. Clinical research on Ayurveda could select any conventional concepts of research design. Both Interventional and observational studies could be preferred as research design in Ayurveda study. Few of the following conventional research design are:-

7.30.2.1 Interventional studies:

- **Cross-over trials:** Cross over trial is pre-post clinical trial in which the subjects act as their own control at the end of the study.
- **Randomized controlled trial (RCT):** RCTs are considered as gold standard of clinical research. In RCTs subjects similar to each other are randomly assigned

either to receive the intervention or not to receive the intervention. Subjects, who are most likely to have a favorable outcome independent of any intervention, are not preferentially selected to receive the intervention being studied. Bias may be further reduced by blinding the studies.

- **Observational studies:** There are so many observational study designs often preferred in clinical research. Few of them are;
- **Cohort studies:** In a cohort study design, one or more samples are followed prospectively after exposing one group into an intervention and outcome is compared between the subjects who have received an intervention and who have not received the same.
- **Case-control studies:** In case control studies, subjects with the disease (case group) are compared to subjects without the disease (control group).
- **Cross-sectional studies:** In a cross-sectional study, data are collected on the whole study population at a single point at a time to examine the relationship between disease (or other health related state) and other variables of interest.
- **Uncontrolled case series studies:** A clinical study that lacks the comparison or control group and only depicts the outcomes in one group.
- **Time-series studies:** Data obtained from regular and long-term observations is compared with outcomes during different time periods.
- **Ecological studies:** In ecological studies the rate of a disease is compared across different populations and investigators seek to identify population traits that may cause the disease.
- **Descriptive epidemiology:** It refers to study designs that assess parameters related to the frequency and distribution of disease in a population, such as the leading cause

of death.

- **Case reports:** It describes observations of a single subject or a small number of subjects.

7.30.2.2 Research synthesis studies: Research synthesis studies, including meta-analyses, may be useful as supporting evidence for a health claim. However sometime conventional concepts of clinical research design may be difficult to apply when using clinical trials to evaluate Ayurveda. In such circumstances, the choice of study design should be discussed on a case-by case basis with experienced traditional medical practitioners. Few of the following designs could also be chosen for clinical trials in Ayurveda.

7.30.2.3 Single-subject design: In single-subject design the single subject serves as his/her own control, rather than using another individual or group. Single-subject designs have the advantage of being adaptable to the clinical needs of the patient and the therapeutic approach of the practitioner, but it has limitations due to lack of generalization to other patients. In this study design treatment can be randomized for a patient, rather than the patient being randomized for a treatment.

7.30.2.4 Black-box design: Ayurveda usually approaches the disease in a holistic manner by treating by various methods at once like a package of treatment, e.g., medication along with nutritional support and life style changes. In this type of interventional study, no component of the treatment "package" is isolated and studied independently. In such situation the study can also be undertaken in a "black-box" manner. This means that the treatment and all of its components are delivered as they would be in the usual clinical situation. This allows the effectiveness of traditional medicine to be determined either within its own theoretical framework or within that of conventional medicine.

7.30.2.5 Ethnographic design: In ethnographic research the researchers observe and/or interact with participants of a study in their real-life environment. Ethnographic studies that document the social and cultural context of Ayurveda practice may be appropriate in situations where there is no available scientific literature or other documentation. These and other qualitative studies can provide baseline information from which hypotheses may be generated, and can lead to further research.

7.30.2.6 Observational design: Observational studies collect findings on a therapeutic or prophylactic treatment under routine conditions. These studies may be conducted with or without a control group. Observational studies have specific advantages over studying aspects of clinical safety in Ayurveda. Observational studies can be designed either within its own theoretical framework or within that of conventional medicine.

7.30.2.7 Reverse pharmacology design: In the realm of Ayurveda medicines, many herb based medicinal formulations have known to have healing effects on many health conditions but such results have not been pursued rigorously through research studies to know the effect of such medications in various complex biological systems. Therefore the concept of Reverse Pharmacology (RP) helps in addressing the issue where the effect of the Ayurveda formulation on a health condition is known but the mechanism of action is not known. In this approach the drug candidate travels a reverse path from 'clinics to laboratory' rather than classical 'laboratory to clinics (Annex II). This concept has three phases as follows;

- RP-Phase I: This involves an experiential phase where comprehensive documentation of clinical observations of the effect of standardized Ayurveda drug on the biological systems is done.

- RP-Phase II: The purpose of this phase is to evaluate the target activity of the Ayurveda formulation/drug/therapy under in-vitro and in-vivo models and exploratory studies for tolerability, drug-interactions and dose-range.
- RP-Phase III: The purpose of this phase is to carry out basic and clinical studies at several levels of biological systems and to identify and correlates of drug safety and efficacy. Studies in this phase should be able to decipher mechanisms of action at multiple biological systems and to optimize safety, efficacy and acceptability of the leads in natural products based on relevant science.

7.30.2.8 Data based studies:

- **Systematic review:** It is the studies based on already published studies. A certain review criteria is decided and with a sound methodology, the results of the published studies are scrutinized and summarized. For example, Effect of herbal medicines with significant effect on Hamilton depression rating scale in the subjects suffering from depression.
- **Meta-analysis:** These studies are also based on already published studies. The study compiles and examines the results of number of valid studies on a particular topic and consolidated results are presented for example Meta-analysis of RCTs on the anxiolytic effect of Ashwagandha.
- **Use of placebo:** Placebo is a medicine or procedure prescribed for the psychological benefit to the patient rather than for any physiological effect. Sometime the use of placebo could be necessary for effective conduction of clinical trials.

If a clinical trial demands the use of placebo for scientific reasons, then certain precautions must be exercised. Application of placebo should be reviewed and approved by the ERB.

7.31 Multi-centric clinical trials in Ayurveda

ERB may approved the multi-centric clinical trials in Ayurveda with due coordination with IRC. Multi-centric clinical trials provide a sound basis for the subsequent generalization of its results.

7.32 Clinical trials of surgical/parasurgical interventions in Ayurveda

Ayurveda is the pioneer medical system to introduce surgery to the humanity. Other complementary medical system also uses surgical intervention. If anybody desirous of conducting a surgical/parasurgical clinical trials regarding Ayurveda should follow the following general principles described below;

7.32.1 In any protocol where an established surgical intervention is to be studied, the researcher must provide references for the procedure and describe the most likely complications in the protocol for the ERB to review and benefit-risk assessment. The commonly faced surgical complication should also be mentioned.

7.32.2 In research where a modification of the established Ayurveda surgical intervention is to be tested, the protocol and ICD must specify the need for this modification and the expected complications, if any.

7.32.3 In research where an entirely new surgical intervention is being tested, the ERB may insist on some animal data/modeling data which establishes the efficacy and safety of the technique or case reports/case series that indicate benefits and describe risks.

7.32.4 During the conduct of a surgical interventional research, all adverse events must be reported to the ERB and sponsor (as applicable) within the specified timelines as described for drug research.

7.32.5 Provision of free treatment and compensation for any study-related injury must

be sure for the study subject. The ERB must determine the compensation amount after the investigator has described the relatedness.

7.33 Basic standards of clinical research

Ayurveda clinical trials should be conducted in accordance with the ethical principles. Basic standards of clinical trials have been described in general consideration of sub-chapter 7.29.

7.34 Approval criteria

The researcher seeking approval for clinical trials in Ayurveda has been described in application requirements criteria of sub-chapter 4.14.

7.35 Study procedures

7.35.1 Screening: Screening is the procedure to evaluate the eligibility of the subjects to include/ exclude in the study. The investigator / Institution shall also maintain a subjects' screening register to document identification of subjects who are screened for the study.

7.35.2 Enrollment/Baseline visit: Apart from the screening registry, a subject's enrolment registry should also be maintained to document chronological enrolment of Participants in a particular study. The baseline visit will be the first day for initiation of the therapy/treatment of enrolled subject/s.

7.35.3 Follow-up visit: The follow up visits are the subsequent visits attended by the subjects in prescribed time period as per the study protocol.

7.35.4 Final Study visit: The final visit is the day of completion of the treatment/study period (follow up period without therapy/treatment, if any) as per the

study protocol.

7.35.5 Re-scheduled visit if any: Re-scheduled visit is the case where the appointment on the scheduled day is not feasible due to certain reasons e.g. either the participant or investigator is not available, etc.

7.35.6 Early termination visit if any: Early termination visit is the case where the subject develops either Adverse Reactions (ADR)/ Adverse Events (AE) or non-compliance of the treatment regimen or termination of the study, etc. The same needs to be informed to the Sponsor and the Ethics Committee within two working days.

7.35.7 Laboratory evaluations: The investigations should be done at accredited laboratories. In case of multi-centre studies, the sponsors will take necessary step for selection of a central laboratory taking into consideration that the branches of such laboratories exist at the vicinity of all participating centers and selected laboratory will not further outsource any of the investigations. Methodology, chemicals/kits, equipments and/or the reference value of the investigations should be uniform at all the centers.

7.35.8 Efficacy evaluation (Assessment criteria): Efficacy of clinical trial drug/therapy/procedure is to be assessed on following parameters.

- Sign and symptoms of concerned disease
- Laboratory parameters
- Samyaka Lakshana of therapy/procedures

7.35.9 Assessment of safety:

- Specifications of safety parameters (both laboratory parameters and signs & symptoms)
- Methods/Procedures and periodicity for assessment and analysis of safety parameters

- Design a specific format for reporting and recording adverse drug events/effect or inter-current illnesses.

7.35.10 Assessment of efficacy:

- Specification of safety parameters (both laboratory parameters and signs & symptoms)
- Methods/ Procedures and periodicity for assessment and analysis of safety parameters
- Designing a specific format for reporting and recording adverse drug events/effect.
- Assessing heena/mithya/atiyoga in the subjects under treatment /therapy /procedures.
- Assessing Dushprabhava and Upadrabha of the treatment/therapy/procedures.

7.35.11 ADRs/AEs/Serious adverse events (SAEs): An unexpected ADR requires expedited review by the ERB. Unexpected AE/ADRs and all SAE should be reported to the sponsor by the investigator within 24 hours and to the ERB that accorded approval to the study protocol within seven days. At the end of the trial, all adverse events whether related to trial or not are to be listed, evaluated and discussed in detail in the final report. The medical management of the adverse event is the responsibility of the investigator, and the protocol for adverse event management with allocation of responsibilities must be pre-defined in the protocol and submitted to the ERB. The Sponsor should provide ADR/AE reporting forms to the Investigator(s) / Institution(s). The Sponsor should expedite the reporting to all concerned (including the ERB and the regulatory authorities) of all serious and/or unexpected adverse drug reactions.

7.35.12 Serious adverse events: Any unexpected SAE as defined in the GCP Guidelines occurring during a clinical trial should be communicated promptly within 14 calendar days by the Sponsor to the Licensing Authority and to the Investigator(s) of other trial sites participating in the study. The reporting of the SAE to the

regulatory authority immediately is to enable it to stop the clinical trials of unapproved drugs or withdraw from market approved drugs based on report of Phase IV studies. All other serious unexpected reactions that are not fatal or life threatening must be filed as soon as possible but not later than 14 calendar days. In the event of death the ERB should also be informed within 24 hours.

7.35.13 Rescue medication: A medication intended to relieve symptoms of the investigated disease immediately. To alleviate any emergency, the use of rescue medication is permitted as per the wisdom/discretion of the Investigator. This is in contrast to preventive medications, which are taken over a long period of time to prevent or manage symptoms (for example: Use of Non-Steroid Anti-inflammatory Drugs (NSAIDs) for relief of severe pain in case of trial participants of *Vatarakta* (Gouty Arthritis) is the rescue medication in contrast to uricosuric agent such as Allopurinol, etc.).

**The details of the given rescue medication should be recorded with the details of the name, dosage form, dose, duration, etc. in the Case Report Form.*

7.35.14 Concomitant medication: A concomitant medication is a drug or biological product, other than a study drug, taken by a participant during a clinical trial for any other medical condition (for example: Simultaneous use of anti-hypertensive drug in a known case of hypertension enrolled in the trial of any other disease conditions).

**The details of concomitant medications prescribed to the participants should be properly recoded with the details of the name, dosage form, dose, duration, etc. in the Case Report Form. The participants will be instructed to avoid the use of any other drugs on their own for any ailment and will be clearly instructed to consult the treating Investigator for any symptom or complaint, or if they feel anything unusual.*

7.36 Monitoring, auditing and DSMB

It is mandatory that all research proposals on involving human participants should be cleared by an appropriately constituted ERB. The Ethics Committees are entrusted not only with the initial review of the proposed research protocols prior to initiation of the study, but also have a continuing responsibility of regular monitoring of the approved programs to foresee the compliance of the ethics during the period of the study.

7.36.1 Local monitoring: The Head of the Institute/Center would ensure periodic review and monitoring of the projects at Institute/Center level and the same needs to be reflected in the progress report of the institute that is being communicated to the Sponsor.

7.36.2 Central monitoring: In case of multi-center studies a Central monitoring Committee should be constituted to monitor the activities as and when required.

7.36.3 Auditing: Sponsor should perform an audit as a part of QA system. This audit should be conducted with the purpose of being independent and separate from routine monitoring or quality control functions. Audit should evaluate the study conduct and compliance with the protocol, SOPs, GCPs and applicable regulatory requirements. For the purpose of carrying out the audit - the sponsor may appoint individuals who has qualified by training and experience to conduct audits. The Auditors should be independent of the parties involved in the study and their qualifications should be documented. The Sponsor should ensure that the auditing is conducted in accordance with the Sponsor's SOPs on what to audit, how to audit, the frequency of audit and the form & content of audit reports. Auditors should document their observations which should be archived by the Sponsors and made available to the Regulatory Authorities when called for. Sponsor should initiate prompt action in case it is discovered that any party involved has not entirely complied with the GCP, SOPs, Protocol and/or any

applicable regulatory requirements. If monitoring/auditing identifies serious and / or persistent noncompliance- the Sponsor should terminate the defaulting party's participation in the study and promptly notify to the regulatory authority.

7.36.4 Data & safety monitoring board: The DSMB is a board, charged with monitoring the accumulating data from a pharmaco-therapeutic clinical trial to detect and report early evidence of pre-specified or unanticipated benefit or harm to trial participants that may be attributable to one of the treatments under evaluation. The DSMB will conduct an independent, objective review of all accumulated data from both blinded and unblinded clinical trials in such a manner as to maximize benefit to the trial participants and to the study. A DSMB may be established to monitor the data and side effects carefully during the period of the study and put in a place where by prompt reporting of adverse event occur. The data should be reviewed at regular intervals. The research team should report immediately to the Investigators and Data and Safety Monitoring Board regarding any life threatening condition, whether they are pursued to be study related or not.

7.36.5 Statistical analysis: The type(s) of Statistical Analysis to be used must be clearly identified and should form basis of the statistical model for the study. Any subsequent deviation(s) should be described and justified in the final report. The need and extent of an interim analysis must be specified in the protocol. The results of the statistical analyses should be presented in a manner that is likely to facilitate.

Section 8: Quality Specifications of Ayurveda Treatment Modalities

Quality specifications are detailed requirements that define the quality of a product or study materials or drug, service or procedures. The study material/s or subject/s must undergo specific quality assessment to standardize product/s or procedure/s.

As Ayurveda treatments modalities are broadly classified into pharmacological (product based) and non-pharmacological (procedures based) modalities, the quality specification also vary according to the modalities used in the study. Product based pharmacological modalities include herbal derivatives, processed minerals and animal derivatives or herbo-minerals derivatives whereas non-pharmacological modalities include procedure based treatment modalities.

If anybody is desirous to conduct a research in Nepal, it is required to specify the quality of the product or procedures to be studied as follow;

8.1 Quality specifications of IP

- The ERB must minutely review the quality specification of IP presented by the researcher before approving the proposal.
- The ERB must minutely review the quality specification of procedures (therapies) based study presented by the researcher, before approving the proposal.
- To ensure the safety, efficacy and reliability of procedure based research; the researcher should enlist the quality of the procedures according to the steps mentioned

in Annex III.

• To ensure the safety, efficacy, quality and reliability of research on IP, the identity and quality of the plant material or preparation must be determined and stipulated.

8.1.1 Quality specification of fresh, dried and processed/crude extracted /distilled IPs: The investigational plant material/s which may be fresh, dry, extract and linctus should be investigated as per Annex III & IV.

8.1.2 Quality specification for polyherbal preparation/s or IP preparation/s: There are many medicinal compositions or preparations from herbal derivatives which are available in the dosages form of Churna (Powder), Kalka (Paste), Swarasa (Juice) Sheeta (infusion), Kwatha (decoctions), Avaleha (Semi-solid), syrups, emulsion, ointment, suppositories, capsules, granules, pills, tablets, liniments, Gandusha (gargles), Kawala (mouth washes), inhalants, spray solutions, oils and aromas. Quality specification of polyherbal formulations/preparations must be determined and stipulated as per the description mentioned in Annex IV.

8.1.3 Quality specifications for procedure based treatments: Procedure-based therapies are therapies that use various techniques and tools, primarily without the use of medication, to provide health care. Procedure-based therapies incorporate various physical, mental, emotional, behavioral, social, and spiritual therapies.

8.1.4 Quality specifications for device trials: A medical device is defined as a medical tool which does not achieve its primary intended action in or on the human body by pharmacological, immunological, or metabolic means but which may be assisted in its intended function by such means. It may be an instrument, apparatus, appliance, implant, material or other article, whether used alone or in combination, including software or an accessory, intended by its manufacturer to be used specially for human beings or animals for one or more of the specific purposes of:

- detection, diagnosis, prevention, monitoring;
- treatment or alleviation of any physiological condition or state of health, or illness;
- replacement or modification or support of the anatomy or congenital deformity;
- supporting or sustaining life;
- disinfection of medical devices; or
- control of conception.

Device trials need following specifications to be considered:

- Clinical trials should be conducted in accordance with the ethical principles described in these guidelines.

- Safety data of the medical device in animals should be obtained and likely risks posed by the device should be considered in the same way as for a new drug.

- Apart from safety considerations of the device, the procedures to introduce the medical device in the patient should also be evaluated for safety.

- Devices should be provided free of cost or, if expensive, at feasible reduced rates.

- Avoid therapeutic misconceptions.

- Any AE/SAE should be reported within timelines as per the schedule for a new drug. Here user error could also be the cause of AE/SAE.

- If the participant wants to withdraw from a trial, it may not be possible to remove the internal device. This must be explained to the participant before enrolling her/him. The participant, however, should be allowed to opt out of continuing in the trial without prejudice to her/his ongoing treatment.

- If feasible, post-trial obligations should emphasized with the sponsor.

- The duration of follow-up should be enough to detect late onset adverse reactions, especially when the device is implanted within the body.

Section 9: New Drug Development in Ayurveda

Medicinal herbs, animal by-products and minerals are mainly used to prepare drugs of different dosage forms in Ayurveda. These drugs are manufactured exclusively in accordance with the composition described in the authoritative books of those Ayurveda systems. However if anyone wants to develop a new composition, formula or dosage form under Ayurveda' theories and concepts which is not ever described in Ayurveda medical texts and has no history of traditional use need to follow following criteria Annex V.

9.1 Different dosage form

Different dosage forms for cure of diseases in Ayurveda. These drugs are prepared under classical or traditional methods described in the authorative texts of those systems of medicines. Researcher/s may develop or modify the classical method to develop standard method of preparation of those dosage forms or may discover a new formula under the dosage forms described in the authorative/classical texts. The different dosage forms described in Ayurveda is to refer Annex VI (A).

Parenteral route of drug administration is not described in authorative/classical texts, If any, new entity derived from medicinal plants is aimed to study through this route, the test drug should be crude extracts in the form of liquid and semi permeable.

9.2 Vanaspati Prayojyanga (Plant parts) used in Ayurveda

Plant based formulations are widely used in Ayurveda. They are first collected in the form of raw materials from wild/cultivated botanical sources. The content of

active constituent most often varies between different parts of a plant, geographical distribution and time of collection. Hence, the plant or plant's part/s will be collected from natural habitat and appropriate seasons. Plant's parts used in preparation of Ayurveda are mentioned in the Annex VI (B).

9.3 Jantava (Animal by products) used in Ayurveda

Some potent herbo-mineral dosage forms constitute animal by-products. These by-products include Singa (horn), Nakha (Nail), Asthi (Bone), Danta (Teeth), Pita (Biles), Vasa (Fat), Majja (Bone marrow), etc. which are used in combination with herbs or minerals or metals. The animals by products used in preparation of Ayurveda are mentioned in the Annex VI (C).

9.4 Khanija (Minerals) used in Ayurveda

Some potent herbo-mineral dosage forms constitute metals which may include Parada (Mercury), Lauha (Iron), Tamra (Copper), etc. The metals used in preparation of Ayurveda are mentioned in the Annex VI (D).

9.5 Standardization of raw drugs

Standardization of a test substance may refer to the process of pharmacological, physical, chemical and biological evaluation which ascertains optimal pharmacological effect on the experimental subjects. Researchers are referred to the Annex III for standardization process of investigational products or test substances in details.

9.6 Cytotoxicity study

A new entity or test substance having origin from known poisonous sources must be investigated in cell-lines to evaluate cytotoxic effect of the drug. Researchers are referred to section 6 & 7 and Annex VII.

9.7 Pre-clinical studies

A new entity or test substance or new dosage form is undergone preclinical studies in suitable animal to evaluate safety and efficacy for definite period of time. Researchers are referred to section 6.3.1and Annex II in details.

9.8 Clinical studies

A clinical study is designed to evaluate efficacy new candidate drug of Ayurveda. Researchers are referred to chapter 7 and Annex I & II.

Section 10: Research in Folklore Medicine

Folkloric studies are one that is used for validation of traditional medical practices. There might be claim of a healing practice from a traditional socio-cultural setting in a particular locality. This claim might not have scientific evidence or other documentation. This can become basis from which hypotheses may be generated, and may be a lead to further research Annex VIII.

10.1 General guidelines for generation of baseline information from Folkloric claims

10.1.1 Identification of genuine traditional knowledge holder: Traditional knowledge (TK) holders use local resources to treat the problems or disorders by the traditional method acquired from their ancestral. TK holders, who are willing to share information regarding medicines and traditional uses, should be prioritized to involve in the study.

10.1.2 Documentation of the drug preparation process: TK holders should document plants and their parts used, method of collection, harvesting, processing and manufacturing process, packaging and labeling of drug making photographs or video.

10.1.3 Priority of ingredients: Drugs having less number of ingredients should be given first priority for the study such as single ingredient of the drug is considered the best one. Huge number of ingredients of the drugs should be given the least priority.

10.1.4 Information of the drugs: TK holders should share information regarding number of plants in the mixture or combination, their parts' used, dosage forms (powder, juice, vati, avaleha, etc.), route of administration, time, duration, Anupana/Sahapana (vehicle), etc.

10.1.5 Preparation of the drug: TK holders should be advised to prepare a sample drug in a single lot.

10.1.6 Confidentiality built-up: Documents maintained should be kept and locked in two separate boxes TK holder should keep one box and NARTC authorized person should keep the other box; and the respective keys will be held by them vice-versa. The process of drug preparation and the drug can be given a code or secrecy can be maintained by coding of the manufacturing process, the herbs or finished products. This process builds confidence between TK holder and research organization. Now, they may share information regarding therapeutic uses.

10.1.7 Disclosure of therapeutic uses of the drugs: TK holder should share information regarding therapeutic uses of the drug. NARTC authorized person should prioritize indications according to the organization focus area of research such as Arbuda (cancer), HIV-AIDS, Madhumeha (diabetes), hypertension, renal failure, Jarajanya vyadhi (Ageing), Sthaulya (obesity), Parkinson's disease, Alzheimer disease, Neurodegenerative diseases, etc. A written letter of confidence must be obtained from the TK holder for the safe use in human being.

10.1.8 Observation and inferences: NARTC authorized Ayurveda physician should observe the use pattern of particular drug in 5-7 patients of specified problem/disorder at the clinic of the TK holders for a period of time. The inferences of the treatment should be drawn, and an effective drug from the observation should be evaluated conducting small scale clinical observation.

10.1.9 Preliminary clinical evaluation: Drug of a particular disease should be prescribed to 5-10 patients by experienced specialist for the period of time as TK holder uses to treat the disease. A longitudinal study will be planned to evaluate required physical, physiological, hematological, biochemical and histopathological

parameters. The data obtained before treatment and after treatment will be compared, and therapeutic efficacy will be evaluated on the basis of the findings.

10.1.10 Validation of therapeutic use: Preliminary clinical study done on the basis of observation may or may not be as per the claim of TK holder. If the preliminary clinical studies would support the traditional use, the drug is further evaluated. Otherwise, it will not be entertained.

This process of validation of therapeutic claim contributes to generate baseline data, which suggests to a lead for further investigation or stop the study here. If baseline data supports the claims, the study is further continued considering the following guidelines;

10.1.11 Memorandum of understanding: A legal document of MoU will be prepared by the authorized lawyer, and will be signed among TK holder, Principal Investigator and Executive chief of NARTC. All the documents including baseline data will be preserved under this team.

10.1.12 Formulation of research team:

In case of drug supply by TK holder,

- NARTC appoints its Principal investigator for the study.
- TK holder suggests his/her qualified and experienced (Ayurveda physician) Co-principal Investigator in the study.

In case of drug supply by any third person,

- NARTC appoints its Principal investigator for the study.
- TK holder will be Co-principal Investigator in the study, if his/her qualification meets the minimal criteria for Co-investigator.

10.1.13 Disclosure of ingredients of the composition: TK holder should disclose identity of the ingredients of the composition in terms of vernacular name, Latin name, plant photo, parts used, availability, geographical distribution, etc.

10.1.14 Literature review: The plant can be authenticated by Davyaguna specialist/taxonomist. NARTC information officer will carry out gathering up to date classical as well as web based information regarding clinical use of particular ingredients, by vernacular and Latin name, classical uses, pharmacognosy, phytochemical, pharmacological activities will be searched for the species. It will provide details information regarding uses of the plant. We can now decide to launch further studies on the plant or not if literature review suggests potentiality in new therapeutic area or existing therapeutic area falling under prioritized research areas.

10.1.15 New species of the plant: Some of the ingredient of the drug may be rarely new species. In this case the species will be identified by botanist and enlisted in the library of binomial nomenclature of plants. The essential areas of study are pharmacognosy (standardization), photochemical studies, toxicity studies, preclinical studies, pharmacological studies and clinical studies. Study design will be same as the design recommended for probable medicinal plants, and all the steps should essentially be carried out to generate data (Refer to Annex VII).

**Pharmacological activities in the new therapeutic area and exploration of other area viz. Cosmetics, Nutraceuticals, Food, etc. should be carried out to examine those activities or possible uses.*

10.1.16 Verification: An authorized NARTC team involved in traditional medicines research should compare previously deposited the documents, photographs and videos with the documents, photographs and videos which will be submitted after MoU to NARTC research team regarding botanical and vernacular name of plants,

geographical distribution, availability, plants parts used, composition, method of preparation, dosage forms, dose, duration, route of administration, Anupana/sahapana (Vehicle), therapeutic uses, etc. If NARTC research team find consistency in both the previously and recently deposited documents, photographs and videos, the team should recommend for further study. Otherwise, it will recommend quitting the evidence generation.

10.1.17 Standardization & quality control of raw material (plants) & finished products: If literature review suggests that the ingredients are the potential candidate for research in the prioritized therapeutic area, they will further be standardized as per described in Annex III.

10.2 Preclinical study

10.2.1 Toxicity study: It requires evaluating toxic, mutagenic, carcinogenic and teratogenic effects of new candidate drug for safe use in human trials as per described in section 6.

10.2.2 Pharmacokinetic and pharmacodynamic study: A new candidate of drug is studied for its administration, absorption, distribution, metabolism and excretion. Furthermore, Studies are required evaluating biochemical and physiological effects of drugs and action within or on the body of the study subjects.

10.2.3 Pharmacological activities: A therapeutic use in folklore medical practice is evaluated in the animal model under a defined condition. It also provides additional data to support the folkloric claims as per described in Annex VIII.

10.3 Large scale clinical trials

A clinical study is conducted in 1000-5000 study subjects to evaluate dose adjustment and respective clinical effects. Refer to chapter 7 in details. The phases are as follows:

- Human pharmacology (Phase I):

1.Maximum tolerated dose

2.Early measurement of Drug activity

- Therapeutic exploratory trials (Phase II)
- Therapeutic confirmatory trials (Phase III)
- Post Marketing Trials (Phase IV)

10.4 Preparation of appropriate dosage

Adjustment of appropriate dose can be done by above clinical trials. Large scale clinical trial of the appropriate dose of new candidate of drug is tested and compared with a known and effective standard medicine of the indication.

10.5 Large scale clinical trial comparing the new drug with a known and effective standard medicine: A final dose of a new candidate of drug from above trial should be adjusted to conduct large scale clinical trial comparing with a known and effective standard medicine of the indication. For this study, a single phase III study may be sufficient to evaluate the efficacy of the new candidate drug.

Section-11: Pharmacological Studies of Ayurvedic/Herbal Formulations

Herbal medicines have various pharmacological effects. Pharmacodynamic of the particular herbal medicine can be evaluated in appropriate experimental animal model. Pharmacodynamic and pharmacokinetic of a new entity should be tested to find how the body response to the test substance and how the test substance acts on body. This evaluation of the test substance further justifies using in human being. These guidelines provide basic concepts and principles which should be of utmost concern (Annex V).

11.1 Animal models

11.1.1 Species: The experimental animal models may include mice, rats, guinea pigs, rabbits, cats, dogs, etc. Characteristics of the animals such as strain, sex, age and their housing conditions should be specified.

11.1.2 Disease model: Disease models can be made by treating animals with certain chemicals or surgical interventions or other modalities. For example, immunologically depressed mice can be made by treating them with an immunosuppressive agent, such as cyclophosphamide, Anti-diabetic pharmacological activity of test substance can be evaluated by Streptozotocin or Streptozocin (STZ) or Alloxan induced diabetic model in particular animals such mice, rats, rabbits, etc.

Animals with genetic defects can also be used to evaluate pharmacological activities for example the autoimmune mouse (NZB/WF1, MRL) and the hypertensive rat (Spontaneously Hypertensive Rat: SHR), etc. The animal models may need to be established according to those principles.

11.1.3 Pharmacodynamic investigations: Test assays can use the following;

- Whole animals;
- Isolated organs and tissues;
- Blood and its components;
- Ex vivo and tissue culture cells; and
- Sub-cellular constituents.

Careful attention must be given during selection of the target organs to investigate the test substance in vitro study, Study on Ayurveda/herbal preparations in vitro, is most often difficult to determine the factors of transforming into active metabolites which may be necessary for the biological activity. On the other hand, body fluids from test animals may contain such biologically active metabolites and be used successfully in less complex test systems.

Special attention should be given to the sensitivity, reproducibility and general acceptance of the test animals or test systems selected.

Review of the literature may help to select the species and test systems which should consider including in the study. This type of study provides desired pharmacodynamic information regarding the test substances.

11.2 Administration of drugs

11.2.1 Route of administration: Since oral dosage forms of Ayurveda/herbal preparations are frequently prescribed clinically, the oral route of administration is commonly the most suitable route of drug administration used to administer drug in experimental animals. However, researchers should administer the drug through the intended route of drug administration in man to investigate the pharmacodynamic of drug in the same route.

11.2.2 Frequency of administration: Ordinarily, doses selected for a study

should be established by means of a dose-response relationship however such relationships often cannot be demonstrated with Ayurveda/herbal preparations in experimental animals. So it may be required to select one or more doses that provide a desired effect. Selection of doses for animal studies should be in accordance with customary clinical doses.

11.2.3 Control group: It is essential that all studies include a negative (vehicle only), control group of animals and, if possible, positive control group of animals (standard/reference) is also included to compare the effect of the test substance with a known drug.

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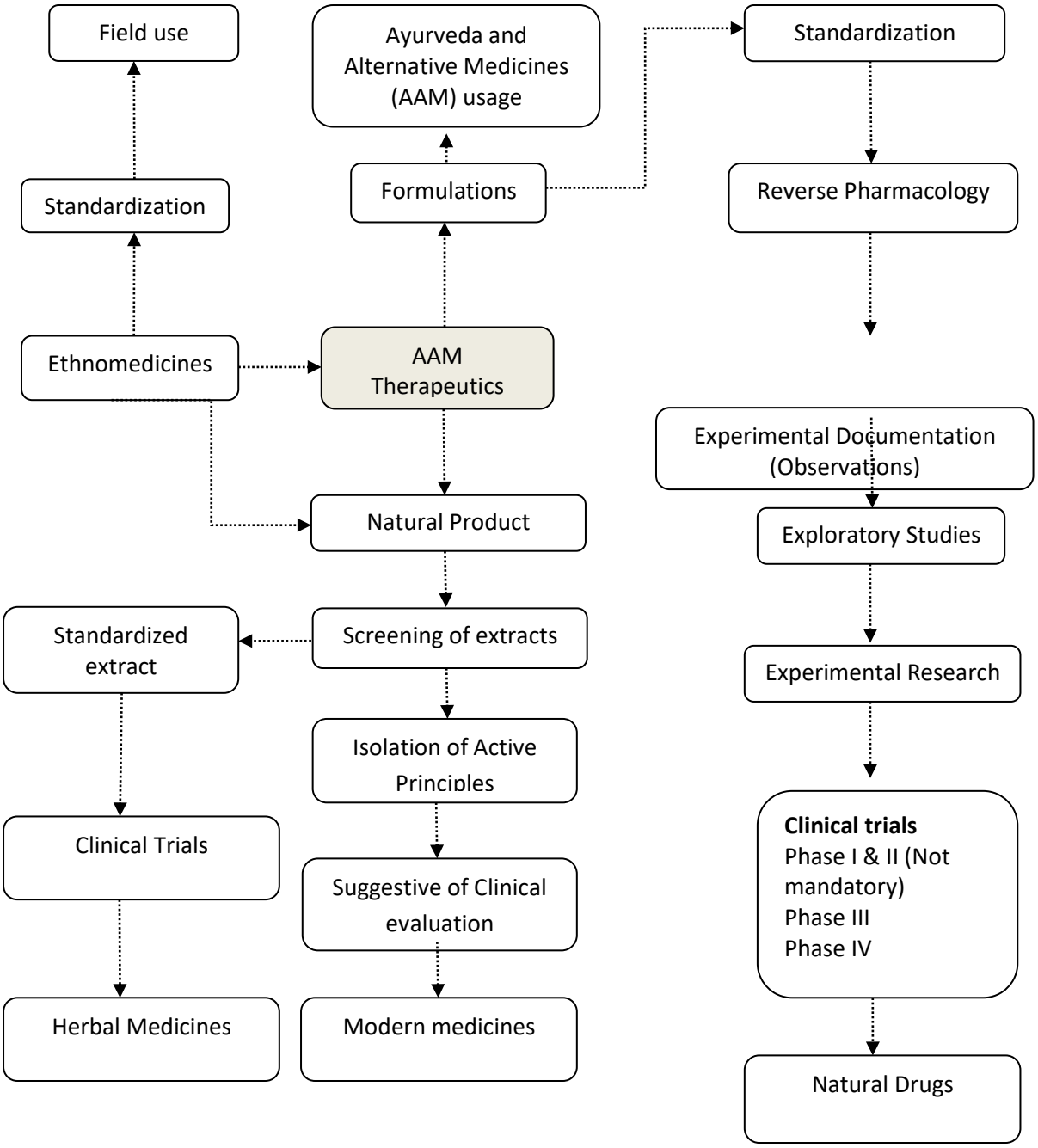
6. General guidelines for clinical evaluation of ayurvedic interventions, Central Council for Research in Ayurvedic Sciences, Ministry of AYUSH, Government of India, 2018.
7. National ethical guidelines for health research in Nepal, Nepal Health Research Council , 2019.

Annex I: Clinical trial protocol

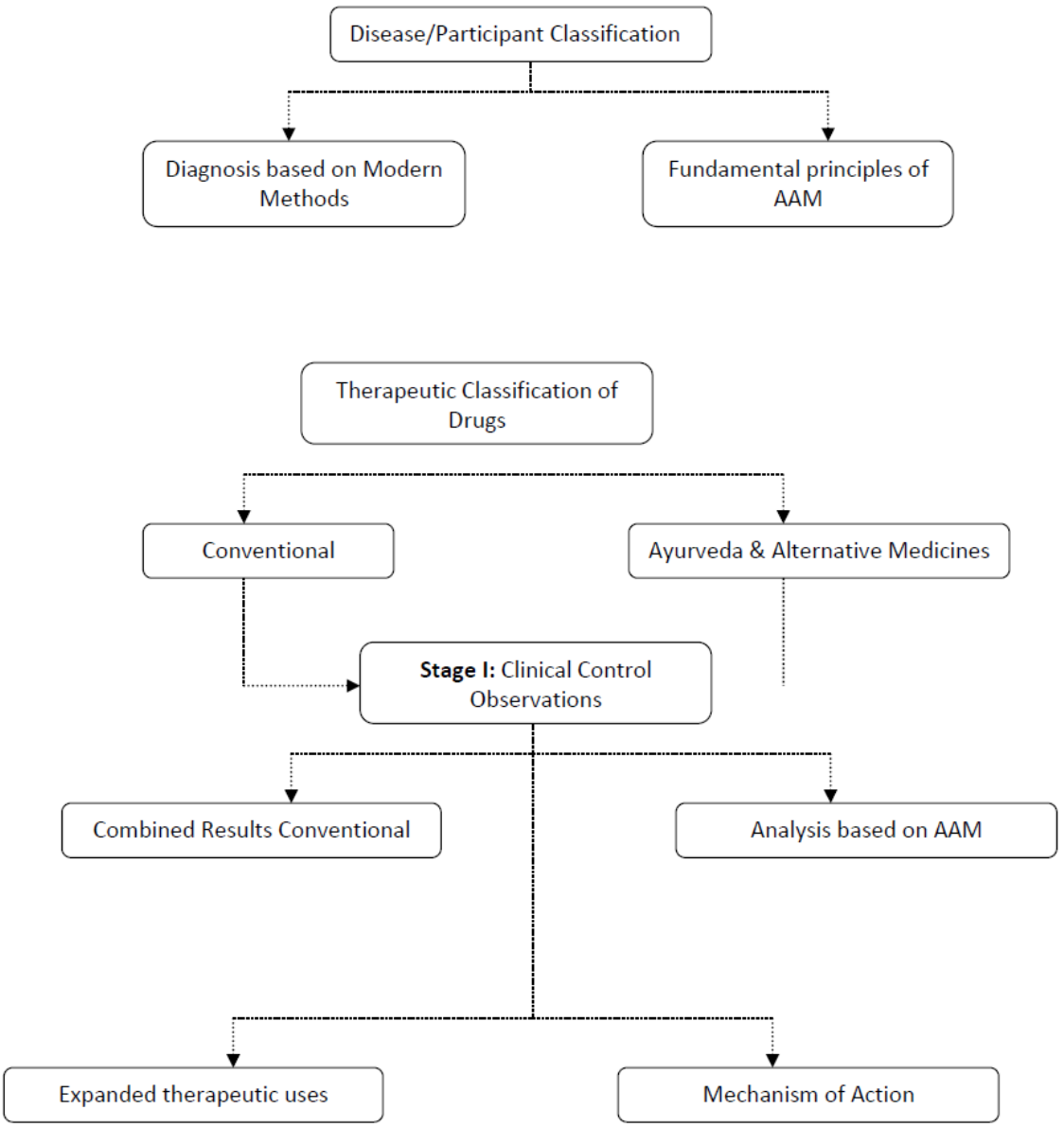
Title	Include title of the study with type of trial (e.g. dose-ranging, observational, double-blind, etc.)
Aim	mention why the world needs the research
Objectives:	Include study objectives; primary or general objectives; secondary or specific objectives.
Outcome measures	Include primary/secondary outcome measures and method by which outcome will be determined; Primary: Secondary:
Population:	Include sample size, gender, age, general health status, geographic location, etc.
Phase:	Mention the phases of the clinical study • Phase I • Phase II • Phase III • Phase IV
Number of Sites:	Single/Multi-centre
Study Design:	Open label, Randomized, Masking, etc.
Sample size	Consideration of sample size calculation
Study Duration:	Provide time from when the study initiation and until the study completion with close out
Participant's participation Duration:	Provide time it will take to conduct the study for each individual participant.
Description of study intervention:	Include name of the intervention along with reference, dose, dosage form, co-medicine, route of administration and references along with the name of the intervention.
Estimated time to complete the enrollment	Provide estimated time from enrollment into study of the first participant to enrollment into study of the last participant
Utility of the study outcome	Mention uses of the study outcomes.
Dissemination	A plan of dissemination result of the study should be mentioned in study protocol
Publication	A publication policy, if otherwise not addressed in a separate agreement, should be described in the protocol.

Annex II (A): Evidence base in Ayurveda: Suggested approach

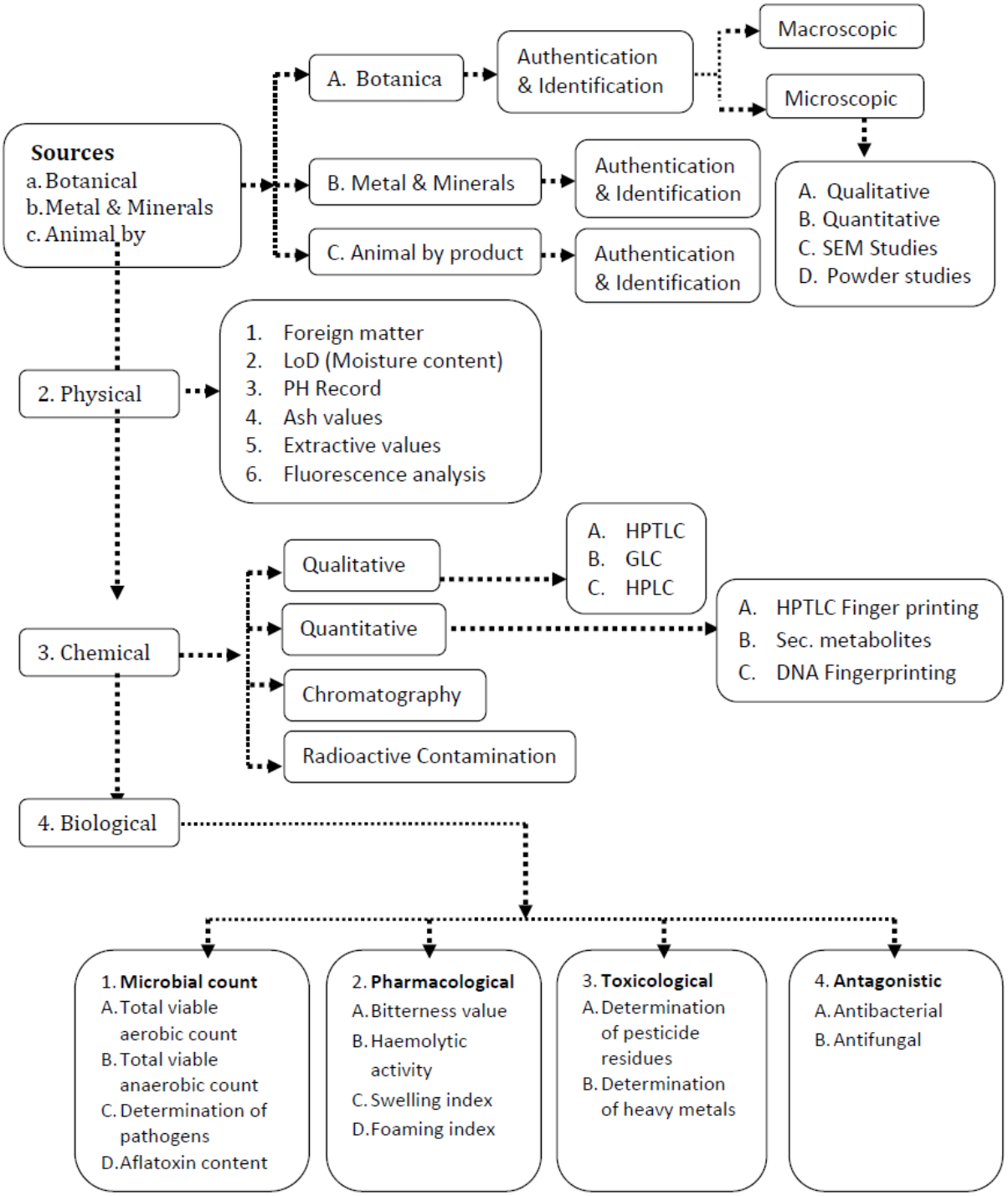


Note: *Reverse pharmacology method can be used to validate therapeutic indications of Ayurveda drugs for evidence generation.*

Annex II (B): Evidence base in Ayurveda: Suggested approach



Annex III: Quality specification of crude drugs used in Ayurveda research



Annex IV:

A) Quality specification of fresh, dried and processed/crude extracted/distilled investigational product/s

1.Family, scientific name and botanical description (with photographs) of the raw material/medicinal plant.

2.Nepali, Sanskrit or classical name if it is described in classical texts and English Name (if available) and folk name (if the folkloric claims is considered).

3.Description of part/s used of the plant for study intervention such as leaves, fruits, flower, buds, stem, rhizome, roots, milk, oil, etc.

4.Season of cultivation, method of harvest or collection, storage and preservation, and other preliminary processing.

5.Method of detoxification (if any).

6.Isolation and characterization of molecules from the plant materials, which may also be the biologically or therapeutically active principle, should be quantified and described with their structural formulae, particularly if they are uncommon.

7.**Authenticity:** A description of the pharmacognostical characteristic (macroscopic, microscopic, powder microscopic and sensory) of the plant should be provided, along with photographs.

8.**Purity:** Limits of foreign organic matter (such as undefined parts of the plants) and foreign mineral matter (such as sand and soil adhering to the plant material) should be specified; ash value should be determined.

9.**Contamination Tests:** Researcher should provide contamination free certificate of study plant material/s. Contaminant of the study material/s may be microbes, fungi, heavy metals, pesticides, etc.

10. **Assay:** A physical, chemical or biological assay of the study material/s or

isolated any known or active fractions should be described and the biological activity of the active molecule and/or the plant materials should be investigated.

11. **Packaging, labeling and storage:** The conditions for packaging, labeling and storage should be recorded clearly.

B) Quality specification for polyherbal preparation/s or IP preparation/s:

1.Mention number 1 to 6 from Annex-1a.

2.Classical, folklore, recent references must be mentioned.

3.Calculate the proportion of each ingredient used in the formulation for 1000 g or 1000 ml of the product. A quantity may be given as a range corresponding to a definite quantity of assayed active constituents. Any excipient used should be specified.

4.Mention method of preparation to produce 1000 g or 1000 ml of the product. The description of the method should include details of any process such as pulverization, and decoction, pills or vati or syrup preparation, detoxification, trituration, solvent used, time and temperature of an extraction and concentration, isolation and characterization as well as the process used to reduce the level of microbial contamination.

5.**Authenticity:** A polyherbal preparation is investigated as per the method mentioned in Annex 1a. Preliminary screening, physical and chemical identification tests should be described and thin-layer chromatographic procedures for the characterizing compounds should be described. A photograph of the chromatogram should be included. For compound preparations, the most important ingredients including the use of a “finger-print” should be obtained by either thin-layer chromatography or high performance liquid chromatography.

6.**Purity.** A polyherbal preparation is investigated as per the method mentioned above.

7.**Assay:** A polyherbal preparation is investigated as per the method mentioned in Annex 1a. The content of biologically or therapeutically active constituents, particularly those which influence the efficacy of the product, should be determined. For herbal mixtures, the most bioactive compounds should be assayed.

8.Tests related to the form of the preparation for both non-clinical and clinical interventions should follow any available regulatory requirements of Member States or the World Health Organization guidelines.

9.**Packaging, labeling and storage:** The conditions for packaging, labeling and storage should be recorded along with the date of manufacture, date of expiry (in years and month), batch number, etc.

C) Quality specification for procedures based research

1.Authentication of the procedures includes classical references, description and method.

2.Provide Nepali, English and Folkloric name (wherever applicable). In case of Folkloric practice, mention folkloric name, references, description and methods..

3.In case of surgical procedures, mention techniques, tools and methods of the followings;

i.Preoperative procedures

ii.Operative procedures

iii.Post-operative procedures

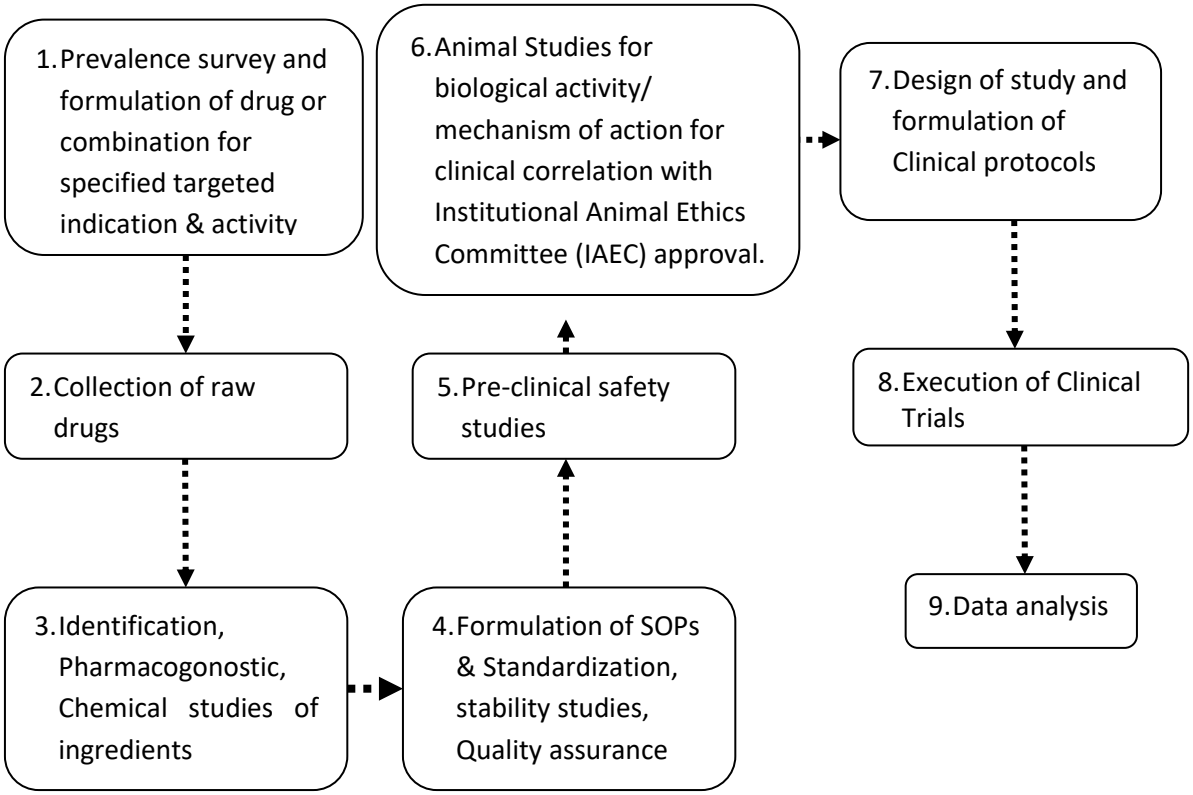
4.Mention time, duration and frequency of the procedure applicable in the therapies.

5.Prescribe do and Don'ts in the procedures such as diet, medications, age of the

patients, exercises, therapies, etc.

6. Submit experience of the expert in the procedure.
7. Describe the most likely complications
8. Submit standard operating protocol (SOP) of the procedure with pictures or a video, if possible.
9. The classical procedure should not be modified. It should be in the form of original classical practice.
10. Subjective feeling and behavioral changes due to study should be mentioned in expected outcomes in the proposal.

Annex V: General research guidelines & methodologies of drug development



1. Appropriate basis of literary survey, previous clinical data of ingredients or any other data of claims, classical evidences, etc.,
2. Considering current good agricultural practices, good field collection practices and classical textual methods.
3. Based on available guidelines and classical methodology.
4. Considering the classical methods and current available physical/chemical, Biological parameters, microbial loads, heavy metal estimation, pesticide residues, etc. for standardization and safety.
5. Acute/sub-acute/chronic studies as per intended therapeutic use with IAEC approval.
6. Preparation of preclinical dossier (Preparation of all documents for preclinical studies).
7. As per current guidelines and adopting Classical methodology (Bulk preparation of quality assured Drug for clinical trial, packing, labeling etc. as per requirement).
8. With approval of IRC/IRB and CTR, trial will conduct and monitored.

Note: *IPR Protection and issues of filing of patent to be addressed at suitable stage.*

Annex VI (A): Different dosage forms described in Ayurveda

SN	Dosage form	SN	Dosage form
1.	Kalka/Choorna (Powder)	18.	Snehana (Oileation)
2.	Swarasa (Juices)	21.	Swedana (Fomentation)
3.	Kwath (Decoctions)	22.	Lepa (Paste)
4.	Phanta (Hot infusion)	23.	Liniments
5.	Shreeta (Cold infusion)	24.	Herbal Bath
6.	Vati (Pills)	25.	Poultices
7.	Asavarista (Fermented preparation)	26.	Inhalants
8.	Avaleha (Semi-solid preparation)	27.	Aromas
9.	Tail (Medicated oil)	28.	Granules
10.	Grita (Ghee preparation)	29.	Confectioneries
11.	Malahara (Ointment)	30.	Emulsion
12.	Basti (Enema)	31.	Tinctures
13.	Varti	32.	Linctuses
14.	Pichhu (Suppositories)	33.	Abhayanga
15.	Gandusa (Gargle)	34.	Dhoomana
16.	Kawal (Mouth washes)	35.	Anjana
17.	Nasya		

Annex VI (B): Vanaspati prayojyanga (Plant parts) used in Ayurveda

SN	Part's used	SN	Part's used
1.	Moola (Root and rhizomes)	15.	Kanda tvaka (Stem bark)
2.	Moola tvaka (Root bark)	16.	Pushpa (Flowers)
3.	Moola (Root stock)	17.	Pushpa patra (Petals)
4.	Kanda (Tuber, bulb, etc.)	18.	Patra (Leaf)
5.	Phala (Fruits)	19.	Panachanga (Whole plant)
6.	Phala tvaka (Fruit peel)	20.	Manjari (Inflorescence)
7.	Phala majja (Fruit pulp)	21.	Keshara (Stigma)
8.	Epicarp (Fruit rind)	22.	Niryasa (Exudate/resin)
9.	Beeja (Seeds)	23.	Gall (Gl.)
10.	Beeja majja (Seed pulp)	24.	Shunga (Leaf bud)
11.	Poongakeshara (Stamen)	25.	Alkali (Kshara)
12.	Satva (Extract)	26.	Tail (Oil)
13.	Kanda (Stem)	27.	Kantaka (Thorn)
14.	Kanda saara (Heart wood)	28.	Paroha (Climbers)

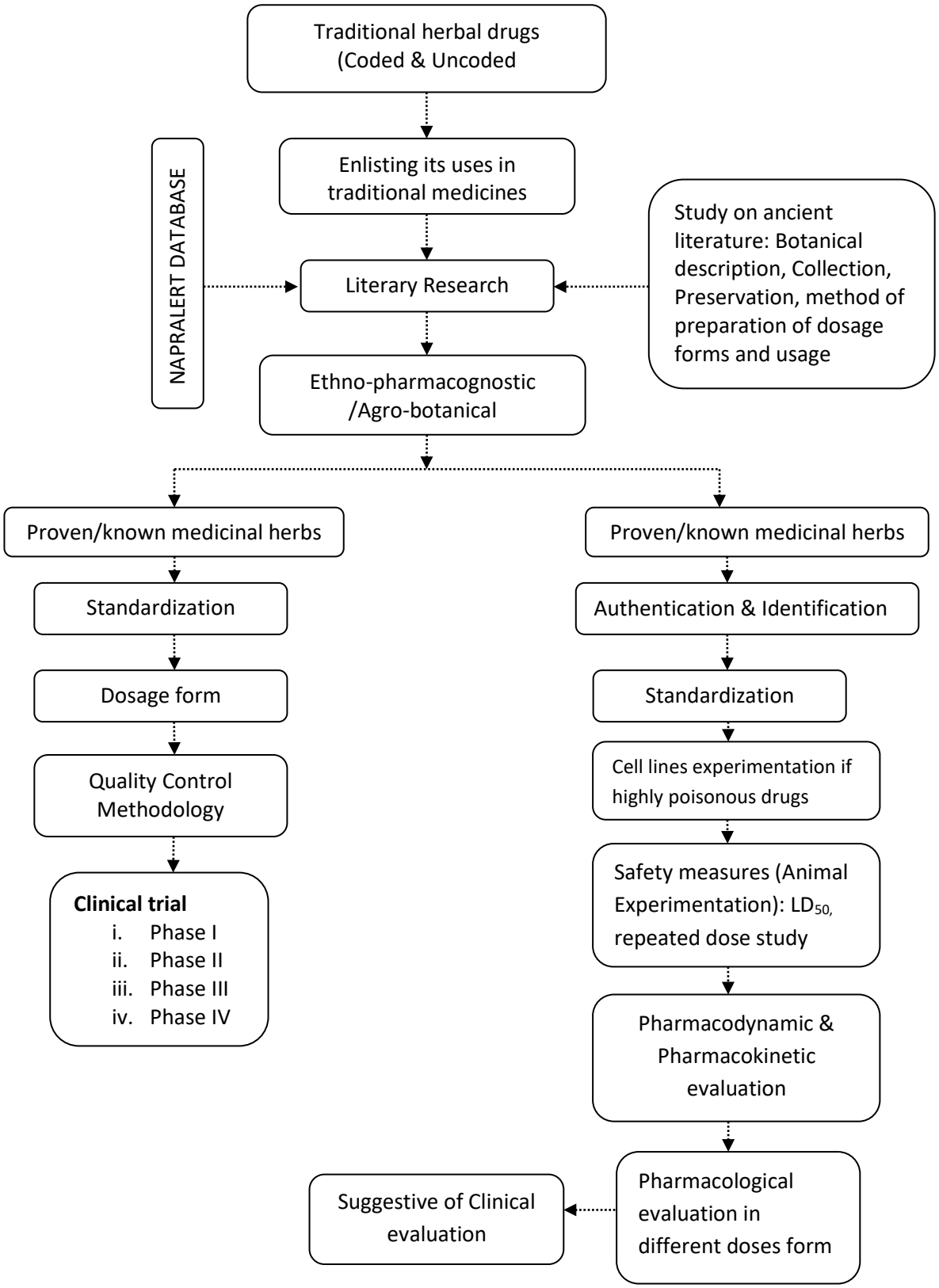
Annex VI (C): Jantava (Animal by products) used in Ayurveda

SN	Name of products	SN	Name of products
1.	Madhu (Honey)	10.	Asthi (Bone)
2.	Gorasa (Milk, Curd, Ghee, etc.)	11.	Snayu (Ligaments)
3.	Pitta (Bile)	12.	Shringa (Horn)
4.	Vasa (Fat)	13.	Nakha (Nail)
5.	Majja (Bone marrow)	14.	Khura (Hoop)
6.	Asringa (Blood)	15.	Kesha (Hair)
7.	Masa (Flesh)	16.	Loma (Body hairs)
8.	Beet (Stool)	17.	Rochana (Bilestone)
9.	Mutra (Urine)	18.	Charma (Skin)
	Mukta		Sankha
	Moti		Sipi

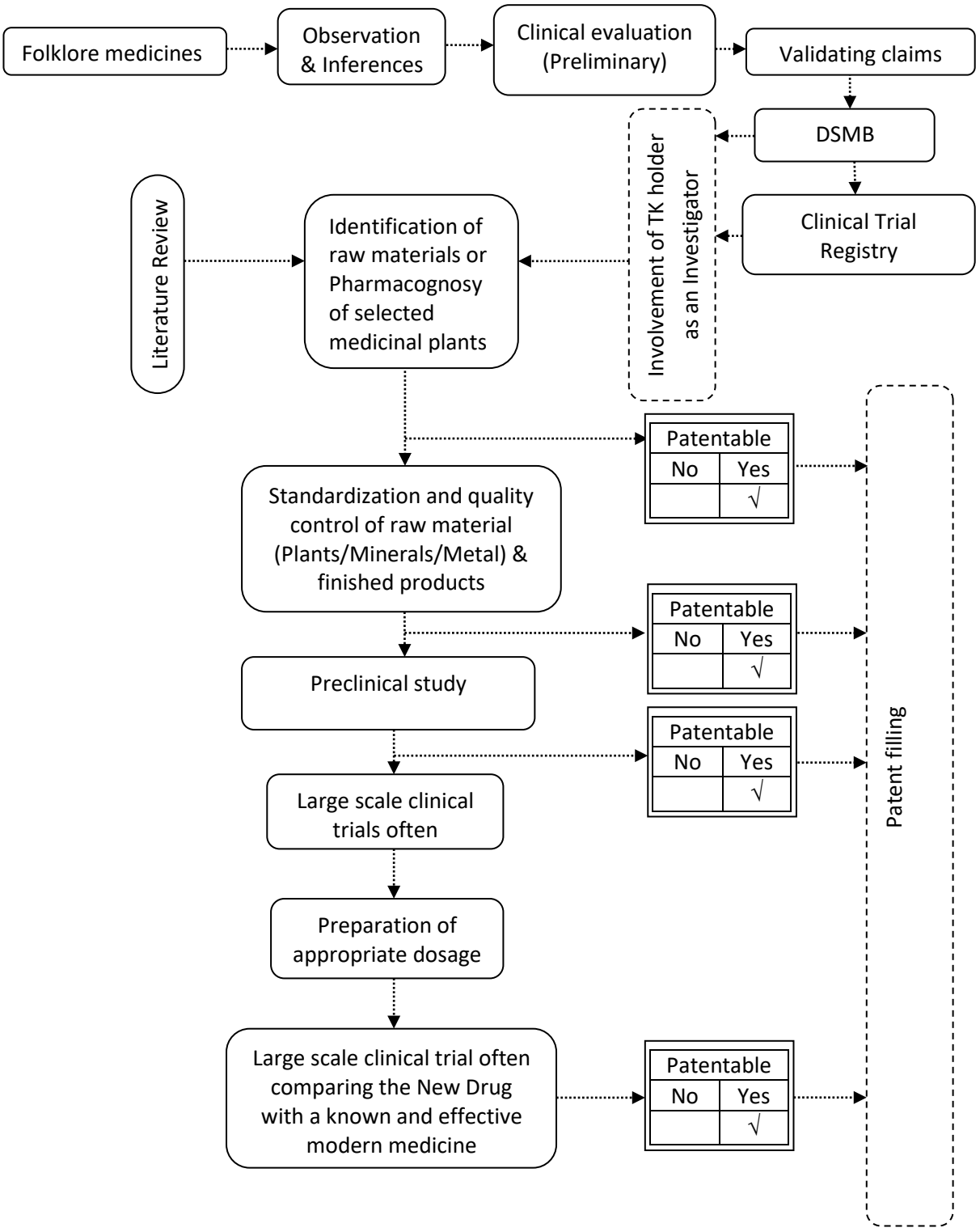
Annex VI (D): Khanija (Minerals and metals) used in Ayurveda

SN	Name of drugs	SN	Name of drugs
1.	Makshika (Pyrite)	18.	Vanga (Tin)
2.	Bimal (Iron pyrite)	19.	Naga (Lead)
3.	Shilajeet (Asphaltum)	20.	Panna (Emerald)
4.	Rajaka (Silver)	21.	Hiraka (Diamond)
5.	Lauha (Iron)	22.	Agnijara (Ambargris)
6.	Hingula (Cinnabar)	23.	Vakranta (Manganese)
7.	Gandhaka (Sulphur)	24.	Abhraka (Mica)
8.	Hartala (Orpiment)	25.	Sasyaka (Copper sulphate)
9.	Manasheela (Realgar)	26.	Yasada (Zinc)
10.	Fitakiri (Potash alum)	27.	Pravala (Coral)
11.	Kasisa (Ferrous sulphate)	28.	Ketu (Cat's eye)
12.	Gairika (Ochre)	29.	Shukti (Oyster)
13.	Kaudi (Cowry or Marine shell)	30.	Mridharashringa (Litharge)
14.	Tankana (Borax)	31.	Savarna (Gold)
15.	Shankha (Conch shell)	32.	Tamra (Copper)
16.	Mukta (Pearl)	33.	Navasadara (Ammonium salts)
17.	Samundrafena (Cuttle fish bone)	34.	Gauripashana (White arsenic)

Annex VII: Scheme for research on herbal medicines



Annex VIII: Suggested approach for the inclusion of folkloric herbal medicines



Annex IX: Additional checklist for the research related to Ayurveda research proposal

1. Plant species of herbal medicine is botanically verified (Latin name, synonyms, local names, and part's used detail of harvesting and storage condition).

Y	N	NA

2. Intervention truly grasps the essence of holistic approach (behavioural rules, *anupana, sahapana).*

Y	N	NA

3. Intervention being used is culture sensitive to use in current study population.

Y	N	NA

4. Review of safety and efficacy literature is included.

Y	N	NA

5. The intervention has a well documented history of traditional use (Literature report).

Y	N	NA

6. If well known medicines are formulated into a new mixture, evidence for safety and efficacy is thoroughly considered.

Y	N	NA

7. The issue that new preparatory methods may alter the chemical toxicological and pharmacological profile of even known and traditionally used medicinal plants is considered

Y	N	NA

8. The drug fulfill pre-clinical toxicology requirement.

Y	N	NA

9. The test substance used in research is standardized so that every individual will receive same intervention (identification, authentication, standardization of raw material).

Y	N	NA

10. If the intervention does not have the evidence of safe clinical use, the research is planned to be conducted in different appropriate phases (Phase 1- tolerability, metabolism and acute toxic effect. Phase 2- Dosage finding, efficacy and toxicity. Phase 3- Effectiveness and side effects. Phase 4- Effectiveness in various condition and drug interactions).

Y	N	NA

11. The research team is composed of relevant Ayurvedic/naturopathic/alternative or complementary medicine expert

Y	N	NA

12. Effective dose (*matra)* is ascertained in a justifiable manner with sufficient explanation.

Y	N	NA

13. Diagnostic/inclusion/exclusion criteria are widely considered, and it is ascertained that intervention will be in line with context and theoretical underpinnings of traditional medicine.

Y	N	NA

14. Practitioners bias is controlled (skill and experience). It is ascertained that therapy will be provided by well trained practitioners.

Y	N	NA

15. It is ascertained that appropriate control is used (well established treatment/ non treatment/ different dose of same treatment/placebo/full scale treatment/minimal treatment/ alternative treatment

Y	N	NA

16. Therapeutic protocol (including lifestyle and dietary counseling) is standardized.

Y	N	NA

17. Quality of the therapeutic equipments and other tools is scientifically considered.

Y	N	NA

18. Most suitable research design is being used for the objective (single case/black box/ ethnographic/observational/ clinical trial/ clinical trial with randomization/ others.

Y	N	NA

19. Description of the therapeutic intervention and the reasons for the selection of the therapeutic interventions are included.

Y	N	NA

20. The type of intervention is clearly defined. Information on the composition and manufacturing of finished products is included.

Y	N	NA

21. Issues concerning the variability of treatment by a single practitioner (intra-practitioner variability) and groups of practitioners (inter-practitioner variability) is addressed (practitioner's diagnostic ability should be reliable).

Y	N	NA

22. If the setting is an important component of a treatment, it's essential features is described.

Y	N	NA

23. The dose, frequency and duration of a treatment are well described. The "dose" used in the study is based on the relevant literature and experience of traditional medical practitioners.

Y	N	NA

24. Temporal issues are considered. The study design takes into account seasonal variations that are important to the traditional medicine systems.

Y	N	NA

25. Appropriate infrastructure is available for the research.

Y	N	NA

26. There is involvement of properly trained research personnel and traditional medical practitioners in the research.

Y	N	NA

27. Have adequate facilities, including laboratories, equipment and sufficient clerical, medical and allied health workers to support the study as required.

Y	N	NA

28. Facilities are available to handle any emergency situation.

Y	N	NA

29. Proposed clinical trial is within the framework of the prevailing law of the country

Y	N	NA