

**GUIDELINES SERIES-III**

**GENERAL GUIDELINES FOR  
CLINICAL EVALUATION OF  
AYURVEDIC INTERVENTIONS**



**CENTRAL COUNCIL FOR RESEARCH IN AYURVEDIC SCIENCES**

**Ministry of AYUSH, Government of India**

**New Delhi**



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# **GENERAL GUIDELINES FOR CLINICAL EVALUATION OF AYURVEDIC INTERVENTIONS**

**Volume - III**



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Volume - II : General Guidelines for Safety/Toxicity Evaluation of Ayurvedic Formulations

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## PROLOGUE

Research and Development in the field of AYUSH system in different areas such as drug development including quality assurance, pre-clinical safety evaluation and Clinical Research are being conducted at different levels such as Research Council under AYUSH, Academic institutions (both AYUSH and non AYUSH institutes such as Medical Colleges, Universities etc.), other Research organizations such as ICMR, CSIR etc. Further, research support is also being extended through grant under Extra Mural Research (EMR) vide Ministry of AYUSH, DST, DBT, ICMR etc. in the area of traditional medicine.

Lot of research is being conducted at different levels as above in the field of AYUSH adopting different guidelines, methods and protocols and ending up research outcomes with low or poor translational value. Only few of them have led to clinical trial and marketing level. This may be attributed to lack of awareness regarding AYUSH strategies for R&D and provisions of Drug & Cosmetic Act related to AYUSH.

In spite of availability of several guidelines such as GCP guidelines for ASU drugs, ICMR Guidelines for Bio medical Research for Human Participants, GCP Guidelines published by CDSCO Ministry of Health and Family Welfare, WHO guidelines for traditional medical research and GCP guidelines for ASU drugs published by Ministry of AYUSH, there is no single comprehensive directive to conduct research in AYUSH sector is available.

This might be one among the major reasons that has led to Research and Development in AYUSH sector with diverse approaches with low translational value.

In view of this, it becomes imperative to develop directives on research practices for various components of AYUSH research sectors for uniform adoption across all stake holders such as research councils, academic institutes, funding agencies engaged in AYUSH research.

Considering this, efforts have been made by CCRAS and developed three comprehensive and concise Guidelines focusing on drug development (Standardization and quality assurance), safety and toxicity and clinical evaluation for ready reference of stakeholders. These Guidelines encompassed with research practices may be suitably adopted and followed by investigators in the field of Ayurveda system such as Research organizations, academic institutions and Investigators seeking grant from schemes of different agencies funding for research on AYUSH system, would certainly help the investigators while designing and formulating the proposals and also planning academic industrial research in the field of AYUSH systems. The users may refer other two documents for having an overall idea concerning drug development and R & D in this field.

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## GLOSSARY

S.No.	Terms with definitions	
1.	Accountability	The obligation of an individual or organization to account for its activities, accept responsibility for them, and to disclose the results in a transparent manner.
2.	Act	Wherever relevant, the Act means Drugs & Cosmetics Act 1940 (23 of 1940) and the Rules made thereunder.
3.	Adverse Drug reactions (ADR)	All noxious and unintended responses to a medicinal product related to any dose used in human for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function. ADRs are classified into six types: dose-related (augmented), non-dose-related (Bizarre), dose-related and time-related (Chronic), time-related (delayed) withdrawal (end of use) and failure of therapy (failure).
4.	Adverse event	Any untoward medical occurrence in a participant or clinical investigation participant administered an investigational product and which does not necessarily have a causal relationship with this treatment. The adverse event can therefore be any unfavorable or unintended sign or experience associated with the use of the investigational product, whether or not related to the product.
5.	Assent	To agree or approve after thoughtful consideration of an idea or suggestion. In these guidelines it means agreement or approval mostly in children > 8 years of age, which has to be corroborated with informed consent of legally authorized representative (LAR).
6.	Assessment form	An official record of the review decision along with comments and dated signature of the reviewer.
7.	Audit	A systematic and independent examination of trial activities and documents to determine whether the review and approval activities were conducted and data were recorded and accurately reported according to the study protocol, SOPs, GCP, Declaration of Helsinki and applicable guidelines and regulatory requirements.
8.	Authority	Authority means the Biomedical and Health Research Authority established under an Act.
9.	Autonomy	It is the ability and capacity of a rational individual to make an independently informed decision to volunteer as a research participant.
10.	Ayurvedic drug	Includes all medicines intended for internal or external use for or in the diagnosis, treatment, mitigation or prevention of disease or disorder in human beings or animals, and manufactured exclusively in accordance with the formulae described in the authoritative texts of ayurvedic system of medicine and Ayurvedic pharmacopeia of India specified in the first schedule of the Drugs & cosmetics Act 1940, Rules, 1945. These are also called as classical drugs which are manufactured and named in accordance with the formulations described in the authoritative texts.
11.	Ayurveda intervention	Includes any existing/ new intervention with drug, therapeutic regimens (Panchakarma and lifestyle advocacy, etc.), or parasurgical (Agnikarma, leech application, Ksharasutra, etc.) or surgical procedure or device in Ayurveda.

12.	Behavioral Research	Refers to studies of the behaviour of individuals, or groups, or organizations or societies.
13.	Biomedical and Health Research	Includes basic, applied and operational research designed primarily to increase the scientific knowledge about diseases and conditions (physical or socio-behavioral), their detection, cause and strategies for health promotion or amelioration of disease and rehabilitation and includes clinical research.
14.	Blinding / Masking	A method of “control experimentation” in which one or more parties involved are not informed of the treatment being given. Single blind refers to the study subject(s) being unaware, while Double blind refers to the study subject(s) and/or investigator(s), monitor, data analyst(s) are being unaware of the treatment assigned.
15.	Blinded studies	A blind or blinded study is an experiment in which information about the test is masked (kept) from the participant, to reduce or eliminate bias, until after a trial outcome is known. Double blinded means even the investigator does not know which is the test intervention.
16.	Case control studies	A study that compares participants who have a disease or outcome of interest (cases) with participants who do not have the diseases or outcome (controls), and looks back retrospectively to compare frequently the exposure to a risk factor is present in each group to determine the relationship between the risk factor and the disease.
17.	Case report form (CRF)	Case record form or case report form is printed, optical or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial participant.
18.	Case series	A case series (also known as a clinical series) is a type of medical research that tracks participants with a known exposure, e.g., participant who have received a similar treatment or examines their medical records for exposure and outcome.
19.	Clinical trials registry- India (CTRI)	A clinical trials registry is an official platform for registering a trial involving human participants in India.
20.	Clinical trial	A clinical trial is any systematic research / study that prospectively assign human participants or groups of humans to one or more health-related intervention/s to evaluation the safety and efficacy.
21.	Confidentiality	Maintenance of privacy of study subjects including their personal identity and all medical information, from individuals other than those prescribed in the Protocol. <i>Confidentiality</i> also covers the prevention of disclosure of sponsor’s proprietary information to unauthorised persons.
22.	Co-Investigator	A person legally qualified to be an investigator, to whom the Investigator delegates a part of his responsibilities.
23.	Data and Safety Monitoring Board	The Data and Safety Monitoring Board (DSMB) is a board, charged with monitoring the accumulating data from a pharmacotherapeutic clinical trial to detect and report early evidence of prespecified 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 research effort.
24.	Documentation	All records (including written documents, electronic, magnetic or optical records, scans, x-rays etc.) that describe or record the methods, conduct and results of the study, and the actions taken. The Documents include Protocol, copies of submissions and approvals from the relevant regulatory authority (if required), ethics committee, investigator(s)' particulars, consent forms, monitor reports, audit certificates, relevant letters, reference ranges, raw data, completed CRFs and the final report. Also see: Essential Documents
25.	Essential Documents	The Documents that permit evaluation of the conduct of a study and the quality of the data generated.
26.	Ethics Committee	An independent review board or committee comprising of medical / scientific and nonmedical / non-scientific members, whose responsibility is to verify the protection of the rights, safety and well-being of human subjects involved in a study. The independent review provides public reassurance by objectively, independently and impartially reviewing and approving the "Protocol", the suitability of the investigator(s), facilities, methods and material to be used for obtaining and documenting "Informed Consent" of the study subjects and adequacy of confidentiality safeguards.
27.	Final Report	A complete and comprehensive description of the study after its completion. It includes description of experimental and statistical methods and materials, presentation and evaluation of the results, statistical analyses and a critical ethical, statistical and clinical appraisal. The Investigator's declaration closing the study is a part of the Final Report.
28.	Good Clinical Practice (GCP)	It is a standard for clinical studies or trials that encompasses the design, conduct, monitoring, termination, audit, analyses, reporting and documentation of the studies. It ensures that the studies are implemented and reported in such a manner that there is public assurance that the data are credible, accurate and that the rights, integrity and confidentiality of the subjects are protected. GCP aims to ensure that the studies are scientifically authentic and that the clinical properties of the "Investigational Product" are properly documented.
29.	Informed Consent	Voluntary written consent of a subject's willingness to participate in a particular study and in its documentation. The confirmation is sought only after information about the trial including an explanation of its status as research, its objectives, potential benefits, risks and inconveniences, alternative treatment that may be available and of the subject's rights and responsibilities has been provided to the potential subject.
30.	Institution	Any public or private medical facility where a clinical study is conducted.
31.	Investigator	A person responsible for the conduct of the study at the trial site.



		Investigator is responsible for the rights, health and welfare of the study subjects. In case the study is conducted by a team of investigators at the study site then the designated leader of the team should be the Principal Investigator. Also see <i>Principal Investigator, Sub-investigator</i> .
32.	Monitor	A person appointed by the Sponsor or Contract Research Organisation (CRO) for monitoring and reporting the progress of the trial and for verification of data. The monitor ensures that the trial is conducted, recorded and reported in accordance with the Protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) and the applicable regulatory requirements.
33.	Multicenter Study	A clinical trial conducted according to one single protocol in which the trial is taking place at different investigational sites, therefore carried out by more than one investigator.
34.	Non-Clinical Study	Biomedical studies that are not performed on human subjects.
35.	Non-Therapeutic Study	A study in which there is no anticipated direct clinical benefit to the Subject(s). Such studies, unless an exception is justified, should be conducted in patient(s) having a disease or condition for which the Investigational Product is intended. Subject(s) in these studies should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.
36.	Pharmaceutical Product(s)	Any substance or combination of substances which has a therapeutic, prophylactic or diagnostic purpose or is intended to modify physiological functions, and presented in a dosage form suitable for administration to humans.
37.	Patent or Proprietary Medicine	In relation to Ayurvedic, Siddha or UnaniTibb systems of medicine, all formulations containing only such ingredients mentioned in the formulae described in the authoritative books of Ayurveda, Siddha or UnaniTibb system of medicine specified in the firstSchedule, but does not include a medicine which is administered by parenteral route and also a formulation included in the authoritative books as specified in clause (a)of Drugs & cosmetics Act, 1940 and rules 1945.
38.	Protocol	A document that states the background, objectives, rationale, design, methodology (including the methods for dealing with AEs, withdrawals etc.) and statistical considerations of the study. It also states the conditions under which the study shall be performed and managed. A list of items to be included in the Protocol is compiled in a subsequent chapter. The content and format of the protocol should take into consideration the adopted SoPs, the regulatory requirements and the guiding principles of GCP. The term Protocol, unless otherwise specified, relates to the latest amended version of the document, read in conjunction with all its appendices and enclosures
39.	Protocol	Any changes or formal clarifications appended to the protocol. All

	Amendment(s)	Protocol Amendments should be agreed upon and signed by the persons who were the signatories to the Protocol.
40.	Quality Assurance (QA)	Systems and processes established to ensure that the trial is performed and the data are generated in compliance with GCP. QA is validated through in-process Quality Control and in and post-process auditing of clinical trial process as well as data.
41.	Quality Control (QC)	The operational techniques and activities undertaken within the system of QA to verify that the requirements for quality of the trial related activities have been fulfilled. QC activities concern everybody involved with planning, conducting, monitoring, evaluating, data handling and reporting. The objective of QC is to avoid exposure of study subjects to unnecessary risks and to avoid false conclusions being drawn from unreliable data.
42.	Randomisation	The process of assigning study subjects to either the treatment or the control group. Randomisation gives all subjects the same chance of being in either group in order to reduce bias.
43.	Raw Data	It refers to all records or certified copies of the original clinical and laboratory findings or other activities in a clinical study necessary for the reconstruction and evaluation of the trial. Also see source data.
44.	Rescue Medicine	A supplementary treatment to relieve the trial subject of the symptoms caused by the investigated disease in a study, usually given to alleviate pain in placebo-controlled trials.
45.	Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (SADR)	An AE or ADR that is associated with death, inpatient hospitalisation (in case the study was being conducted on out-patients), prolongation of hospitalisation (in case the study was being conducted on in patients), persistent or significant disability or incapacity, a congenital anomaly or birth defect, or is otherwise life threatening.
46.	Source Data	Original documents (or their verified and certified copies) necessary for evaluation of the Clinical Trial. These documents may include Study Subjects' files, recordings from automated instruments, tracings, X-Ray and other films, laboratory notes, photographic negatives, magnetic media, hospital records, clinical and office charts, Subjects' diaries, evaluation check-lists, and pharmacy dispensing records.
47.	Sponsor	An individual or a company or an institution that takes the responsibility for the initiation, management and / or financing of a Clinical Study. An Investigator who independently initiates and takes full responsibility for a trial automatically assumes the role of a Sponsor.
48.	Study Product	Any Ayurvedic drug / Patent or Proprietary Medicines / therapies or comparator product used in a clinical study

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## Background

Quests for healthy and long life are perhaps as old as human existence and efforts are unremitting to address the challenges and triumph over the bottlenecks across this journey. Ayurveda—the science of life, evolved as a comprehensive system of healthcare systematically through scientific experimentations of high order backed by sound and reproducible evidence base and stood the test of the time. Several strategies and road maps are being drawn to carry forward merits of this science so as to meet the current day health needs and mainstream its core strengths alongside through research & development in this country and across the globe.

The fundamental aspects of holistic systems need adequate positioning, while designing clinical trials to examine the safety and efficacy of Ayurveda approaches. Furthermore, the other challenges and issues related to quality and safety viz. dosage forms/delivery system, diverse concepts and complex approaches in trial design, diagnosis and therapy, outcomes of clinical efficacy and drug interactions also pose certain limitations in research. A holistic approach may be adopted to validate the therapies and approaches with integration of principles of Ayurveda and bio-medicine without losing the vital fundamentals of both systems. Such an approach with well designed research plans could possibly facilitate to generate tangible evidence.

The areas of clinical research broadly comprise validation of the fundamental principles of Ayurveda; Validation and development of diagnostic/assessment tools ; standardization and validation of the therapy/ procedures; to establish dosage form, dose, duration, indication of any given drug as per the classics and to develop new regimen.

The expertise and experience of the investigators, all the equipments and infrastructure, trial drugs, necessary diagnostic methods and availability of participants according to the requirements of research question should be examined carefully and thoroughly to achieve the outcomes (*Upaya*).

A critical review of Ayurvedic literature reveals the reflection of epistemology of Ayurveda and its robust approach towards Research & Development. The methodical approaches adopted from *Darshanas* (Doctrines of Philosophy) form the basis of research tools for generation of evidence and development of classical Ayurvedic texts i.e. *Samhitas*. They comprise the following-

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- *Aptopadesa* (Evidence base on therapeutic leads)
- *Pratyaksha* (Direct evidence)
- *Anumana* (Logical inference)
- *Upamana* (Analogy:Comparative /Control design)
- *Yukti* (Reproducible Experimental Evidence)

The two way approach of experimentation and drug trials as mentioned in *Samhitas* forms the roots of clinical trial. As such, Sushruta Samhita narrated the methods and approaches viz. feasibility of test intervention (*Tatlingatwat*), observational design (*Dristaphalatwat*), System validation (*Agamaatsya*), for testing an intervention and interpretation of observations in the context of *Kriyakala* (stages of etiopathogenesis of a disease) which reflect the reverse pharmacology or reverse renovation approach of contemporary period. This could be well utilized as fast screening method of test interventions.

Further, Maharshi Charak's approach emphasizes on meticulous design and reproducibility. This comprise the issues such as Feasible ideology / Hypothesis (*Budhipashyati-ya-bhavaan*), multi dimensional approach in planning and assessment (*Bahukaranayogajaan*), appropriate design (*Yukti-Yojna*) perpetually valid outcome and reproducibility (*Yuktihtrikalah*).

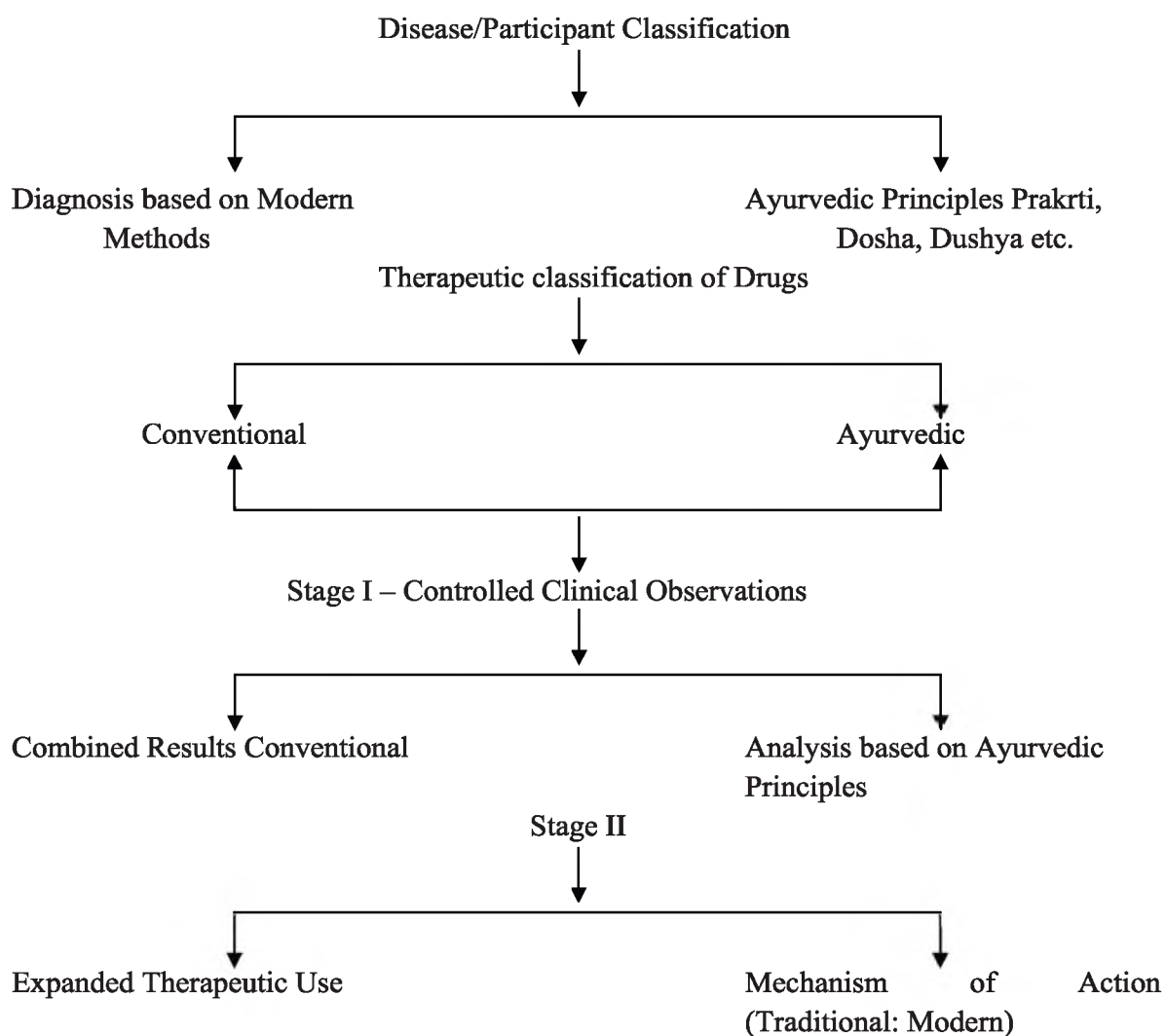
The concepts and methods are developed in course of time adding several new drugs, interventions and approaches right from Vedic period, Samhita period, medieval period and current era enriching the Ayurvedic pharmacopoeia and pharmaco-therapeutics. The evolution of Ayurvedic Pharmacopoeia is depicted in **Table 1**.

**Table 1: Evaluation of Ayurvedic pharmacopoeia**

Period	Plants	Remarks on changes	Literature
3000 BC - 1000 BC	289	Building a Pharmacopoeia (Atharvaveda)	Vedic texts
1500 BC - 500 AD	650	Incorporation/discarding drugs	Ayurvedic Texts <ul style="list-style-type: none"> <li>• Charaka Samhita</li> <li>• Sushrut Samhita</li> <li>• AstangaSamgraha</li> </ul>

500 AD-1900 AD	2000	Incorporation/discarding drugs Varieties identified Substitutes identified Expansion in applications	16 major Nighantus (like Dhanvantri Nighantu, Bhavprakash Nighantu, Raj Nighantu upto Shaligram Nighantu)
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In light of the above it is essential to adopt an interdisciplinary approach for validation of Ayurvedic drugs and therapies without losing core fundamentals of Ayurveda. The suggested model is in **Figure 1**.



**Figure 1: Evidence Base in Ayurveda: Suggested Approach**

# General Methodologies & Guidelines of Drug Development

## PREPARATORY PHASE (1)

Prevalence survey and Formulation of drug /combination for Specific targeted indication and activity (1) (Appropriate basis of literary survey, previous clinical data of ingredients /any other data of claims, classical evidences, etc.)

Formulation of SOPs and Standardization, stability studies, Quality assurance (4) (Considering the classical methods and current available physical/ chemical, Biological parameters, microbial loads, heavy metal estimation, pesticide residues, etc. for standardization and safety).

Design of study and formulation of

Clinical protocols (7) (As per current guidelines and adopting Classical methodology)

Bulk preparation of quality assured Drug for clinical trial, packing labeling etc. as per requirement

## DRUG DEVELOPMENT PHASES (2-8)

Collection of raw drugs (2) (considering current good agricultural practices good field collection practices and classical textual methods)

Pre clinical safety studies (5) (acute/sub-acute/chronic studies as per intended therapeutic use with IAEC approval)

Execution of Clinical Trial (8)

with approval of IEC/IRB and CTRI registration Trial conduct and monitoring

Data analysis

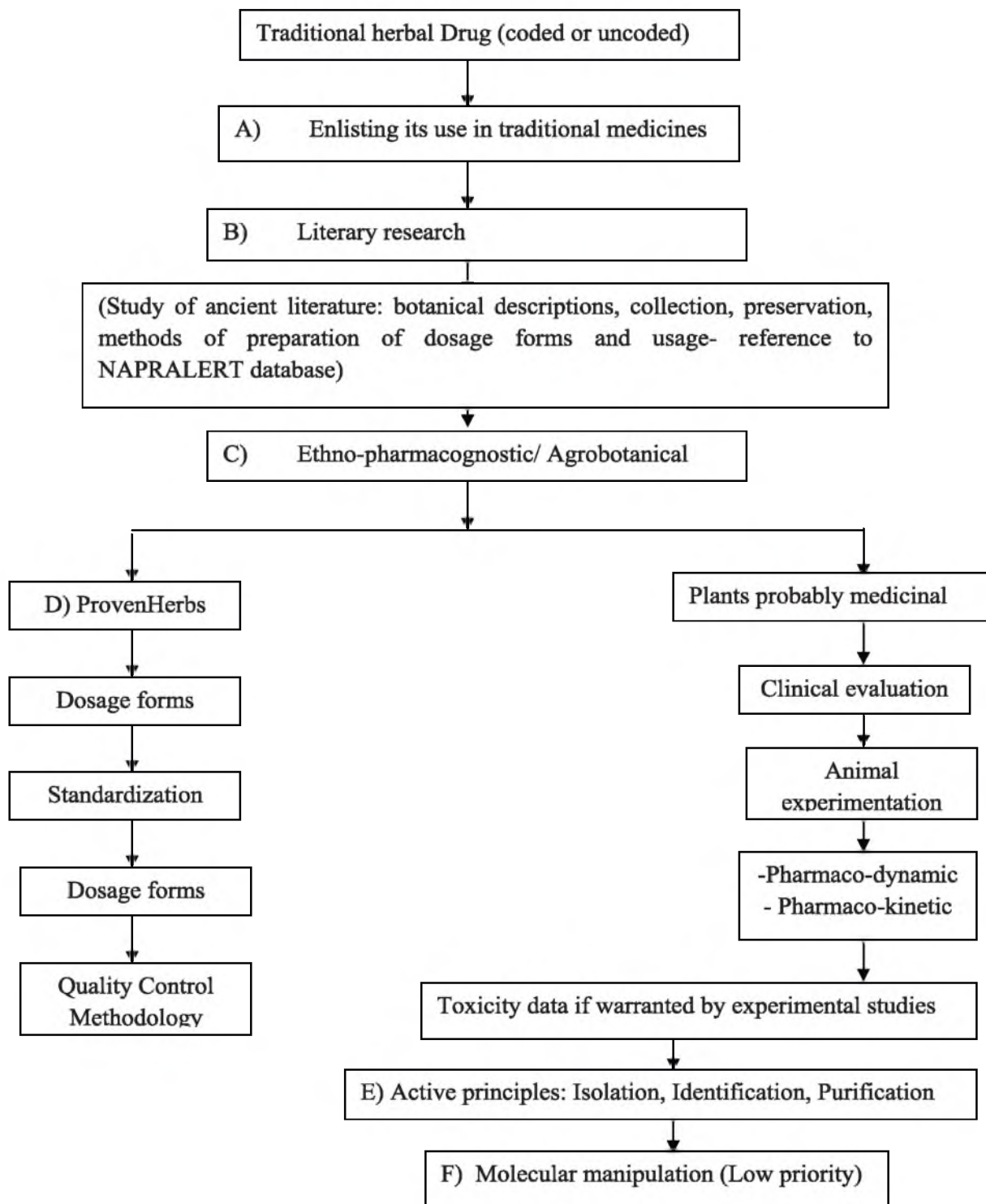
Botanical identification/ Pharmacognostic/Chemical studies of ingredients. (3) (based on available guidelines and classical methodology.)

Animal Studies for biological activity and /or mechanism of action for clinical correlation (6) with IAEC approval. (preparation of preclinical dossier)

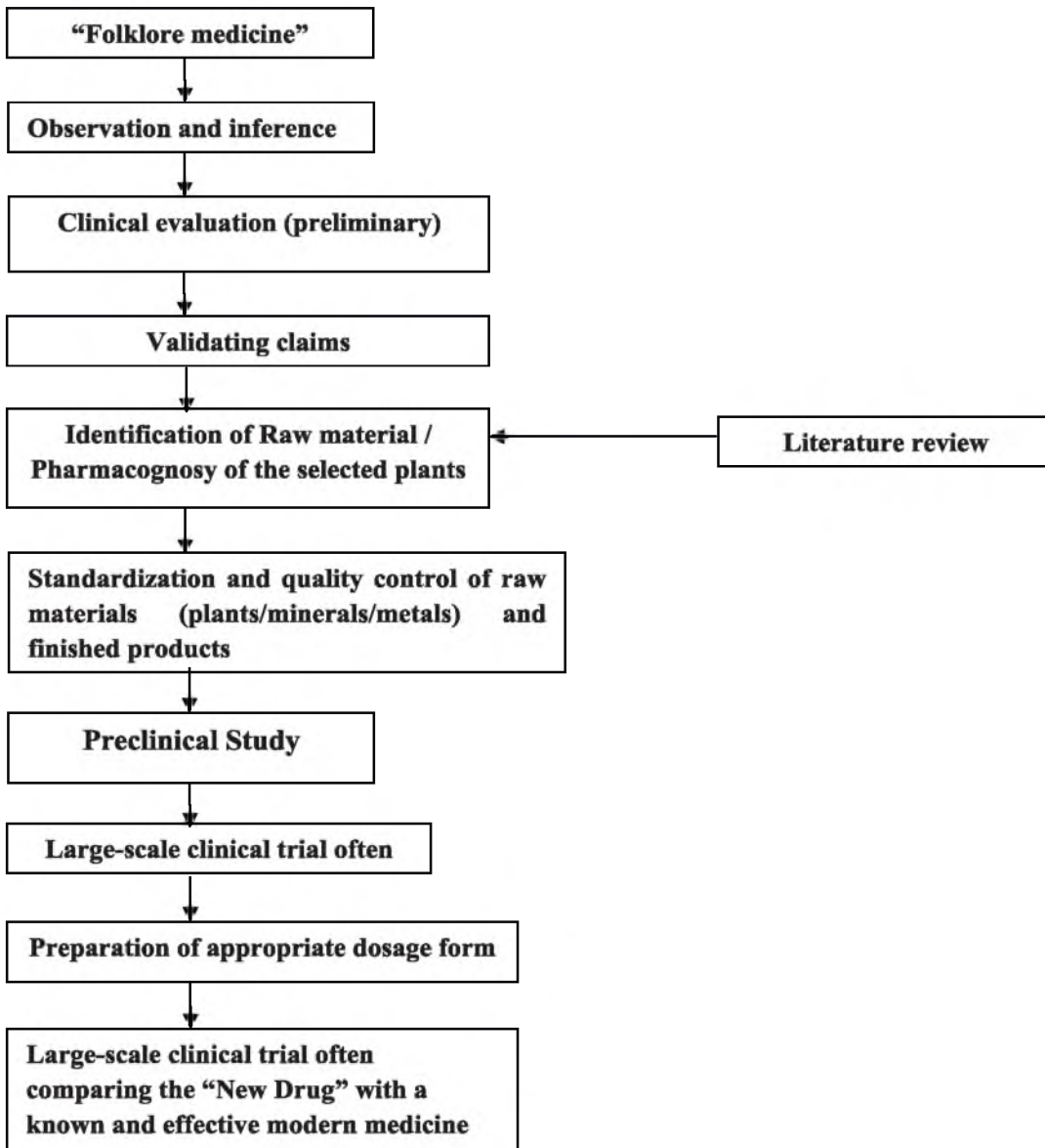
Note: IPR Protection and issues of filing of patent to be addressed at suitable stage.

Figure 2: General Research Guidelines and Methodologies for Drug Development at a Glance





**Figure 3: Scheme for Research on herbal medicines**



**Figure-4: Suggested approach for the inclusion of “Folklore” herbal medicines in modern Pharmacopoeia**



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## 1. Clinical Research protocol at a Glance (Limit to 1-2 pages)

<b>Title:</b>	<i>Include title of the study with type of trial (e.g., dose-ranging, observational, double-blind, etc.)</i>
<b>Objectives:</b>	<i>Include study objectives Primary: Secondary:</i>
<b>Outcome measures</b>	<i>Include primary/secondary outcome measures and method by which outcome will be determined. Primary: Secondary:</i>
<b>Population:</b>	<i>Include sample size, gender, age, general health status, geographic location, etc</i>
<b>Phase:</b>	<i>Mention the phase of the study (I, II, III, IV)</i>
<b>Number of Sites:</b>	<i>Single/ Multi-centre</i>
<b>Study Design:</b>	<i>Open label, Randomized, Masking etc.</i>
<b>Study Duration:</b>	<i>Provide time from when the study initiation and until the study completion with close out. .</i>
<b>Participant's participation Duration:</b>	<i>Provide time it will take to conduct the study for each individual participant.</i>
<b>Description of study intervention:</b>	<i>Include name of the intervention alongwith reference, dose, dosage form, Anupana (vehicle), route of administration and references along with the name of the intervention</i>
<b>Estimated time to complete the enrollment</b>	<i>Provide estimated time from enrollment into study of the first participant to enrollment into study of the last participant.</i>
<b>Utility of the study outcome</b>	

## 2. Pre-Requisite for Clinical Research

### 2.1. Intervention Details

#### 2.1.1. Drug

##### a. Quality assurance & standardization of the trial drugs

The standardized drugs (as per pharmacopoeial standard/ in house standard) should be



taken for the trial. The physical characteristics along with passport data of raw drugs, standard operating procedures for preparation, certification of analysis of both raw materials and finished product should be properly documented. (*For this purpose, the guidelines for quality assurance, CCRAS 2018 can be referred*).

- b. Safety/ toxicity studies & Biological activity:***For this purpose, the guidelines and directives for safety/toxicity of Ayurvedic interventions, CCRAS 2018 can be referred.*

### 2.1.2. Therapy/ Procedure

Following factors may be considered while designing efficacy studies/validation of the therapy or procedures

#### General consideration for *Panchakarma*/other Procedures

- Suitable, unsuitable persons for the therapy/procedures/diseases
- Pre and post therapeutic procedures
- Ideal season/periods
- 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/Procedures
- Quality of medicine
- Subjective and objective parameters of evaluation

#### 2.1.2.1. *Panchakarma* procedures

(Please refer Guidelines on basic training and safety in *Panchakarma*-available at CCRAS Website)

i. *Poorvakarma* (Preparatory procedures)

*Deepana*(Appetizer),*Pachana* (Digestive) ,*Snehana* (internal/external use of oil/ghee) and *Swedana* (Medicated sudation)

- Source of procurement of trial drug
- SoPs for the preparation of drug(s)
- Dose and Dosage form
- Route of administration
- Time of administration
- Duration

ii. *Pradhankarma* (Main Procedures)

*Vaman Karma*(Therapeutic Emesis),*Virechan Karma* (Therapeutic purgation), *Anuvasan*



*Basti*(Oil/Unctuous Enema), *Asthapana Basti* (Decoction based enema) and *Nasya Karma*(Nasal administration of medicaments)

- Source of procurement of trial drug(s)
- SoPs for the preparation
- Dose and Dosage form
- Route of administration
- Time of administration
- Duration
- vehicle along with justification (classical/published data)
- End Point of the Procedure( *Samyak lakshan*)

iii. *Paschatkarma* (Post Therapy Procedures)

- Specific *paschatkarma* according to *pradhan karma*
  - *Samsarjana karma* (Special Dietary regimen) with duration
  - *Pathya-apathya* (Diet and Life style)
- Assessment of Participant compliance with study Intervention
- Procedure for monitoring the participant compliance to therapy
- Protocol for any other procedures like *Shirodhara, Shiobasti, Janubasti, Uttara basti, Janudhara, Katibasti, Tarpana, Vidalaka*, etc. may be designed as per above said panchakarma guidelines

iv. *Samsarjana karma* (Special Dietary regimen) with duration

After *pradhan karma*, digestion power diminishes, hence as per Ayurvedic principles researcher should advise the participants to take diet in a specific manner gradually increasing from liquids to semisolids and then to solid materials in a specific time according to the *Pravara/madhyama/ avara shudhhi* (Detoxification) achieved in the procedure.

Special diet can be given in the meal timings (Twice/day) which start after *Pradhan karma* from the evening of that day. . It may last for 7 days in *Pravara*, 5 days in *Madhyama* and 3 days in *Avara Shuddhi*. Later, the person may be allowed to take normal diet.

### **2.1.2.2. Parasurgical Procedures**

i. ***Ksharasutra***

- Description of material and method
- Source of procurement if any
- SOPs for Preparation



- Time of administration
  - Duration
  - Pre and post-operative procedures
- ii. ***Agni karma***
- Description of material and method
  - Time of administration
  - Duration
  - Pre and post operative procedures
- iii. ***Rakta Mokshana***
- Description of material and method
  - Time of administration
  - Duration
  - Pre and post operative procedures
  - *Samyaka Lakshana*

## **2.2. Data on pilot/preliminary study (If applicable)**

Data on pilot study is essential in order to evaluate the feasibility, time, cost, adverse events, and effect size (statistical variability) for calculating the appropriate sample size and the study design prior to plan a clinical trial.

## **2.3. Study Protocol**

Study protocol is the plan of the study to attempt or achieve the research question. It is the vision of an Investigator by which the work is carried out to accomplish.

### **2.3.1. General Information**

- Protocol title, protocol identifying number and date. All amendments should bear amendment number and date(s)
- Name, address & contact details of the sponsor and the monitor / CRO
- Name and designation of the persons authorised to sign the protocol and the protocol amendments for the sponsor.
- Name, title, address and contact details of the sponsor's medical expert for the study
- Name(s), title(s), address(es) and details of the investigator(s) who is / are responsible for conducting the study, along with their consent letter(s)





- Name(s), address(es) and details of the institution(s) - clinical laboratories and / or other medical and technical departments along with the particulars of the head(s) of the institution(s) and the relevant department(s)

### **2.3.2. Background information and Scientific Rationale**

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

#### **2.3.2.1. Research question/Hypothesis (*Pratisthapana*)**

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 and do not have sufficient information to answer a question; there is a gap in the result of previous study(s) or the results or explanation of several investigators disagree with each other's or desire for an innovation; *review and discussion of important literature and data that are relevant to the trial- 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.*

#### **2.3.2.2. Description and justification for the population to be studied**

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

#### **2.3.2.3. Interventions (if applicable)**

The name and description of the study intervention/investigational products(s)/ therapy along with references; *Justification for the selection of the interventions* along with the route of administration, dosage, dosing regimen, intervention periods, or behavioral intervention methods; *findings/ leads from previous clinical studies; findings of the pre-clinical studies (in vitro or in vivo) that potentially have clinical significance, etc. should be in detail.*

#### **2.3.2.4. Potential Risks**

The relevant literature or other sources of information with reference may be reviewed for any potential risks of the study/interventions to human participants and should be provided in the background. Any risk reported in the pre-clinical study must also be provided. Further, if the Principal Investigator (PI) predicts any other risks to human participants should be addressed in the background.



### 2.3.2.5. Potential Benefits

The potential benefits in terms of physical, psychological, social, legal, economic, or any other benefits (payment to the participant if any, is not considered) to the human participants Should be mentioned. Further, if Investigator predicts any other benefit that may also be recorded.

## 2.4. Study Objective

An objective is the reason for performing the study i.e. to find answer of the research question by the analysis of data collected during the study. The objectives of a study should be clearly specified from the beginning as it forms the basis for study design.

These typically include:

- Statement of purpose, e.g., to assess, to determine, to compare, to evaluate
- General purpose, e.g., efficacy, safety, health seeking trends, epidemiological studies
- Specific purpose, e.g., dose-response, superiority to placebo, non-inferiority to current standard of care.
- Name(s) of intervention (e.g., procedure, drug, behavioral intervention) being evaluated, specification of doses or dose ranges to be studied, dose regimens etc.

A clinical study mainly has a **primary or core objective**. Other additional objectives, if any, are called **secondary objectives**. For example- If in a study, the effect of *Medohara Guggulu* on *Sthaulya* (obesity) is to be assessed then the primary objective may be written as “To assess the effect of *Medohara Guggulu* on weight loss/ *Sthaulya* (obesity) and if the clinical safety/improvement in the quality of life or increase in work efficiency, etc. have to be assessed, then these maybe treated as secondary objectives.

## 2.5. Study Outcomes

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*.

### 2.5.1. 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).



### 2.5.2. 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- If 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 1<sup>st</sup> or 2<sup>nd</sup> or 3<sup>rd</sup> 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.*

### 2.6. 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)
- A discussion of the rationale for design features
- 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 study enrollment
- The expected duration of participant participation
- Identification of the test agent and specifics 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 stratifications



- Methods for collecting data for assessment of study objectives
- Other protocol-specific details, such as centralization of evaluations (e.g., central laboratory or central reading center for clinical scans)
- Interim analysis plans

### 2.6.1. Phases of clinical trial for Ayurvedic drug / Patent or Proprietary Medicines

A systematic study of Ayurvedic drug / Patent or Proprietary Medicines on human participants – (Whether participants or non-participant volunteers) – in order to discover or verify the clinical, pharmacological (including pharmacodynamics / pharmacokinetics), and / or adverse effects, with the object of determining their safety and / or efficacy.

#### 2.6.1.1. Human Pharmacology (Phase I)

- i. The objective of studies in this Phase is the estimation of safety and tolerability with the initial administration of an Ayurvedic Drugs / Patent or Proprietary Medicines into human(s). Studies in this Phase of development usually have non-therapeutic objectives and may be conducted in healthy volunteers or certain types of participants. Ayurvedic drug / Patent or Proprietary Medicines with probable toxicity e.g. Ayurvedic drug / Patent or Proprietary Medicines with Schedule E-I ingredients are to be studied in participants. Phase I trials should preferably be carried out with access to the necessary facilities to closely observe and monitor the Participants.
- ii. Studies conducted in Phase I, usually intended to involve one or both of the following objectives:-
  - a. **Maximum tolerated dose:** To determine the tolerability of the dose range expected to be needed for later clinical studies and to determine the nature of adverse reactions that can be expected. These studies include both single and multiple dose administration.
  - b. **Early measurement of Drug activity:** Preliminary studies of activity or potential therapeutic benefit may be conducted in Phase I as a secondary objective. Such studies are generally performed in later Phases but may be appropriate when drug activity is readily measurable with a short duration of drug exposure in participants at this early stage.

#### 2.6.1.2. Therapeutic exploratory trials (Phase II)

- i. The primary objective of Phase II trials is to evaluate the effectiveness of an Ayurvedic drug / Patent or Proprietary Medicines for a particular indication or indications in



participants with the condition under study and to determine the common short term side-effects and risks associated with the drug. Studies in Phase II should be conducted in a group of participants who are selected by relatively narrow criteria leading to a relatively homogeneous population. These studies should be closely monitored. An important goal for this Phase is to determine the dose(s) and regimen for Phase III trials. Doses used in Phase II are usually (but not always) less than the highest doses used in Phase I. These studies should be intended to provide an adequate basis for marketing approval for Ayurvedic drug / Patent or Proprietary Medicines.

- ii. Additional objectives of Phase II studies can include evaluation of potential study endpoints, therapeutic regimens (including concomitant medications) and target populations (e.g. mild versus severe disease) for further studies in Phase II or III.
- iii. These objectives may be served by exploratory analyses, examining subsets of data and by including multiple endpoints in trials.

#### **2.6.1.3. Therapeutic confirmatory trials (Phase III)**

- i. Phase III studies have primary objective of demonstration or confirmation of therapeutic benefits(s). Studies in Phase III are designed to confirm the preliminary evidence accumulated in Phase II that a drug is safe and effective for use in the intended indication and recipient population. Studies in Phase III may also further explore the dose-response relationships (relationships among dose, and clinical response), use of the drug in wider populations in different stages of disease, or the safety and efficacy of the drug in combination with other drug(s).
- ii. For Ayurvedic drug / Patent or Proprietary Medicines intended to be administered for long periods, trials involving extended exposure to the drug are ordinarily conducted in Phase III, although they may be initiated in Phase II. These studies carried out in Phase III complete the information needed to support adequate instructions for use of the drug (prescribing information).
- iii. For Ayurvedic drug / Patent or Proprietary Medicines approved outside India, Phase III studies needs to be carried out primarily to generate evidence of efficacy and safety of the Ayurvedic drug / Patent or Proprietary Medicines in Indian participants when used as recommended in the prescribing information. Prior to conduct of Phase III studies in Indian participants.
- iv. If the application is for the conduct of clinical trials as a part of multi-national clinical development of the drug, the number of sites and participants as well as the justification





for undertaking such trials in India should be provided to the Licensing Authority along with the application.

#### **2.6.1.4. Post Marketing Trials (Phase IV)**

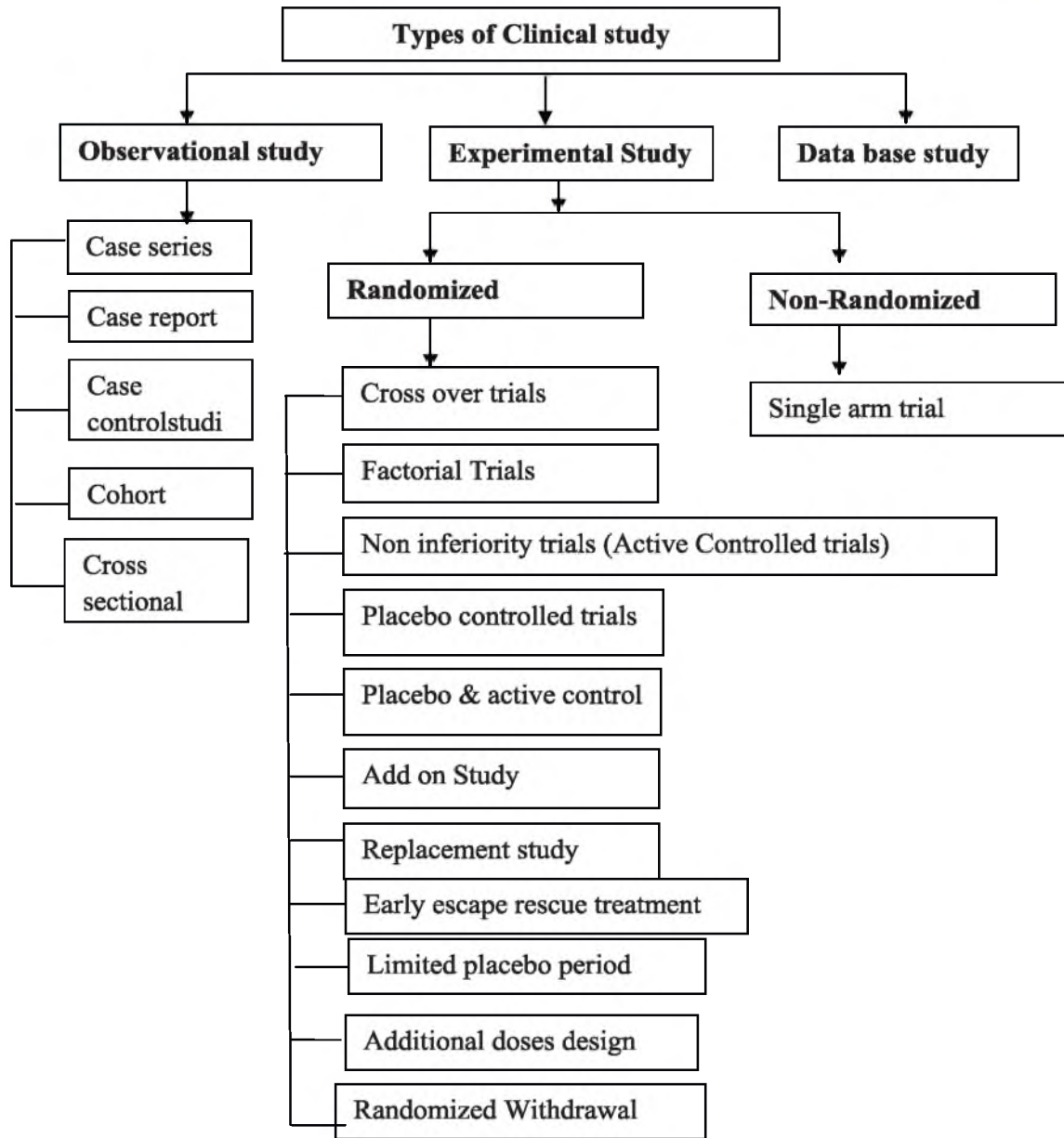
Post Marketing trials are studies (other than routine surveillance) performed after drug approval and related to the approved indication(s). These trials go beyond the prior demonstration of the drug's safety, efficacy and dose definition. These trials may not be considered necessary at the time of new drug approval of Ayurvedic drug / Patent or Proprietary Medicines but may be required by the Licensing Authority for optimizing the drug's use. They may be of any type but should have valid scientific objectives. Phase IV trials include additional drug-drug interaction(s), dose-response or safety studies and trials designed to support use under the approved indication(s), e.g. mortality/morbidity studies, epidemiological studies etc.

#### **NOTE:**

- For classical Ayurvedic drugs with same textual indications, directly phase III/IV trial may be conducted.
- For classical Ayurvedic drug with new indications/Patent or Proprietary Medicines, directly phase II trial may be conducted.
- Patent or Proprietary Medicines with Schedule E-I ingredients, Phase I trials may be conducted as appropriate.

#### **2.6.2. Types of the clinical study**

A clinical study involves research using human volunteers (also called participants) that is intended to add to medical knowledge. There are mainly two types of clinical studies: **experimental studies and observational studies**. *Brief descriptions of these studies are as under:*



**Figure 5: Types of clinical studies**

### **2.6.2.1. Observational Study**

An observational study is one which tries to explore the cause-and-effect relationships. Like experimental study the Investigators is not able to control the participants by allocating in groups or assigning any particular treatment. The Investigators only observe the participants involved and their responses by asking questions, or taking some measurements, or looking at clinical records. A sample survey is an example of an observational study. Followings are observational studies:



**Case series studies:** Case-series is a descriptive study design wherein a series of cases of any particular disease that one might observe in one's clinical practice, hospital and so on is presented. There is no control group in this type of study. In terms of evidence, this is a weak study design but *it can help provide leads in designing research studies*.

**Case reports:** Documentation of reports on a single participant constitutes case reports. They do not use control groups and hence do not have high statistical validity or cannot provide conclusion about the causality *but can provide leads to formulation of a hypothesis for potentially high impact research studies*.

**Case control studies:** When a correlation is drawn between factors or exposures as causal in participants who have a specific health condition. These studies are *retrospective* when the history and reports of the participant is analyzed and a correlation is drawn if they might have been causal. This is compared with the history and reports of participants who do not have the health condition. This level of evidence in such studies is low when compared to randomized controlled trials or cohort studies because just a statistical association do not necessarily conclude cause and effect relationship. *For example- tobacco and cancer*.

**Cohort studies:** A 'cohort' meaning is a population who are exposed to similar environmental conditions. This is a kind of observational study where one group of a cohort with exposure to a particular causative agent or a treatment is compared with a similar group who are not exposed. They are followed up prospectively. The level of evidence here is lower when compared to randomized controlled trials. *For example, tobacco use among working and none working adolescents*.

**Cross sectional studies:** A cross sectional study is an observational study that aims at determining the exposure and prevalence of disease at the same point in time in a given population for e.g., prevalence of post traumatic stress disorders in people after Tsunami. It can also be used in determining the sensitivity and specificity of new diagnostic tests.

#### **2.6.2.2. Experimental Study**

In a clinical trial, participants receive specific interventions according to the research plan or protocol created by the Investigators. These interventions may be medical products, such as drugs or devices; procedures; or changes to participants' behavior, such as diet. Clinical trials may compare a new medical approach to a standard one that is already available, to a placebo that contains no active ingredients, or to no intervention. Some clinical trials compare





interventions that are already available to each other. When a new product or approach is being studied, it is not usually known whether it will be helpful, harmful, or no different than available alternatives (including no intervention). The investigators try to determine the safety and efficacy of the intervention by measuring certain outcomes in the participants. *The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design.*

**Single arm trials:** Single arm trial is the simplest trial design. A sample of participants with a particular disease is administered an intervention and the effect is measured after a decided period of time to observe the response. This design is adopted where placebo effect is minimal or there is no scope for incorporating or it is unethical to include a placebo arm. The level of evidence is low in this design usually. *However, it is apt for validation of Panchakarma procedures, application of leech, Agnikarma, Ksharasutra, etc.*

**Cross over trials:** In a cross over design, the objective is to compare the effect of therapies. The trial participant is randomly allocated to one treatment protocol for a period of time and then later after a wash out period, the same participant is randomly allocated to another treatment protocol and the effects of treatments are compared.

**Factorial Trials:** Factorial designs are considered when the objective of the study is to compare effects of a minimum of two treatment protocols either alone or in combination. For example, if there are two interventions A and B then group-1 is given intervention A, group- 2 is given B, group- 3 is administered both A and B and group- 4 is given neither. *Factorial designs are considered when the effects of more than two interventions are to be evaluated.*

**Non inferiority trials (Active Controlled trials):** This type of trial design consists of testing the effect of a particular treatment in comparison with an available standard treatment. Non inferiority trials are designed to effectively evaluate the effect of a particular intervention where incorporation of a placebo group is unethical.

**Parallel design: Placebo controlled trials:** A placebo is an agent that produces an effect on the disease through a psychological mechanism i.e., through a non specific effect which does not comply with a definable, physiological mechanism. Therefore, placebo effect needs to be nullified to prove that drug /therapy /formulation intended to produce an effect on the disease occurs genuinely through a definable bio - physiological mechanism. Placebo controlled design with randomization and blinding produces highest evidence. They require large sample sizes.



**Three arms trial: Placebo & active control:** This design involves inclusion of a placebo as well as an active control group and provides good internal evidence of sensitivity.

**Add on Study:** An add on study is a placebo-controlled trial wherein a new agent is concomitantly administered in participants in addition to receiving a standard treatment. These kind of studies are useful when the existing treatment is not fully effective and there is evidence that another treatment in addition can bring about better outcomes and if there are no adverse drug reactions or interactions.

**Replacement study:** In this design a new drug or placebo is randomly added to the conventional treatment and the conventional treatment is then slowly withdrawn usually by tapering. This design can effectively evaluate the ability of the participant to maintain the baseline status after withdrawal of the conventional treatment.

**Early escape rescue treatment:** If in a trial, administration of a treatment protocol is either ineffective or if it results in worsening of the disease and who otherwise would require a rescue treatment like in seizures or angina then the trial treatment is withdrawn. Here the need to change the treatment becomes the study end point. This design evaluates short term effectiveness of a treatment protocol.

**Limited placebo period:** In situations where it is not possible to continue the participants for long duration of placebo administration the placebo group is maintained for a short duration and then the trial would go on with an active control group without the placebo group. This design evaluates short term effectiveness of a treatment protocol.

**Additional doses design:** This design involves randomizing participants into parallel groups of different fixed doses of a certain treatment protocol. This design evaluates dose based response.

**Randomized withdrawal:** In this design participants getting a test treatment for a particular period of time are randomly assigned to continued test treatment and placebo. Difference between those receiving continued treatment and those on placebo reveals the effect of active treatment and evaluates the status of remission or aggravation of a particular disease and long term efficacy.

**No-treatment concurrent control:** No treatment concurrent control design involves randomization of participants into test treatment and no treatment. This design can be used when it is not possible to use double blinding.



**External control (including historical control):** This is a comparative trial where participants receiving an active treatment is compared with a control from another study at another setting at the same point of time (External control) or if it is taken from a study conducted at an earlier point of time (historical control) it is known as external control.

### **Designs Amenable to test Ayurvedic Therapies**

#### **Black-box design**

Generally Ayurvedic treatments are not just isolated administration of a therapeutic molecule or a single drug but, are a combination of drugs/procedures that constitute a therapy for a particular health condition for a particular individual. Therefore, a traditional treatment that may consist of a set of therapeutic procedures should be considered as one single module which is studied in comparison with either placebo or a standard treatment. This allows the Ayurvedic treatments to be determined within its theoretical framework and not compromising with the fundamental principles of traditional medicine.

#### **Reverse Pharmacology Design**

In the realm of traditional 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 Ayurvedic 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. 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 Ayurvedic drug on the biological systems is done.

**RP-Phase II:** The purpose of this phase is to evaluate the target activity of the Ayurvedic 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 organization 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.



### **Ethnographic design for folk claims**

Ethnographic design is one that is used in 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 can lead to further research.

Designing a placebo in most of the Ayurvedic interventions is not possible as principles of Ayurveda follow the system biology approach where the response to a therapy is evaluated in terms of the body as a whole and not confined individual system. Most of the drugs are also poly formulations consisting of ingredients from plant, mineral and animal origins and not an active molecule as in case of the modern system of medicine. It is very difficult to have the trial drug and placebo are prepared in a way that they are similar in colour, taste, size, weight, same smell and same consistency.

Therapy in Ayurvedic system of medicine also involves procedural interventions like Panchakarma in Ayurveda and so on for which designing placebo becomes impossible. In such cases, appropriate control groups can be incorporated like active controls or no interventions etc. Different controls can be used in clinical trials to answer different questions. The use of a placebo, when possible, is desirable, because it generates evidence of better quality. Placebo-controlled trials are intended to establish whether treatment is valuable over and above what might be achieved by a control treatment, and not whether treatment is valuable at all. Thus, it allows Investigators to distinguish specific from non-specific effects of treatment in order to determine whether the additional cost, risk and effort of a specific treatment are worthwhile. It is also important for understanding the mechanism of a treatment. This is true for the evaluation of all drugs. It is not only of academic interest, but is also practical value, especially for developing new treatments from traditional ones. However, in some cases, placebo controlled trials may not be possible.

#### **2.6.2.3. Data Based Studies**

**Systematic reviews:** These are 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 e.g., Effect of herbal medicines with significant effect on Hamilton depression rating scale in participants 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.

*Data based studies on Ayurvedic drugs can provide much needed evidence to recommend use of Ayurvedic interventions among scientific community.*

Conventionally, the level of evidence is ranked in order of risk of bias and from top to bottom ranked as Meta-analyses, Systematic reviews, Interventional studies, Observational studies and experts' opinions. (See Annexure III- Level of evidence)

However, due to classical textual evidence, long history of use and vast clinical experience, this hierarchical ranking of level of evidence may not be completely apt for Ayurveda and its approaches.

## **2.7. Randomization**

Randomization is used to develop comparable groups to assess therapeutic interventions. It is essential to control various known, and even unknown, biases. Nevertheless, there are many situations where randomization can be impossible or unethical. The best way to solve this problem is probably by the proper selection of control treatments.

### **2.7.1. Randomization method and procedure (wherever applicable)**

**Simple random samples:** This is a procedure where each individual of a population has equal probability of being selected. A simple random sample is representative of a population and gives external validity. The results obtained have good generalize ability of results. Random number generators are available online. It can also be generated using excel sheet.

**Random allocation:** Random allocation is a procedure of randomly allocating an identified sample to different groups. Each participant has the same probability of being assigned to a particular group.

**Block randomization:** This randomization procedure helps in achieving same sample size in two or more groups. Block randomization is done by generating random permuted blocks (blocking). For e.g., in a block size of six consecutively enrolled participants three can be allocated to one treatment group and three to another. The ratio of allocation can also change. This method helps in interim analysis.





### **Stratified randomization**

To avoid imbalances among baseline characteristics, pre-randomization stratification is done based on requirement like Age, Gender, prognostic factors etc.

#### **2.7.2. Methods of blinding**

Blinding is a process of ensuring that the people involved in a research study (participants or investigators) do not know about what treatment they are receiving. This procedure is incorporated to minimize the biases that arise due to differences in treatment, management, investigator who is carrying out the study, rather who assesses the participants or one who interprets the results. These biases arise because participants who know about the active treatment might report more favorable outcomes. The Raters or Investigators who know about the treatment may over enthusiastically rate the response to a treatment or they might undermine the response to placebo or no treatment. Knowledge of treatment might influence the people to use favorable statistical tests.

**Open:** The participants, investigators, and data analyst know about what treatment they are receiving.

**Single blind:** Here either the participant or investigator does not know about the treatment.

**Double blind:** Here neither the participant nor the investigator knows about the treatment.

**Triple blind:** This is a blinding procedure in which the participant, the investigator and the data analyst does not know about the treatment.

#### **2.7.3. Randomization Codes and Procedures for Breaking the Code**

##### **Breaking the codes/Un-blinding in case of emergency**

Randomization codes are computer generated. Requirement for unblinding arises out of an emergency. The Investigator gets the primary information about the emergency and therefore he should have a developed mechanism for breaking the codes. The investigator should access to sealed envelopes 24 hours a day. He can also delegate a suitable person to carry out the code break. The sponsor should be notified about the code break within 24 hours. In a non emergency situation the code- break cannot be done without the approval of the sponsor.

##### **Breaking the codes/Un-blinding at the end of the trial**

Breaking the codes/un-blinding is done by a formal request to the Sponsor and head of the Institute but should not be done until the following events have been completed

- Completion of last follow up of the participant
- All data has been entered and validated and there is no scope for further changes



- It is better that the statistician is also blinded until the analysis is complete.

*\*Information on establishment of study code, where it will be kept and when, how, and by whom it can be broken in the event of an emergency.*

### **Allocation concealment**

Allocation concealment is a procedure that ensures that either participants or investigators does not know what is being received by the participant. Ideally, the procedure is done as follows: The trial drug and placebo are prepared in a way that they are similar in colour, taste, size, weight and smell.

In double blind study a random sequence of codes is generated centrally and assigned to the prospective participants. Sequentially numbered sealed opaque coded envelopes with aluminium foils to prevent revealing against bright light are assigned to each trial participant with details of the treatment inside. After obtaining the consent, the random code is assigned to the participant. The envelopes are generally stored in the pharmacy and the pharmacist gives the containing drug or placebo to the participant.

In single blind studies where the investigator knows about what the participant is going to receive, the centrally generated random sequence of numbers is assigned to the prospective participants in terms of who is going to receive drug or placebo. The sequentially numbered sealed envelopes are coded for drug or placebo. The codes should not be in such a way that if the un-blinding is done for one participant in case of emergency then, it should not reveal the codes for all the participants. For example, if '0' is used to code placebo and '1' to drug, then if an emergency situation necessitates, un-blinding the information about all the participants is automatically revealed.

The codes could be generated and kept by the sponsor / central funding agency and will be broken by them in case of emergency.

### **Documentation of decoding during the study**

Following information needs to be documented before code break-

- The identity of the person requesting code break
- Reason for requesting the code break
- Bottle or box number of the trial medication
- Participant number
- Name of the person authorizing the code break procedure

*\*This information should be documented and preserved along with the case record form*



## Blind assessment

Blind assessment is a critical component of conventional evaluation of therapeutic interventions. However, in the evaluation of efficacy of procedure-based therapies (such as *Panchakarma therapy, Ksharasutra, Agnikarma, Jalauka therapy*, etc) and Multi drug regime it may be difficult, impractical or impossible for the Investigator to be kept ignorant of what treatment the participants are receiving.

Treatment blinding in the evaluation of Ayurvedic medicines should adopt the approach of conventional medicines, e.g. using active and control formulations with similar appearance, taste and weight. However, if the Ayurvedic medicine cannot be administered in a predetermined standardized formulation, it will be impossible to keep the treatment blinded.

## 2.8. Study period

### 2.8.1. Total duration of the study

Mention the total duration of the study from preparatory phase to analysis of the data.

### 2.8.2. Timelines with deliverables

A timeline is a way of displaying a list of events in chronological order to be happened in the project. Project timeline outline the deliverables (important milestones and task) of a project in chronological sequence. This helps all project resources and stakeholders see what deliverables need to be accomplished next and by what date. Having a visual project timeline that clearly communicates the important milestones and tasks is an essential tool for successful planning or project management. An example is given below-

Deliverables	Time Lines
Pre-trial preparations: Procurement of drugs and equipment, engagement of staff, preparation of CRFs, Institution ethical clearance, arrangement for laboratory investigations, publicity, registration in the CTRI wherever applicable	1-3 months
Recruitment and data collection	4-18 months
Data compilation and analysis	19-24 months

**Duration of the Treatment:**Duration of the participant participation and a description of the sequence of all study periods including follow-up, if any should be recorded.





## 2.9. 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

## 2.10. Participant enrollment and withdrawal

### 2.10.1. Participant Inclusion Criteria

Provide a statement that participant must meet all the inclusion criteria in order to be eligible to participate in the study and then list each criterion.

*Example:*

- Willing to participate and comply with all study procedures for prescribed trial period.
- Willing for giving the written consent
- Age and gender
- Clinical Signs and symptoms fit for the diagnostic criteria of the specific disease condition of the trial
- Laboratory parameters within a specific range

### 2.10.2. Participant Exclusion Criteria

Provide a statement that any participant meeting any of the exclusion criteria at baseline will be excluded from study participation and then list each criterion.



*Example:*

- Medical condition, laboratory finding, or physical exam finding (e.g., vital signs outside of specific range) that precludes participation
- Use of disallowed concomitant medications (*specify*)
- Pregnancy or lactation
- Known allergic reactions to components of the study product(s)
- Treatment with another investigational drug or other intervention (within a specified time frame)
- History of drug/alcohol abuse
- Characteristics of household or close contacts (e.g., household contacts who are immune-compromised, residence in same household as a participant already participating in study, if blinding or compliance could potentially be compromised)
- Anything that, in the opinion of the investigator, would place the participant at increased risk or preclude the participant's full compliance with or completion of the study.

### **2.10.3. Withdrawal criteria**

#### **Reasons for Withdrawal and handling of withdrawals**

Provide a list of reasons participants may be discontinued from the study. It may be appropriate to provide distinct discontinuation criteria for participants. Also note that participants may withdraw voluntarily from participation in the study at any time. Participants may also withdraw voluntarily from receiving the study intervention for any reason.

*Example:*

- Any clinical adverse events (AE), laboratory abnormalities, inter current illness, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant meets any exclusion criteria (either newly developed or not previously recognized).

#### **Handling of Withdrawals**

Describe the efforts to follow participants who withdraw from the study. It is vital to collect safety data of any participant discontinued because of an AE or SAE. In any case, every effort must be made to undertake protocol-specified safety follow-up procedures and be given appropriate care under medical supervision until the symptoms of any AE resolve or the



participant's condition becomes stable. If voluntary withdrawal occurs, the participant should be convinced by the Investigator to complete an end-of-study evaluation.

## **2.11. Study Procedures**

### **2.11.1. Screening**

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

### **2.11.2. Enrollment/Baseline visit**

A Participant's enrolment register apart from the screening register shall 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 participants/participants.

### **2.11.3. Follow-up Visit**

The follow up visits are the subsequent visits attended by the participant in prescribed time period as per the study protocol.

### **2.11.4. 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.

### **2.11.5. 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.

### **2.11.6. Early Termination Visit-if any**

Early termination visit is the case where the participant develops either any serious ADR/ADE or non-compliance of the treatment regimen / termination of the study, etc. The same needs to be informed to the Sponsor and the Ethics Committee within two working days.

### **2.11.7. Laboratory Evaluations**

The investigations should be done preferably from NABL 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 centers.

#### **2.11.8. Efficacy evaluation(Assessment criteria)**

Efficacy of trial drug/therapy /procedure is to be assessed on following parameters.

1. Sign and symptoms of concerned disease
2. Laboratory parameters
3. *Samyak Lakshana* of therapy/procedures

#### **2.11.9. Assessment of safety**

- Specifications of safety parameters (both laboratory parameters and signs & symptoms)
- Methods/ Procedures and periodicity for assessment and analysis of safety parameters
- Designing a specific format for reporting and recording adverse drug events/effect or inter-current illnesses.

##### **2.11.9.1. Adverse Reactions (ADR) / Adverse Events (AE)**

An unexpected ADR requires expedited review by the Institutional Ethics Committee (IEC). Unexpected AE/ADRs and all SAE (serious adverse event) should be reported to the sponsor by the investigator within 24 hours and to the IEC 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 Institutional Ethics Committee. 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 Ethics Committee and the regulatory authorities) of all serious and/or unexpected adverse drug reactions.

##### **2.11.9.2. Serious Adverse Events**

Any unexpected SAE as defined in the Indian GCP (Good Clinical Practice) 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 (ADRs) 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 EC should also be informed within 24 hours.

*\*Collection of laboratory data should be limited to those laboratory parameters that are relevant to safety, study outcome measures, and/or clinical outcome. The toxicity tables will define what values or findings are considered abnormal. Reporting will be dependent on the abnormality, the study intervention, and the study population and should be stated specifically. Consider the context of the trial and adjust reporting procedures appropriately for the study population and agent being studied.*

## **2.12. 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 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.*

## **2.13. Concomitant Medication**

A concomitant medication (con-med) 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 recorded 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.*

## **2.14. 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





the interpretation of their clinical importance, e.g. by estimates of the magnitude of the treatment effect / difference and confidence intervals rather than sole reliance on significance testing. Missing, unused and spurious data should be accounted for during the statistical analyses. All such omissions must be documented to enable review.

## **2.15. Criteria for the Discontinuation of the Study (Partial Or Whole)/ Termination of study**

Study Discontinuation is the case where the participant develops either any serious ADR/ADE or non-compliance of the treatment regimen / termination of the study, etc. The same needs to be informed to the Sponsor and the Ethics Committee within two working days. Further, the discontinuation of a trial should be ordered if the IEC finds that the goals of the trial have already been achieved midway or unequivocal results are obtained.

The study may be prematurely terminated if, in the opinion of the Investigator or the Sponsor or the Data Safety Monitoring Board (DSMB) there is sufficient reasonable cause. Written notification, documenting the reason for study termination, will be provided by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Insufficient adherence to protocol requirements.
- Data that is not sufficiently complete and/or evaluable.
- Plans to modify, suspend or discontinue the development of the study drug.

If the study is prematurely terminated or suspended, Sponsor will promptly inform the investigators/institutions, and the regulatory authority (ies) about the termination or suspension and the reason(s) for the termination or suspension. The Independent Review Board (IRB)/ Independent Ethics Committee (IEC) will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the Investigator /Institution, as specified by the applicable regulatory requirement(s).”

*\* All studies that are still analyzing data or samples (even if accrual has stopped) are submitted to the IRB/IEC for continuing review as per IRB policies. The IRB does not review the consent form, although under the IRB continuing review rules the consent form must be resubmitted with continuing review.*



## **2.16. Monitoring , Auditing and Data & Safety Monitoring Board (DSMB)**

It is mandatory that all research proposals on involving human participants should be cleared by an appropriately constituted Institutional Ethics Committee (IEC), also referred to as Institutional Review Board (IRB) or Ethics Review Board (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.

### **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.

### **Central Monitoring**

In case of multicentre studies a Central Monitoring Committee should be constituted to monitor the activities as and when required.

*\*Template for Monitoring is annexed at Annexure -IV.*

### **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 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.



### **Data & Safety Monitoring Board**

The Data and Safety Monitoring Board (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 research effort.

A Data and Safety Monitoring Board (DSMB) may be established to carefully monitor the data and side effects 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 Investigator(s) and Data and Safety Monitoring Board regarding any life threatening condition, whether they are pursued to be study related or not.

*(Please see the DSMB guidelines at Annexure-V)*

## **3. Ethics and Safety Consideration**

### **3.1. Ethical Principles**

All researches involving human participants should be conducted in accordance with the ethical principles and should respect four basic principles namely justice, respect for persons (autonomy), beneficence (to maximize benefits and to minimize harms and wrongs) and non-maleficence (to do no harm) for dignity, safety, right and wellbeing of the study participants as defined in revised “*National Ethical Guidelines for Biomedical and Health Research Involving Human Participants*” issued by the Indian Council of Medical Research and any other laws and regulations of the country.

The following principles are to be followed for conducting a research:

**Principles of essentiality:** The principle says that after thorough consideration of all alternatives in the proposed area of research, the participation of human being for a research is considered to be essential. This should be duly vetted by an Ethics committee independent of the proposed research.

**Principles of voluntariness:** To agree or not to agree to participate in research, or to withdraw from research at any time, the decision of the participant is supreme as per the principle. The informed consent process ensures that participants’ rights are safeguarded.

**Principles of non-exploitation:** As per this principle, the selection of the participants in a research and the benefits and burdens of the research should be distributed fairly without any





discrimination irrespective of their social and economic condition or status, or literacy or educational levels. Sufficient safeguards to protect vulnerable groups should be ensured.

**Principle of social responsibility:** The research should be planned and conducted meticulously to avoid the creation or deepening of social and historic divisions or in any way disturb social harmony in community relationships.

**Principles of privacy and confidentiality:** The principle says the privacy of the participant, her/his identity and records are kept confidential and access is limited to only those authorized. However, under certain circumstances (suicidal ideation, homicidal tendency, HIV positive status, when required by court of law etc.) privacy of the information can be breached in consultation with the IEC for valid scientific or legal reasons as the right to life of an individual supersedes the right to privacy of the research participant.

**Principles of risk minimization:** As per this principle due care is taken by all stakeholders (including but not limited to researchers, IECs, sponsors, regulators) at all stages of the research to ensure that the risks are minimized and appropriate care and compensation is given if any harm occurs.

**Principles of professional competence:** The principle says that the person/Researcher involved in planning, execution, evaluation and monitoring of a research should be competent and having the appropriate and relevant qualification, experience and/or training.

**Principles of accountability and transparency:** As per this principle, the research plan and outcomes emanating from the research should be brought into the public domain through registries, reports and scientific and other publications while safeguarding the right to privacy of the participants. Stakeholders involved in research should disclose any existing conflict of interest and manage it appropriately. The research should be conducted in a fair, honest, impartial and transparent manner to guarantee accountability. Related records, data and notes should be retained for the required period for possible external scrutiny/ audit.

**Principles of the maximization of benefits:** Due care should be taken to design and conduct the research in such a way that the research participants and/or the society directly or indirectly will get maximum benefits from the research.

**Principles of institutional arrangements:** The institutions responsible for conducting the research should have policies for appropriate research governance, and take the responsibility to facilitate research by providing required infrastructure, manpower, funds and training opportunities.



**Principles of totality of responsibility:** All stakeholders involved in research are responsible for their actions. The professional, social and moral responsibilities compliant with ethical guidelines and related regulations are binding on all stakeholders directly or indirectly.

**Principle of environmental protection:** There searchers in compliance with existing guidelines and regulations are accountable for ensuring protection of the environment and resources at all stages of the research.

### **3.2. Ethics Committee**

The Sponsor and / or Investigator should seek the opinion of an Institutional Ethics Committee 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 Ethics Committees are entrusted not only with the initial view 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 Biomedical Research on Human participants” 2006, as amended from time to time by Indian Council of Medical Research, New Delhi.

#### **3.2.1. Basic Responsibilities**

The basic responsibility of an IEC 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. The IECs should specify in writing the authority under which the committee is established, membership requirements, the terms of reference, the conditions of appointment, the offices and the quorum requirements.

#### **3.2.2. Composition of IEC**

- a. IEC should be multidisciplinary and multi-sectorial in composition. Independence and competence are the two hallmarks of an IEC.
- b. The number of persons in an Ethics Committee to be kept fairly small (5-7 members). It is generally accepted that a minimum of five persons 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. 12 to 15 is the maximum recommended number
- c. The Chairperson of the committee should preferably be from outside the Institution and not head of the same Institution to maintain the independence of the committee. The Member



Secretary who generally belongs to the same Institution should conduct the functioning of the Committee. 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- A technical person with research background
2. Member secretary
3. Clinicians -1-2 Ayurvedic practitioners/ clinicians from different Institutes
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 or retired Judge
6. One Social Scientist / philosopher / ethicist / theologian / representative of Non-Governmental Voluntary Agency
7. One lay person from the community

The Ethics Committee at any Institution can have as its members, individuals from other Institutions or Communities if required. There should be adequate representation of age, gender, community; etc. in the Committee to safeguard the interests and welfare of all sections of the community/Society. Members should be aware of local, social and cultural norms, as this is the most important social control mechanism. If required concerned subject experts could be invited to offer their views.

*\*In case where the IEC approval will be obtained is non AYUSH organization, two experts from Ayurveda should be kept as IEC members.*

### **3.2.3. Terms of Reference for IECs**

The IEC members should be made aware of their role and responsibilities as committee members. Any change in the regulatory requirements should be brought to their attention and they should be kept abreast of all national and international developments in this regard. The Terms of References should also include a statement on Terms of Appointment with reference to the duration of the term of membership, the policy for removal, replacement and resignation procedure etc. Each committee should have its own operating procedures available with each member.

- The TOR for the IEC and its members should be clearly specified by the institution in the IEC SoPs (*Please refer Annex VI for the List of SoPs*).
- Every IEC should have written SoPs according to which the committee should function.
- The IEC can refer to ICMR guidelines in preparing the SoPs for all biomedical and health research and to CDSCO guidelines for drug and device trials under the purview of the



licensing authority. The SOPs should be updated periodically to reflect changing requirements. A copy of the latest version of SOPs should be made available to each member and they should be trained on the SOPs. The SOPs must be available in the secretariat of the IEC as both hard and soft copies. The scope, tenure and renewal policy of the IEC should be stated.

- Members of the IEC should not have any known record of misconduct.

#### **3.2.4. Review Procedures**

The Ethics Committee should review every research proposal on human participants within reasonable period of time. It should ensure that a scientific evaluation has been completed before ethical review is taken up. The Committee should evaluate the possible risks to the participants with proper justification, the expected benefits and adequacy of documentation for ensuring privacy, confidentiality and justice issues. The ethical review should be done through formal meetings and should not resort to decisions through circulation of proposals.

#### **3.2.5. Submission of Application**

The Investigator should submit an appropriate application to the IEC in a prescribed format along with the study protocol at least three weeks in advance. The application should include the following:

- Clear research objectives and rationale for undertaking the investigation in human participants in the light of existing knowledge.
- Recent curriculum vitae of the Investigators indicating qualification and experience.
- Participant recruitment procedures.
- Inclusion and exclusion criteria for entry of participants in the study.
- Precise description of methodology of the proposed research, including intended dosages and routes of administration of drugs, planned duration of treatment and details of invasive procedures if any.
- A description of plans to withdraw or withhold standard therapies in the course of research.
- The plans for statistical analysis of the study.
- Procedure for seeking and obtaining informed consent with sample of participant information sheet and informed consent forms in English and vernacular languages.
- Safety of proposed intervention and any drug to be tested, including results of relevant laboratory and animal research.



- For research carrying more than minimal risk, an account of plans to provide medical therapy for such risk or injury or toxicity due to over-dosage should be included.
- Proposed compensation and reimbursement of incidental expenses.
- Storage and maintenance of all data collected during the trial.
- Plans for publication of results - positive or negative - while maintaining the privacy and confidentiality of the study participants.
- A statement on probable ethical issues and steps taken to tackle the same.
- All other relevant documents related to the study protocol including regulatory clearances.
- Agreement to comply with national and international GCP protocols for clinical trials.
- Details of Funding agency / Sponsors and fund allocation for the proposed work.

### 3.2.6. Decision Making Process

The IEC should be able to provide complete and adequate review of the research proposals submitted to them (at least 1 week) to review the proposal and related documents, except in the case of expedited review. It should meet periodically at frequent intervals to review new proposals, evaluate annual progress of ongoing ones and assess final reports of all research activities involving human beings through a previously scheduled agenda, amended wherever appropriate.

The decision must be taken by a broad consensus after the quorum requirements are fulfilled to recommend / reject / suggest modification for a repeat review or advice appropriate steps. The Member Secretary should communicate the decision in writing.

#### **Types of the decision by the IEC-**

An IEC can give one of the following decisions:

- *approved – with or without suggestions or comments;*
- *revision with minor modifications/amendments – approval is given after examination by the Member Secretary or expedited review, as the case may be;*
- *revision with major modifications for resubmission – this will be placed before the full committee for reconsideration for approval; or*
- *Not approved (or termination/revoking of permission if applicable) – clearly defined reasons must be given for not approving/terminating/revoking of permission.*
- A member must voluntarily withdraw from the IEC while making a decision on an application which evokes a conflict of interest which should be indicated in writing to the chairperson prior to the review and should be recorded so in the minutes.





- If one of the members has her/his own proposal for review, then the member should not participate when the project is discussed.
- A negative decision should always be supported by clearly defined reasons.
- An IEC may decide to reverse its positive decision on a study in the event of receiving information that may adversely affect the benefit/risk ratio.
- The discontinuation of a trial should be ordered if the IEC finds that the goals of the trial have already been achieved midway or unequivocal results are obtained.
- In case of premature termination of study, notification should include the reasons for termination along with the summary of results conducted till date.

**The following circumstances require the matter to be brought to the attention of IEC:**

- Any amendment to the protocol from the originally approved protocol with proper justification;
- Serious and unexpected adverse events and remedial steps taken to tackle them;
- Any new information that may influence the conduct of the study.
- If necessary, the Applicant/Investigator may be invited to present the protocol or offer clarifications in the meeting. Representative of the participant groups or interest groups can be invited during deliberations to offer their viewpoint.
- Subject Experts may be invited to offer their views, but should not take part in the decision making process. However, her/his opinion must be recorded.
- Meetings are to be Minutes which should be approved and signed by the Chairperson.

### **3.2.7. Interim Review**

The IEC should decide and record the special circumstances and the mechanism when an interim review can be resorted-to instead of waiting for the scheduled time of the meeting. This can be done for the following reasons:

- i) Re-examination of a proposal already examined by the IEC;
- ii) Research study of a minor nature such as examination of case records etc.;
- iii) An urgent proposal of national interest.

### **3.2.8. Record Keeping**

- All documentation and communication of an IEC should be dated, filed and preserved according to written procedures.
- Confidentiality should be maintained during access and retrieval procedures by designated persons.



- All active and inactive (closed) files should be appropriately labelled and archived separately in designated areas.
- Records can be maintained in hard copies as well as soft copies.
- All records must be archived for a period of at least 3 years after the completion/termination of the study.
- Documents related to regulatory clinical trials must be archived for 5 years after the completion/termination of the study or as per regulations.
- Records may be archived for a longer period, if required by the sponsors/regulatory Bodies
- IEC should describe archival and retrieval mechanisms in SOPs.
- IEC records should be accessible for inspection by authorized representatives of regulatory agencies.

### **3.2.9. Special Considerations**

While all the above requirements are applicable to Ayurvedic Medicine research as a whole irrespective of the specialty of research, there are certain specific concerns pertaining to specialized areas of research which require additional safeguards / protection and specific considerations for the IEC to take note of. Examples of such instances are research involving children, pregnant and lactating women, vulnerable participants and those with diminished autonomy besides issues pertaining to commercialization of research and international collaboration. The observations and suggestions of IEC should be given in writing in unambiguous terms in such instances.

### **3.3. 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 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.





### 3.3.1. 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 modern 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.

### 3.3.2. Informed Consent form

#### 3.3.2.I. 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 /Legally Authorized Representative (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

#### **3.3.2.2. 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 Participant(s) 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)



### **3.3.2.3. 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.

### **3.3.2.4. 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.

#### **3.3.2.5. 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.

### **3.4. Waiver of consent**

The researcher can apply to the IEC 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 IEC 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.

### **3.5. Responsibilities of the Researcher**

- The researcher should only use the IEC approved version of the consent form, including its local translations.
- Adequate information necessary for informed consent should be communicated in a language and manner easily understood by prospective participants.



- In case of differently abled participants, such as individuals with physical, neurological or mental disabilities, appropriate methods should be used to enhance the participants' understanding, for example, braille for the visually impaired.
- There should be no restriction on the participant's right to ask questions related to the study or to discuss with family and friends or take time before coming to a decision.
- The researcher should not give any unjustifiable assurances or influence or intimidate a prospective participant to enroll in the study.
- The researcher must ensure that the participant is competent and has understood all aspects of the study and that the consent is given voluntarily. Where the participant and/or the LAR are illiterate, an impartial literate person, not connected to the research, should be present throughout the consent process as witness.
- The researcher should administer a test of understanding whenever possible for sensitive studies. If need be, the test may be repeated until the participant has really understood the contents.
- When a participant is willing to participate but not willing to sign or give a thumb impression or cannot do so, then verbal/oral consent may be taken on approval by the IEC, in the presence of an impartial witness who should sign and date the consent document. This process can be documented through audio or video recording of the participant, the PI and the impartial witness, all of whom should be seen in the frame. However, verbal/oral consent should only be taken in exceptional circumstances and for specific, justifiable reasons with the approval of the IEC. It should not be practiced routinely.
- The researcher must assure prospective participants that their decision whether or not to participate in the research will not affect their rights, the patient-clinician relations nor any other benefits to which they are entitled.
- Reimbursement may be given for travel and incidental expenses/participation in research after approval by the IEC.
- The researcher should ensure free treatment for research related injury (disability, chronic life-threatening disease and congenital anomaly or birth defect) and if required, payment of compensation over and above medical management by the investigator and/institution and sponsor(s), as the case may be.
- The researcher should ensure that the participant can continue to access routine care even in the event of withdrawal of the participant.





### **3.6. Responsibilities of the Institution for conducting a research in alliance with industries/commercial companies**

Academic institutions conducting research in alliance with industries/commercial companies require a strong review to probe possible conflicts of interest between scientific responsibilities of Investigators and business interests (e.g. ownership or part ownership of a company developing a new product). In cases where the review board/committee determines that a conflict of interest may damage the scientific integrity of a study or cause harm to research participants, the board should advise accordingly. Institutions need self-regulatory processes to monitor, prevent and resolve such conflicts of interest. Prospective participants in research should also be informed of the sponsorship of research, so that they can be aware of the potential for conflicts of interest and commercial aspects of the research. Undue inducement through compensation for individual participants, families and populations should be prohibited. This prohibition however, does not include agreements with individuals, families, groups, communities or populations that foresee technology transfer, local training, joint ventures, provision of health care reimbursement, costs of travel and loss of wages and the possible use of a percentage of any royalties for humanitarian purposes.

### **3.7. Selection of Vulnerable groups as Research Participant**

The word vulnerability is derived from the Latin word *vulnerere* which means 'to wound'. Vulnerable persons are those individuals who are relatively or absolutely incapable of protecting their own interests because of personal disability; environmental burdens; social injustice; lack of power, understanding or ability to communicate or are in a situation that prevents them from doing so. Vulnerable populations have an equal right to be included in research so that benefits accruing from the research apply to them as well. These vulnerable persons have some common characteristics which are listed below-

- socially, economically or politically disadvantaged and therefore susceptible to being exploited;
- incapable of making a voluntary informed decision for themselves or whose autonomy is compromised temporarily or permanently, for example people who are unconscious, differently abled;
- able to give consent, but whose voluntariness or understanding is compromised due to their situational conditions; or
- unduly influenced either by the expectation of benefits or fear of retaliation in case of refusal to participate which may lead them to give consent.



**Following are some examples of vulnerable populations or groups:**

- economically and socially disadvantaged (unemployed individuals, orphans, abandoned individuals, persons below the poverty line, ethnic minorities, sexual minorities – lesbian/gay/bisexual and transgender (LGBT), etc.);
- unduly influenced either by the expectation of benefits or fear of retaliation in case of refusal to participate which may lead them to give consent;
- children (up to 18 years);
- women in special situations (pregnant or lactating women, or those who have poor decision-making powers/poor access to healthcare);
- tribals and marginalized communities;
- refugees, migrants, homeless, persons or populations in conflict zones, riot areas or disaster situations;
- afflicted with mental illness and cognitively impaired individuals, differently abled – mentally and physically disabled;
- terminally ill or are in search of new interventions having exhausted all therapies;
- suffering from stigmatizing or rare diseases; or
- have diminished autonomy due to dependency or being under a hierarchical system (students, employees, subordinates, defence services personnel, healthcare workers, institutionalized individuals, under trials and prisoners).

**3.7.1. Pregnant or nursing women**

Pregnant or nursing women should in no circumstances be the participant of any research unless the research carries no more than minimal risk to the fetus or nursing infant and the object of the research is to obtain new knowledge about the foetus, pregnancy and lactation. As a general rule, pregnant or nursing women should not be participants of any clinical trial except such trials as are designed to protect or advance the health of pregnant or nursing women or foetuses or nursing infants, and for which women who are not pregnant or nursing would not be suitable participants.

The justification of participation of these women in clinical trials would be that they should not be deprived arbitrarily of the opportunity to benefit from investigations, drugs, vaccines or other agents that promise therapeutic or preventive benefits. Example of such trials are-

- a. Test the efficacy and safety of a drug for reducing peri-natal transmission of HIV infection from mother to child





The trials for detecting fetal abnormalities and for conditions associated with or aggravated by pregnancy, etc. Women should not be encouraged to discontinue nursing for the sake of participation in research and in case she decides to do so, harm of cessation of breast feeding to the nursing child should be properly assessed except in those studies where breast feeding is harmful to the infant.

b. Research related to termination of pregnancy

Pregnant women who desire to undergo Medical Termination of Pregnancy (MTP) could be made participants for such research as per the Medical Termination of Pregnancy Act, Government of India, 1971.

c. Research related to pre-natal diagnostic techniques

In pregnant women such research should be limited to detect the foetal abnormalities or genetic disorders as per the Prenatal Diagnostic Techniques (Regulation and Prevention of Misuse) Act, GOI, 1994 and not for sex determination of the foetus.

### 3.7.2. Children

Before undertaking trial in children below the age of 18 years the Investigator must ensure that –

- a. Children will not be involved in research that could be carried out equally well with adults;
- b. The purpose of the research is to obtain knowledge relevant to health needs of children. For clinical evaluation of a new Ayurvedic drug / Patent or Proprietary Medicines the study in children should always be carried out after the phase III clinical trials in adults. It can be studied earlier only if the Ayurvedic drug / Patent or Proprietary Medicines have a therapeutic value in a primary disease of the children;
- c. A parent or legal guardian of each child has given proxy consent;
- d. **The Assent** of the child should be obtained to the extent of the child's capabilities such as in the case of mature minors, adolescents etc.

#### Considerations for assent

- There is no need to document assent for children below 7 years of age.
- For children between 7 and 12 years, verbal/oral assent must be obtained in the presence of the parents/LAR and should be recorded.
- For children between 12 and 18 years, written assent must be obtained. This assent form also has to be signed by the parents/LAR.
- Adolescents may have the capacity to give consent like adults. However, as they have not attained the legal age to provide consent, it is termed as assent and the consent of the parents/LAR should be obtained. If the latter will affect the validity of the study,



waiver of consent from the relevant adult should be taken and recorded with the approval of the IEC, for example, in behavioural studies in IV drug users where parental consent may not be possible.

- e. Research should be conducted in settings in which the child and parent can obtain adequate medical and psychological support;
- f. Interventions intended to provide direct diagnostic, therapeutic or preventive benefit for the individual child participant must be justified in relation to anticipated risks involved in the study and anticipated benefits to society;
- g. The child's refusal to participate in research must always be respected unless there is no medically acceptable alternative to the therapy provided/tested. *The consent has to be obtained from parents/guardian;*
- h. Interventions that are intended to provide therapeutic benefit are likely to be at least as advantageous to the individual child participant as any available alternative interventions;
- i. The risk presented by interventions not intended to benefit the individual child participant is low when compared to the importance of the knowledge that is to be gained.

#### **4. Registration of clinical trial**

Clinical trials hold enormous potential for benefiting participants, improving therapeutic regimens and ensuring advancement in medical practice that is evidence based. Registration of trials will ensure transparency, accountability and accessibility of clinical trials.

The Clinical Trials Registry- India (CTRI) hosted at the ICMR's National Institute of Medical Statistics (NIMS), is a free and online ([www.ctri.nic.in](http://www.ctri.nic.in)) public record system for registration of clinical trials being conducted in India

Today, any Investigator who plans to conduct a trial involving human participants of any intervention such as drugs, surgical procedures, preventive measures, lifestyle modifications, devices, educational or behavioral treatment, rehabilitation strategies as well as trials being conducted in the purview of the Ministry of AYUSH (<http://indianmedicine.nic.in/>) is expected to register the trial in the CTRI before enrollment of the first participant. Trial registration involves public declaration and identification of trial Investigators, Sponsors, Interventions, Participant population, Trial site, etc. before the enrollment of the first participant. Submission of Ethics approval and Ministry of AYUSH approval (if applicable) is essential for trial registration in the CTRI. Multi-country trials, where India is a participating country, which have been registered in an international registry, are also expected to be registered in the CTRI.



In the CTRI, details of Indian investigators, trial sites, Indian target sample size and date of enrollment are captured. After a trial is registered, investigators are expected to regularly update the trial status or other aspects as the case may be. After a trial is registered, all updates and changes will be recorded and available for public display.

Being a Primary Register of the International Clinical Trials Registry Platform (ICTRP) (<http://www.who.int/ictrp/search/en/>), registered trials are freely searchable both from the WHO's search portal, the ICTRP as well as from the CTRI ([www.ctri.nic.in](http://www.ctri.nic.in)).

## **5. Record Keeping and Data Handling**

The basic concept of record-keeping and handling of data is to record, store, transfer, and where necessary convert efficiently and accurately the information collected on the trial participant(s) into data that can be used to compile the Study Report.

### **5.1. Documentation**

All steps involved in data management should be documented in order to allow step-by step retrospective assessment of data quality and study performance for the purpose of audit following the SoPs facilitates documentation. Documentation of SoPs should include details of checklists and forms giving details of actions taken, dates and the individuals responsible, etc.

### **5.2. Corrections**

All corrections in the CRFs or any other study related documents should be made in a way that does not obscure the original entry. The correct data should be inserted with the reason for the correction if such a reason is not obvious. The corrections should carry the date and initials of the Investigator or the authorized person.

### **5.3. Electronic Data Processing**

For electronic data processing only authorized person should be allowed to enter or modify the data in the computer and there should be a recorded trail of the changes and deletions made. A security system should be set-up to prevent un-authorized access to the data. If data is altered during processing the alteration must be documented and the system should be validated. The systems should be designed to permit data changes in such a way that the data changes are documented and there is no deletion of data once it has been entered. A list of authorized persons who can make changes in the computer system should be maintained. Adequate backup of the data should be maintained.



#### **5.4. Validation of Electronic Data Processing Systems**

If trial data are entered directly into the computer there must always be an adequate safeguard to ensure validation including a signed and dated printout and backup records. Computerized systems – hardware as well as software - should be validated and a detailed description of their use be produced and kept up-to-date.

#### **5.5. Language**

All written documents, information and other material used in the Study should be in a language that is clearly understood by all concerned (i.e. the Participants, paramedical staff, Monitors etc.)

#### **5.6. Responsibilities of the Investigator**

Investigator should ensure that the observations and findings are recorded correctly and completely in the CRFs and signed by the responsible person(s) designated in the Protocol. Laboratory values with normal reference ranges should always be recorded on a CRF or enclosed with the CRF. Values outside the clinically accepted reference range or values that differ importantly from previous values must be evaluated and commented upon by the Investigator. Data other than that requested by the Protocol may appear on the CRF clearly marked as the additional findings and their significance described by the investigator. Units of measurement must always be stated and transformation of units must always be indicated and documented. In the medical records of the participant(s) it should be clearly indicated that the individual is participating in a clinical trial. The immediate transport facility should be provided to the study personnel to nearby hospital for medical referral.

#### **5.7. Responsibilities of the Sponsor and the Monitor**

The sponsor must ensure that electronic data processing system conforms to the certain documented requirements for completeness, accuracy, reliability and consistent intended performance (i.e. validation). The Sponsor must maintain SoPs for using these systems.

The Monitor should take adequate measures to ensure that no data is overlooked. If the computer system automatically assigns any missing values – the fact should be clearly documented.

Sponsor should safeguard the blinding, if any, particularly during data entry and processing. The Sponsor should use an explicit Participant identification code that allows identification of all the data reported for each Participant. Ownership of the data and any transfer of the ownership of data should be documented and intimated to the concerned party (ies).



## **6. Publication Policy**

A publication policy, if not addressed in a separate agreement, should be described in the protocol.

## **7. Common Problems in Research Protocols**

**Some of the common mistakes are:**

- Inadequate literature review or conducting a quick survey when a systematic review is needed.
- Vague research question, this means the question is too broad or unanswerable, and needs to be focused.
- Flawed research design: Do not select a study type that will not answer the question. Much time and effort will be wasted. Most research failures can be traced to the early planning stages.
- A project is too ambitious than the research skills of Investigator or the institutional resources is not sufficient in the institution responsible for.
- Too many research questions: lacks focus and not achievable in time
- Inadequate number of participants to answer the question: Do not count on the IEC to alert the researcher about this problem, which poses no risk to participants, even though it wastes the time of willing volunteers.
- Inappropriate plan for statistical analysis: The statistician is planning to use the wrong tests to look at the data.
- Poorly written consent form: The IEC will send the consent form back for rewriting if not comprehensive and legally sound.
- A budget inadequate for the project, or even too high.
- Failure to reach consensus on all aspects of the protocol.

## **8. Final steps**

After the Research Protocol is written (and re written a few times), it should be reviewed by a “Critical Reader” may be colleague or peer. This will help to identify the problems with organization or in the grammar that may detract from the merits of the idea. If the “critical-reader” colleague is not research-savvy, especially in your area of investigation, it may be reviewed by an experienced investigator.





## 9. References

1. Good clinical practice guidelines for clinical trials in Ayurveda, Siddha & Unani medicine (GCP-ASU), Published by Dept. of AYUSH, Ministry of Health & family welfare, Govt. Of India, New Delhi, March 2013.
2. Good Clinical Practice Guidelines, Central Drugs Standard Control Organization (CDSCO), Ministry of Health, Govt. of India.
3. Guidance for Industry on Submission of Clinical Trial Application for Evaluating Safety and Efficacy (General considerations for conducting Clinical Trial as per Drugs and Cosmetics Act 1940 and Rules 1945) Document No. - CT/71108, Version – 1.1, Central Drugs Standard Control Organization Ministry of Health, Govt. of India.
4. Ethical Guidelines for Biomedical Research on Human Participants, Published by Indian Council of Medical Research, New Delhi, 2017.
5. Pandey A, Aggarwal AR, Seth SD, Maulik, M, Bano R. Juneja A. Clinical Trials Registry India: Redefining the conduct of clinical trials. *Indian J Cancer* 2008; 45 (3): 79-82.
6. Pandey A, Aggarwal A, Maulik, M, Seth SD. Clinical trial registration gains momentum in India. *Indian J Med Res [Letter to Editor]* 2009; 130: 85-86.
7. Pandey A, Aggarwal AR, Seth SD, Maulik, M. Clinical Trials Registry ♦ India: Raising the veil. *Natl Med J India [Letter to Editor]* 2010; 23 (3):187 -188.
8. Schulz KF, Chalmers I, Hayes RJ, Altman D. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled clinical trials. *JAMA* 1995; 273:408-12.
9. Jni P, Altman DG, Egger M. Assessing the quality of controlled clinical trials. *BMJ* 2001; 323: 42-6.
10. Altman DG, Schulz KF, Moher D for the CONSORT Group. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001; 134: 663-94.
11. International Committee of Medical Journal Editors (ICMJE). Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Available at <http://www.icmje.org>.





12. Indian Council of Medical Research. Ethical Guidelines for Biomedical Research on Human Participants. New Delhi: Indian Council of Medical Research, 2000
13. Bhushan Patwardhan , Ashok D. B.Vaidya , Mukund Chorghade and Swati P. Joshi, Reverse Pharmacology and Systems Approaches for Drug Discovery and Development Current Bioactive Compounds 2008, 4, 000-000
14. Kenneth F Schulz, David A Grimes, Generation of allocation sequences in randomised trials: chance, not choice. Lancet 2002; 359: 515–19
15. Rathai Rajagopalan, Priyadarshini M.Deodurg, Srikanth Overview of Randomized Controlled Trials. Asian J Pharm Clin Res, Vol 6, Issue 3, 2013, 32-38.
16. Ethical Guidelines, for Biomedical research on Human participants. Indian council of medical research. New Delhi, 2006. [http://www.icmr.nic.in/ethical\\_guidelines.pdf](http://www.icmr.nic.in/ethical_guidelines.pdf)
17. Kenneth F Schulz, David A Grimes. Allocation concealment in randomised trials: defending against Deciphering THE LANCET. Vol 359, February 16: 2002. [.www.thelancet.com](http://www.thelancet.com)
18. ICH Guidance for Industry M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (April 1997)



## 10. Further Reading Materials

1. Sacks HS, Berrier, J, Reitman D, Ancona-Berk VA, Chalmers T. Meta-analyses of randomized controlled trials. *New England Journal of Medicine* 1987;316:450-
2. Sacks HS, Berrier, J, Reitman D, Ancona-Berk VA, Chalmers T. Meta-analyses of randomized controlled trials: and update. In : Balder WC, Mosteller F, eds. *Medical Uses of Statistics*, 2<sup>nd</sup> ed. pp427-442 Boston, MA: NEJM Books, 199
3. Sacks HS. Meta analyses of clinical trials. In: Perman IA, Rey J, eds. *Clinical Trials in Infant Nutritional, Nesle Nutrition Workshop series, Vol. 40pp 85-99*. Philadelphia, PA; Vevey/Lippincott-Raven Publishers, 1998
4. Lachman L et al. Quality control charts. In: *The theory and practice of industrial pharmacy*. Philadelphia, Lea & Fbiger, 1986: 817-824 WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-first report. Geneva, World Health Organization, 1990 (WHO Technical Report Series, No. 790) p.47.
5. Good manufacturing practices: guidelines on the validation of manufacturing processes. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. *Thirty-fourth report*. Geneva, World Health Organization, 1996 (WHO Technical Report Series, No. 863) 80-96.
6. Lowe DA. *Guide to international recommendations on names and symbols for quantities and on units of measurement*. Geneva, World Health Organization, 1975.
7. *The SI for the health professions*. Geneva, World Health Organization, 1977.
8. WHO Expert Committee on Specifications for Pharmaceutical Preparations. *Thirty-first report*. Geneva, World Health Organization, 1990 (WHO Technical Report Series, No. 790) Annex 2, pp.34-47
9. Codex Alimentations Commission. *Guide: Codex maximum limits for pesticide residues, Part 2 April 1992 Rome*, Food and Agriculture Organization of the United Nations, 1992 (unpublished FAQ document CX/PR2-1992; available in hard copy and electronic format from FAQ).
10. International Consultative Group on Food Irradiation, *Consultation on microbiological criteria for foods to be further processed including by irradiation*. Geneva, World Health Organization, 1989; 21(unpublished WHO document WHO/EHE/FOS/89.5; available on



request from Office of Global and Integrated Environmental Health, World Health Organization, 1211 Geneva 27, Switzerland).

11. Anonymous,, Quality control methods for Medicinal plant materials, WHO, Geneva 1998
12. Anonymous, Guide lines for methodologies on research & evaluation of research of Traditional medicine, WHO, Geneva., 2000,
13. Anonymous, Ethical guidelines for biomedical research, ICMR, New Delhi, 2000
14. Ramachandra Reddy K, Bhaishajya kalpana vignanam Choukhamba publications Varanasi 1998 ,
15. Charaka, Charaka Samhita, Choukhamba Sanskrit Series, Varanasi. 1997
16. Susruta, Susruta Samhita, Chowkhamba Sanskrit Series, Varanasi. 1962
17. Sharangadhara , Sharangadhara samhita, Choukhamba publications, Varanasi. 1984
18. Vagbhata, Astanga hridaya, Choukhamba publications, Varanasi. 1992
19. Sharma P.V, Dravya guna vignana, Choukhamba publications, Varanasi. 1978
20. Sharma P.V, Dravya guna sutram, Choukhamba publications, Varanasi. 1994
21. Singh R.H., The Holistic principles of Ayurvedic Medicine Choukhamba publications, Varanasi1998.
22. Bhavamishra , Bhavaprakasha, Choukhamba publications , Varanasi. 1998.
23. Bhagavan Dash, Fundamenatal principles of Ayurveda,Konark publications, 1989.
24. Dwarakanath C., Introduction to Kaya Chikitsa, Choukhamba publications, Varanasi. 1986.
25. Quality control methods. In: Remington: the science and practice of pharmacy, 19<sup>th</sup> ed. Easton, PA, MACK, 1995: 118-119.
26. The international pharmacopoeia, 3<sup>rd</sup> ed. Geneva, World Health Organization, Vol.1: General methods of analysis, 1979. Vol.2: Quality specifications, 1981. Vol. 3 Quality specifications, 1988; Vol. 4: Tests, methods and general requirements. Quality specifications for pharmaceutical substances, excipients, and dosage forms, 1994
27. Public health impact of pesticides used in agriculture. Geneva, World Health Organization, 1990.



**RULE 158 (B) - GUIDELINES FOR ISSUE OF LICENSE WITH RESPECT TO  
AYURVEDA, SIDDHA OR UNANI DRUGS**

**I. (A). Ayurveda, Siddha Unani Medicines under, section 3 (a):-**

Ayurveda, Siddha or Unani drugs includes all medicines intended for internal or external use for or in the diagnosis, treatment, mitigation or prevention of disease

or

disorder in human beings or animals, and manufactured exclusively in accordance with the formulae described in the authoritative books of Ayurvedic, Siddha and Unani Tibb system of medicine, as specified in the First Schedule;

**(B). Patent or Proprietary medicine under section 3(h);**

- (i) In relation to Ayurvedic, Siddha and Unani Tibb system of medicine of all formulations containing only such ingredients mentioned in the formulae described in the authoritative books of Ayurveda, Siddha or Unani Tibb system of medicines specified in the First Schedule, but does not include a medicine which is administered by parenteral route and also a formulation included in the authoritative books as specified in clause (a);
- (ii) **Balya/Poshak/Muqawi/Unavuporutkal/positive health Promoter** formulations having ingredients mentioned in books of First Schedule of the Drugs and Cosmetics Act and recommended for promotional and preventive health.
- (iii) **Saundarya Prasadak (Husane afza)/Azhagh-sadhan formulation** having ingredients mentioned in Books of First Schedule of the Drugs and Cosmetics Act and recommended for oral, skin, hair and body care.
- (iv) **Aushadh Ghana (Medicinal plant extracts – dry/wet) extract** obtained from plant mentioned in books of First Schedule of the Act including Aqueous or hydro-alcohol.

**II. (A) For issue of licence to the medicine with respect to Ayurvedic, Siddha and Unani, the conditions relating to safety study and the experience or evidence of effectiveness shall be such as specified in columns (5) and (6) of the Table given below:-**

S. No.	Category	Ingredient (S)	Indication (s)	Safety study	Experience/Evidence of Effectiveness	
(1)	(2)	(3)	(4)	(5)	(6)	
					Published Literature	Proof of Effectiveness
1.	(A)	As per text	As per text	Not	Required	Not Required



	Ayurveda, Siddha and Unani drugs. given in 158.B as referred in 3(a)			Required		
2.	(B) Any change in dosage form of Ayurveda Siddha and Unani drugs as described in section 3(a) of the Drugs and Cosmetics Act, 1940	As per text	As per text	Not Required	Required	Not Required
3.	(C) Ayurveda, Siddha and Unani drugs referred in 3(a) to be used for new indication	As per text	New	Not Required	If Required	Required

**II. B. For issue of license with respect to patent or proprietary medicine. The conditions relating to Safety studies and experience or evidence of effectiveness shall be specified as follows:-**

S. No.	Category	Ingredient (S)	Indication (s)	Safety study	Experience/Evidence of Effectiveness	
(1)	(2)	(3)	(4)	(5)	(6)	
					Published Literature	Proof of Effectiveness
1.	Patent or Proprietary medicine	As per text	Textual rationale	Not required	Of Ingredients	* Pilot study as per relevant protocol for Ayurveda and Siddha and Unani drugs.
2.	Ayurveda Siddha, Unani drug with any of the ingredients of Schedule E (1) of the Drugs and Cosmetics Act, 1940	As per text	Existing	Required	Required	Required



(V). For issue of license with respect to medicine Aushadh Ghana [extract of medicinal plant (dry/wet)]

S. No.	Category	Ingredient (S)	Indication (s)	Safety study	Experience/Evidence of Effectiveness	
					Published Literature	Proof of Effectiveness
(1)	(2)	(3)	(4)	(5)	(6)	
1.	(A) Aqueous	As per text	As per text	Not Required	Not Required	Not Required
2.	(A1) Aqueous	As per text	New Indication	Not Required	Not Required	Required
3.	(B) Hydro-Alcohol	As per text	As per text	Not Required	If Required	Not Required
4.	(B1) Hydro-Alcohol	As specified	New Indication**	Required	If Required	Required
5.	Other than Hydro/ Hydro-Alcohol	As specified	As specified	Required Acute, Chronic, Mutagenicity and Teratogenicity	If Required	Required

\* The standard protocol with also include concept of Anupan, Prakriti & Tridosh etc. published by Central Research Councils Ayurveda, Siddha, Unani and other Government/Research Bodies.

\*\* New Indication means which is other than mentioned in 1<sup>st</sup> schedule books of Drugs & Cosmetics Act, 1940



**GAZETTE NOTIFICATION FOR PHYTOPHARMACEUTICAL DRUGS**

गैजट्टी सं० डी० एल०-33004/99

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**भारत का राजपत्र**  
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असाधारण

EXTRAORDINARY

भाग II—खण्ड 3—उप-खण्ड (i)

PART II—Section 3—Sub-section (i)

प्राधिकार से प्रकाशित

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(स्वास्थ्य और परिवार कल्याण विभाग)

अधिमूचना

नई दिल्ली, 30 नवम्बर, 2015

सा.का.नि. 918(अ).—औषधि और प्रमापन सामग्री नियम, 1945 का और संशोधन करने के लिए औषधि और प्रमापन सामग्री अधिनियम, 1940 (1940 का 23) की धारा 12 और धारा 33 द्वारा स्थापित कतिपय नियमों का प्रारूप भारत सरकार के स्वास्थ्य और परिवार कल्याण मंत्रालय (स्वास्थ्य और परिवार कल्याण विभाग) की अधिमूचना सं. सा.का.नि. 702(अ) तारीख 24 अक्टूबर, 2013 द्वारा भारत के राजपत्र, असाधारण, भाग II, खंड 3, उपखंड (i), तारीख 24 अक्टूबर, 2013 में प्रकाशित किए गए थे, उन पर उन सभी व्यक्तियों से जिनके उससे प्रभावित होने की संभावना है, एक अधिमूचना के राजपत्र की प्रतियां बनना की उपलब्ध होने की तारीख से पैंतालीस दिनों की अवधि के भीतर आक्षेप और सुझाव व्यक्त किए गए थे ;

और राजपत्र की प्रतियां बनना की 29 अक्टूबर, 2013 को उपलब्ध करा दी गई थी ;

और एक प्रारूप नियम के संबंध में जनता से प्राप्त आक्षेपों और सुझावों पर केन्द्रीय सरकार द्वारा विचार कर विचार किया गया है;

अतः, अब केन्द्रीय सरकार, औषधि और प्रमापन सामग्री अधिनियम, 1940 (1940 का 23) की धारा 12 और धारा 33 द्वारा प्रदत्त शक्तियों का प्रयोग करते हुए, औषधि तकनीकी सहायकार बोर्ड में परामर्श करने के पश्चात्, औषधि और प्रमापन सामग्री नियम, 1945 का और संशोधन करने के लिए निम्नलिखित नियम बनाती है, अर्थात् :-

- (1) इन नियमों का संक्षिप्त नाम औषधि और प्रमापन सामग्री (आठवां संशोधन) नियम, 2015 है ।
- (2) ये राजपत्र में उनके अंतिम प्रकाशन की तारीख को प्रवृत्त होंगे ।

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(1)

2. अधवि और प्राणत मागधी निवम, 1945 (निसे दसमें दसके परवत्त उक्त निवम सदा तथा हे) के निवम 2 में, बंद (उक्त) के परवत्त निमतिवित बंद अंतःस्वयवित किया जाएगा, अर्थात् :-

“उक्त” आरपसेवकीय अधवि” में मानव या प्राणियों के आंतरिक या बाह्य उपयोग के लिए और मानव या प्राणियों के निवम, उपचार निवधी अधिमाती, निवार के लिए आरवित उपयोग के लिए पाठ्यों या उनके आरवण या पाठ्यों के भावों के संशोधन में उपयुक्त प्रसंगगत या अरवत्तुत मानकीकृत मानत्रियां, उनके (पुष्पात्मक और भावात्मक रूप में मूल्यांकित) स्वरतम चार परिभाषित क्षेत्र मंत्रिय या पाठसेवकीय रसावन संघटक के भार बुद्धिगत और मानकीकृत अंश अतिवित हैं किन्तु इसके अंतर्गत अधिवार भावों से उन्हें प्रविष्ट करना अनिमत नहीं है:” ।

3. उक्त निवमों के निवम 122क में:-

(i) उक्तनिवम (1) के बंद (घ) में दूसरे परंतुक में “परिनिष्ट 1 या परिनिष्ट 1क” शब्दों, अंकों और अक्षर के स्थान पर, “परिनिष्ट 1 या परिनिष्ट 1क या परिनिष्ट 1घ” शब्द, अंक और अक्षर रखे जाएंगे;

(ii) उक्तनिवम (2) में “परिनिष्ट 1 या परिनिष्ट 1क” शब्दों, अंकों और अक्षर के स्थान पर, “परिनिष्ट 1 या परिनिष्ट 1क या परिनिष्ट 1घ” शब्द, अंक और अक्षर रखे जाएंगे;

4. उक्त निवमों के निवम 122ख में:-

(i) उक्तनिवम (1) के बंद (घ) में दूसरे परंतुक में “परिनिष्ट 1 या परिनिष्ट 1क” शब्दों, अंकों और अक्षर के स्थान पर, “परिनिष्ट 1 या परिनिष्ट 1क या परिनिष्ट 1घ” शब्द, अंक और अक्षर रखे जाएंगे;

(ii) उक्तनिवम (2) में “परिनिष्ट 1 या परिनिष्ट 1क” शब्दों, अंकों और अक्षर के स्थान पर, “परिनिष्ट 1 या परिनिष्ट 1क या परिनिष्ट 1घ” शब्द, अंक और अक्षर रखे जाएंगे;

5. उक्त निवमों के निवम 122क के बंद (घ) में, “परिभाषा में अधवि पठार्थ” शब्दों के परवत्त “या पाठसेवकीय अधवि” शब्द अंतःस्वयवित किए जाएंगे ।

6. उक्त निवमों के अंत्युक्ती में में परिनिष्ट 1क के परवत्त निमतिवित परिनिष्ट अंतःस्वयवित किया जाएगा, अर्थात् :-

शैक्षणिक परीक्षण करने या देश में पारदर्शकताय शैक्षणिक का आवाज या विनिर्माण करने के लिए आवेदन के साथ प्रस्तुत किया जाने वाला शर्त।

भाग 1

1. आवेदक द्वारा प्रस्तुत किया जाने वाला शर्त :

1.1 पाठ्य का भाग (जिनके अंतर्गत भागों लागू हों, देशी भाषा या संस्कृत भाग हैं) विनिर्देशों और प्रविष्ट करने का कार्य, गुणक उपचारकर्ता जिनके लिए यह उपबंधित है और पारदर्शकताय उपाय के लिए, किए गए कार्य शामिल हैं देशी रूप, पारदर्शकताय शैक्षणिक का प्रतिबन्ध विवरण का आवाज ।

1.2 पाठ्यों का उपायों पर पारदर्शकताय सहित पारदर्शकताय आवाज या कठिनाय शैक्षणिक के रूप में प्रस्ताव सहित प्रकाशित माहित्य सहित और देशी पारदर्शकताय विनिर्देशों में प्रतिबन्धित/प्रतिबन्धित के उपायों और उपायों के लिए संघटना, विहित प्रक्रिया, गुणक या उपायों की विधि, पूर्वोक्त संघटकों का अनुपात के संबंध में प्रस्तावों और अन्य दस्तावेजों के प्रतिनिर्देश भी उपलब्ध कराएँ।

1.3 किन्हीं अल्प निर्देशनों, पारदर्शकताय आवाज या कठिनाय शैक्षणिक माहित्य या विनिर्देशनों के विद्यमान उपाय पर रिपोर्टों में वर्णित एकर प्रभाव ।

1.4 विद्यमान के लिए आवेदनित वास्तु शैक्षणिक आवाज के लिए प्रस्तावित गुणक और शैक्षणिक संस्थाओं की कानून प्रकाशित शैक्षणिक रिपोर्टें,

(क) बहुत पारदर्शकताय शैक्षणिक आवाजि में जाने गए उपायों में प्रक्रिया और उपायों उनके अनुक्रम या समान हैं ; और

(ख) बहुत पारदर्शकताय शैक्षणिक आवाजि में जाने गए उपायों में प्रक्रिया और उपायों भिन्न हैं ।

1.5 किन्हीं अन्वयन में किन्हीं अल्प निर्देशनों, एकर प्रभावों पर प्रस्ताव, रिपोर्टें और कार्य के दौरान पाठ्य शैक्षणिक के विद्यमान उपायों के दौरान रिपोर्ट किए गए एकर प्रभावों और प्रतिबन्धित प्रभावों पर प्रस्ताव, बहुत लागू हों ।

1.6 पाठ्य शैक्षणिक शैक्षणिक का विद्यमान उपायों - उपायों का प्रतिबन्धित प्रकाशित करने के लिए उपाय, विनिर्देशन, विचार की गई भाषा, मातृक अन्वयन पर उन्वयन का परिचय और उन कार्य की संख्या, जिनमें उपाय का विचार किया जा रहा है, के प्रति देशी ।

## 2. मानव या नैदानिक भेषज गुणविज्ञान सूचना :

2.1 मानव अध्ययन या नैदानिक अध्ययन महामारी रोग अध्ययन सहित भेषज गुणविज्ञान अध्ययनों की बाबत, जो विषयन के लिए अज्ञात पादप भेषजीय औषध से सुसंगत हैं, प्रकाशित वैज्ञानिक रिपोर्टे,-

- (क) जहाँ पारंपरिक औषधि या रुद्रिगत औषधि में जाने गए उत्पाद में प्रक्रिया और उपयोग उनके अनुरूप या समान हैं; और  
(ख) जहाँ पारंपरिक औषधि या रुद्रिगत औषधि में जाने गए उत्पाद में प्रक्रिया और उपयोग भिन्न हैं।

## 2.2 भेषज गुणविज्ञान अध्ययन सूचना (यदि उपलब्ध हो)

2.3 पादप या उत्पाद या सब्जि या पादप भेषजीय उत्पाद पर प्रकाशित योनीग्रन्थ, कोर्ड हों। [सभी प्रकाशनों की संघेकी अनुबाद के साथ प्रतियां संलग्न करें]

## भाग-2

### आवेषक द्वारा सूचित आंकड़े

3. निष्कर्षण तथा विखंडन के लिए उपयोग किए गए पादप की पहचान, अधिप्रमाणन और स्रोत :-
- 3.1 पादप भेषजीय औषध के स्रोत के रूप में प्रयुक्त किए गए पादप की वर्गीकृत पहचान तथा बानस्पतिक पहचान जिसमें बंध, जाति तथा कुटुंब का विवरण सम्मिहित हो। इसके साथ कर्णीकरण प्राधिबारी जिसने जाति का नामकरण किया है या खेतिहर (यदि कोई हो) के नाम का वर्णन करना भी आवश्यक है।
- 3.2 आकारिकी एवं अरीर रचनात्मक विवरण इसमें नैदानिक लक्षण तथा पादप का चित्र/या अक्षि अभिज्ञान की पुष्टि हेतु पादप का भाग (योग्य कर्णीकरण द्वारा प्रदत्त बानस्पतिक पहचान की पुष्टि का प्रमाण-पत्र प्रस्तुत करें)।
- 3.3 पादप का प्राकृतिक पर्यावास और भौगोलिक वितरण तथा यह भी वर्णन करें कि क्या इसनेमान लिए जाने वाला पादप का भाग नवीकरणीय है या विखंडनात्मक और क्या स्रोत की खेती की जाती है या अन्य है।

- 3.4 संग्रह करने की शक्त या समय ।
- 3.5 पादप के श्रोत जिसके अंतर्गत भौगोलिक अवस्थिति है तथा उसके संग्रहण की शक्त या समय ।
- 3.6 एक विवरण जिसमें यह उपदर्शित हो कि प्रजाति निम्नलिखित में से कोई एक है--
- (क) जंगली पशु पौधों के संकटापन प्रजाति अधिनियम या अन्य राष्ट्रीय और जनशक्ति की संकटापन प्रजातियों में अंतरराष्ट्रीय व्यापार अभिलेख के अधीन संकटापन या परिसंरक्षित में अवधारित समझी गई है;
- (ख) वैश्व विविधता अधिनियम, 2002 (2003 का 18) के अधीन विशेष संरक्षण हेतु हकदार है;
- (ग) प्रजाति की कोई मात्र जीन प्रकृति, रसायन प्रकृति तथा पारिस्थितिकी प्रकृति परिवर्तित।
- 3.7 उत्पादक या अपूर्णिकताओं (नाम तथा पते सहित) की सूची और प्रत्येक उत्पादक या अपूर्णिकता के लिए निम्नलिखित सतों पर सूचना, यदि उपलब्ध हो, यह पहले ही गृहण कर ली गई है, जिसके अंतर्गत प्राथमिक इतरक्षण की सूचना भी है, अर्थात्-
- (क) फसल की तबन्धित;
- (ख) उपज की स्थितियां;
- (ग) फसल के समय पादप वृद्धि का प्रक्रम;
- (घ) फसल का समय;
- (ङ) संग्रहण, भोजन, शुक्लन और परिशोधन स्थितियां;
- (च) इस्तेमाल, विकृतिकरण और परिव्यजन;
- (छ) पादप सामग्री को पिलाना, बौटाना ; और
- (ज) किसी गई पादप सामग्री से स्थान आकार के कण प्राप्त करने के लिए छानना ।



- 3.8 गुणवत्ता विशिष्टियां अर्थात् -
- (क) विज्ञानीय पदार्थ;
  - (ख) कुल भयम्;
  - (घ) अल्प में अप्रत्यानीय भयम्;
  - (ङ) नाशकारीयमार अवरोध;
  - (च) भारी धातु संकुचन;
  - (ज) सूक्ष्मजीवीय मार;
  - (झ) पादप रसायनिक संदर्भ मार्कर (एस) सहित वर्गीकृत आंगुलि;
  - (ञ) जैव सक्रिय या पादप रसायनिक संपदकों के लिए परम्ब;
  - (ट) किसी नमूने के रसायन भेषजीय औपग्र (कोटी क्लोरोक्रीकरण) के लिए गुणवत्ता नियंत्रण के अधीन ही गई परीक्षण विधि के अनुसार रसायन भेषजीय अनुवी छिंट ।
- 3.9 योग्य टेक्नोनोमिस्ट द्वारा जारी अभिज्ञानपुष्टि प्रमाण-पत्र की छायाप्रति तथा पूर्वतः लेखनीकृत पादप के नमूना प्रतिदर्श की संपूर्णता का अनुबंध जिलके साथ प्राधिकार की पुष्टि हेतु प्रयुक्त होने वाले सामान्यतः उपकरण की नैदानिक, आकारिकी तथा उलक विज्ञानी लक्षणों के चित्र या छायाप्रति संग्रह हो।

4. सत्य की प्रक्रिया और पर्याप्तवर्ती विभाजन और मुद्रिकरण :-

- 4.1 प्रारम्भिक सामग्री के लिए गुणवत्ता विशिष्टियां और परीक्षण विधियां।
- 4.2 प्रसंस्करण में अंतर्भवित कदम
- (क) उपयोग किए गए विभाजक, सत्य मूल्य, विभाजक अवशिष्ट परीक्षण या भीमारु, भौतिकी-रसायन परीक्षण, सूक्ष्मजीवीय मार, भारी धातु संकुचन, पादप भेषजीय संवर्ध मारकरों सहित वर्ण मुद्रिक आंगुल मुद्रण शोकाहल के विवरण सक्रिय पदकों या सक्रिय मारकरों की मिलेपकारु यदि सक्रिय संपटक प्राप्त नहीं है;
  - (ख) अंतिम मुद्र किए गए विभाजन का विशेषीकरण;
  - (घ) अंतिम मुद्र किए गए विभाजन के जैव सक्रिय संपदकों पर हाता;
  - (ङ) इन्वोमान किए गए अवसक्रिय पदार्थ या पोषक या स्थिरक या परिपक्षक पर सूचना ।
- 4.3 मुद्रि और विशेषीकृत अंतिम उत्पाद की पैकेजिंग, संवर्धन स्थितियों और लेखनीकरण के स्वीरे ।

5. आवेदित की गई पादप भेषजीय औपग्र की विनिर्मिति -

- 5.1 संपटक, सत्य या पादप भेषजीय की प्रति प्रकाई सुराक का अनुपात, सभी अनुदन्वों, स्टैबसाइडरों और उपयुक्त किसी अन्य अधिकारों, पैकेजिंग सामग्रियों का नाम और अनुपात के स्वीरे।
- 5.2 पादप भेषजीय की पत्रवान के लिए परीक्षण ।
- 5.3 सक्रिय तथा निष्क्रिय पादप भेषजीय के वर्ण मुद्रिक आंगुल मुद्रण शोकाहल हेतु स्वामिती विशिष्टियां तथा सक्रिय संपटक तथा प्राथमिक भेषर हेतु परम्ब, यदि सक्रिय संपटक प्राप्त नहीं है।

6. विनिर्मिति की विनिर्माण प्रक्रिया:-

- 6.1 पर्यावरण नियंत्रणों, अंतः प्रक्रिया गुणवत्ता नियंत्रण परीक्षण और स्वीकृति हेतु सीमाओं सहित सुराक विन्म के विनिर्माण की रूपरेखा।
- 6.2 उपयोग की गई सभी पैकेजिंग सामग्रियों, पैकेजिंग के प्रकृत और अंतिम पैकों के विवरण के स्वीरे।



- 6.3 तैयार उत्पाद, गुणवत्ता विशिष्टिणां विस्तार अंतर्गत सुराक प्ररूप के लिए विशिष्ट परीक्षण, पादप भेषजीय संकर्म मारकट के माध फिस्को, तथा बर्णमुक्तिक अंगुल छाप अंतराक्षण हेतु निर्मित उत्पादों, गुणवत्ता विशिष्टियों का विवरण है।
7. स्थायित्व अंकडा:-
- 7.1 0, 1, 2, 3 और 6 मास हेतु क्ख तापमान तथा 40 डिग्री +/- 2 डिग्री सेल्सियस/75 प्रतिशत आर्.एच. +/- 5 प्रतिशत आर्.एच. पर अंडारित मास्य वा यस्वर शेषजीय पदार्थ तैसा इतरोक यद 4.0 पर बर्णित है के स्थायित्व अंकडो।
- 7.2 विपणन के उदैलय से एक 0, 1, 2, 3 तथा 6 मास हेतु 40 डिग्री +/- 2 डिग्री सेल्सियस/75 प्रतिशत आर्.एच. +/- 5 प्रतिशत आर्.एच. तथा क्ख तापक्रम पर अंडारित पादप भेषजीय (बै) की सुराक की फिस्को की तापको के स्थायित्व अंकडो।
8. सुरक्षा तथा भेषजनुषा विज्ञान सूचना:-
- 8.1 सुरक्षा और पादप भेषजीय अक्षयनों पर डाटा उपलब्ध कराया जाना है।
- 8.2 पशु विशाक्तता तथा सुरक्षा अंकडे:-
- (क) पशुको की दो जातियों पर रोहार्द गर्द भौतिक विशाक्तता की सुराक 28 से 90 दिनों तक।
- (ख) इन बिट्रो डिनोटोक्सीमिटी अंकडा (अनुसूची म के अनुसार एमी परीक्षण तथा ओमोमोमल एडिरेलन)।
- (ग) बाह्य उपयोग उत्पादों हेतु डर्मल टोक्सीमिटी परीक्षण।
- (घ) डेरमटोजीनोमिटी जलजल (मात्र यदि पादप भेषजीय औषध सर्भास्वा के डीएज उपयोग द्वारा बांशित है)।
9. मानव अक्षयन:-

- 9.1 पादप भेपजीय औषध का नैदानिक परीक्षण नई औषधों के लिए लागू नियमों और मार्गदर्शक सिद्धांतों के अनुसार संचालित किया जाएगा।
- 9.2 सामल पादप भेपजीय औषध हेतु- बरफ 1 के आंकड़े (अधिकतम सहनीय सुराक तथा संबंधित विषाणुजा निर्धारण हेतु) तथा प्रोटोकॉल अध्ययन प्रारम्भ करने से पहले प्रस्तुत करने होंगे।
- 9.3 अध्ययन प्रारम्भ करने से पूर्व संबंधित फिने गए सुराक खोज अध्ययन के परिणाम के आंकड़े प्रस्तुत करने होंगे। परंतु यदि पादप भेपजीय औषध पाँच वर्ष की अवधि से अधिक से विपणित हो रहा है या जहाँ पादप भेपजीय औषध की सुरक्षा से संबंधित समुचित प्रकाशित तथ्य है तो अध्ययन को संशेषित, संशोधित या शिथिल किया जा सकता है।
10. पुष्टिपूर्व नैदानिक परीक्षण।
- 10.1 पादप भेपजीय उत्पाद की प्रस्तावित विभिन्न दशता अध्ययन या किसी विधित या विशेष सुरक्षा हेतु अनुसोदनार्थ प्रोटोकॉल प्रस्तुत करें।
- 10.2 पादप भेपजीय सुराक की किम्म या उत्पाद हेतु सुरक्षा तथा दशता आंकड़े तैयार या कैथ करने के लिए समुचित मानव नैदानिक अध्ययन हेतु अनुसोदन के प्रस्तावित प्रोटोकॉल प्रस्तुत करें।
- 10.3 उपरोक्त अध्ययन के दौरान किम्म प्रकार विनिबन्धित की गुणवत्ता अनुदशित की जाएगी पर मूचना प्रस्तुत करें।
11. विनियामक स्थिति:-
- 11.1 किसी राष्ट्र में विपणित किसी श्रेणी जैसे किवाल्सक, भोजन या सुराक अनुपूरक या चारम्बरिक औषध के रूप में या अनुसोदित औषध के रूप में पादप भेपजीय औषध की स्थिति।
12. विपणन मूचना:-
- 12.1 विनशित होने वाले पादप भेपजीय औषध के शैलिन में रज्डी गई शैली मूचना गर्ची का विकरण।
- 12.2 शैलन तथा कार्टन हेतु पाठ का आकम्प।

## 13. विषयोत्तर निगरानी (रीएम्पल)

13.1 औषध के अनुमोदन के उपरोक्त आवेदक आवधिक सुरक्षा अद्यतन रिपोर्ट पहले दो वर्ष तक प्रत्येक सत्राब्दी प्रस्तुत करेगा।

13.2 पञ्चासवर्षी की वर्ष तक आवधिक सुरक्षा अद्यतन रिपोर्ट वार्षिक आधार पर प्रस्तुत की जानी आवश्यक है।

## 14. कोई अन्य सुसंगत सूचना

कोई अन्य सुसंगत सूचना जिसे आवेदक समझता है कि वह आवेदन के वैज्ञानिक मूल्यांकन में सहायक होगी।

[फा. सं. एक्स. 11014/2/2012-डीएफसी]

कुन्दन लाल शर्मा, संयुक्त सचिव

टिप्पण : मूल नियम भारत के राजपत्र में अधिसूचना संख्यांक एफ 20-10/45-एच (1), तारीख 21 दिसम्बर, 1945 द्वारा प्रकाशित किए गए थे और इसमें अंतिम संशोधन अधिसूचना संख्यांक वा.फा.नि. 828(अ) तारीख 30 अक्टूबर, 2015 द्वारा किया गया था।

## MINISTRY OF HEALTH AND FAMILY WELFARE

(Department of Health and Family Welfare)

## NOTIFICATION

New Delhi, the 30th November, 2015.

**G.S.R. 918(E).**—Whereas a draft of the rules further to amend the Drugs and Cosmetics Rules, 1945, was published, as required by section 12 and section 33 of the Drugs and Cosmetics Act, 1940 (23 of 1940), vide notification of the Government of India in the Ministry of Health and Family Welfare (Department of Health and Family Welfare), number G.S.R. 702(E), dated the 24<sup>th</sup> October, 2013, in the Gazette of India, Extraordinary, Part II, Section 3, Sub-section (i), dated the 24<sup>th</sup> October, 2013, inviting objections and suggestions from all persons likely to be affected thereby before the expiry of a period of forty-five days from the date on which the copies of the Official Gazette of the said notification were made available to the public;

And whereas copies of the Gazette were made available to the public on the 29<sup>th</sup> October, 2013;

And whereas, the objections and suggestions received from the public on the said draft rules have been considered by the Central Government.

Now, therefore, in exercise of the powers conferred by section 12 and section 33 of the Drugs and Cosmetics Act, 1940 (23 of 1940), the Central Government, after consultation with the Drugs Technical Advisory Board, hereby makes the following rules further to amend the Drugs and Cosmetics Rules, 1945, namely:—

1. (1) These rules may be called the Drugs and Cosmetics (Eighth Amendment) Rules, 2015.
- (2) They shall come into force on the date of their publication in the Official Gazette.
2. In rule 2 of the Drugs and Cosmetics Rules, 1945 (hereinafter referred to as the said rules), after clause (ca) the following clause shall be inserted, namely:—
 

“(cb). “Phytopharmaceutical drug” includes purified and standardised fraction with defined minimum four bio-active or phyto-chemical compounds (qualitatively and quantitatively assessed) of an extract of a medicinal plant or its part, for internal or external use of human beings or animals for diagnosis, treatment, mitigation or prevention of any disease or disorder but does not include administration by parenteral route.”.
3. In rule 122-A of the said rules:—
  - (i) in sub-rule (1), in clause (b), in the second proviso, for the words, figures and letter “Appendix I or Appendix IA”, the words, figures and letters, “Appendix I or Appendix IA or Appendix IB”, shall be substituted;
  - (ii) in sub-rule (2), for the words, figures and letter “Appendix I or Appendix IA”, the words, figures and letters, “Appendix I or Appendix IA or Appendix IB”, shall be substituted.

4. In rule 122-B of the said rules,-
  - (i) in sub-rule (1), in clause (b), in the second proviso, for the words, figures and letter "Appendix I or Appendix I A", the words, figures and letters, "Appendix I or Appendix IA or Appendix I B", shall be substituted;
  - (ii) in sub-rule (2), for the words, figures and letter "Appendix I or Appendix IA", the words, figures and letters, "Appendix I or Appendix IA or Appendix IB", shall be substituted.
5. In rule 122-E of the said rules, in clause (a), after the words "bulk drugs substance," the words "or phytopharmaceutical drug" shall be inserted.
6. In Schedule Y of the said rules, after APPENDIX IA, the following Appendix shall be inserted, namely:-

"APPENDIX I B

**DATA TO BE SUBMITTED ALONG WITH APPLICATION TO CONDUCT CLINICAL TRIAL OR IMPORT OR MANUFACTURE OF A PHYTOPHARMACEUTICAL DRUG IN THE COUNTRY**

**PART - I**

**1. Data to be submitted by the applicant:**

- 1.1. A brief description or summary of the phytopharmaceutical drug giving the botanical name of the plant (including vernacular or scriptural name, wherever applicable), formulation and route of administration, dosage, therapeutic class for which it is indicated and the claims to be made for the phytopharmaceutical product.
- 1.2. Published literature including information on plant or product or phytopharmaceutical drug, as a traditional medicine or as an ethno medicine and provide reference to books and other documents, regarding composition, process prescribed, dose or method of usage, proportion of the active ingredients in such traditional preparations per dose or per day's consumption and uses.
- 1.3. Information on any contraindications, side effects mentioned in traditional medicine or ethno medicine literature or reports on current usage of the formulation.
- 1.4. Published scientific reports in respect of safety and pharmacological studies relevant for the phytopharmaceutical drug intended to be marketed,-
  - (a) where the process and usages are similar or same to the product known in traditional medicine or ethno medicine; and
  - (b) where process or usage is different from that known in traditional medicine or ethno medicine.
- 1.5. Information on any contraindications, side effects mentioned or reported in any of the studies, information on side effects and adverse reactions reported during current usage of the phytopharmaceutical in the last three years, wherever applicable.
- 1.6. Present usage of the phytopharmaceutical drug, - to establish history of usages, provide details of the product, manufacturer, quantum sold, extent of exposure on human population and number of years for which the product is being sold.

**2. Human or clinical pharmacology information:**

- 2.1. Published scientific reports in respect of pharmacological studies including human studies or clinical studies or epidemiological studies, relevant for the phytopharmaceutical drug intended to be marketed,-
  - (a) where the process and usages are similar or same to the product known in traditional medicine or ethno medicine; and
  - (b) where process or usage is different from that known in traditional medicine or ethno medicine.
- 2.2. Pharmacodynamic information (if available).
- 2.3. Monographs, if any, published on the plant or product or extract or phytopharmaceutical. (Copies of all publications, along with english translation to be attached.)

**PART - II**

**Data generated by applicant**

**3. Identification, authentication and source of plant used for extraction and fractionation:**

- 3.1. Taxonomical identity of the plant used as a source of the phytopharmaceutical drug giving botanical name of genus, species and family, followed by the authority citation (taxonomist's name who named the species), the variety or the cultivar (if any) needs to be mentioned.



- 3.2 Morphological and anatomical description giving diagnostic features and a photograph of the plant or plant part for further confirmation of identity and authenticity. (Furnish certificate of confirmation of botanical identity by a qualified taxonomist).
  - 3.3 Natural habitat and geographical distribution of the plant and also mention whether the part of the plant used is renewable or destructive and the source whether cultivated or wild.
  - 3.4 Season or time of collection.
  - 3.5 Source of the plant including its geographical location and season or time of collection.
  - 3.6 A statement indicating whether the species is any of the following, namely:-
    - (a) determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered species (CITES) of wild fauna and Flora;
    - (b) entitled to special protection under the Biological Diversity Act, 2002 (18 of 2003);
    - (c) any known genotypic, chemotypic and ecotypic variability of species.
  - 3.7. A list of grower or supplier (including names and addresses) and information on the following items for each grower or supplier, if available or identified already, including information of primary processing, namely:-
    - (a) harvest location;
    - (b) growth conditions;
    - (c) stage of plant growth at harvest;
    - (d) harvesting time;
    - (e) collection, washing, drying and storage conditions;
    - (f) handling, garbling and transportation;
    - (g) grinding, pulverising of the plant material; and
    - (h) sieving for getting uniform particle size of powdered plant material.
  - 3.8. Quality specifications, namely:-
    - (a) foreign matter;
    - (b) total ash;
    - (c) acid insoluble ash;
    - (d) pesticide residue;
    - (e) heavy metal contamination;
    - (f) microbial load;
    - (g) chromatographic finger print profile with phytochemical reference marker;
    - (h) assay for bio-active or phytochemical compounds; and
    - (i) chromatographic fingerprint of a sample as per test method given under quality control of the phytopharmaceutical drug (photo documentation).
  - 3.9. An undertaking to supply specimen sample of plant duly labeled and photocopy of the certificate of identity confirmation issued by a qualified taxonomist along with drawings or photographs of the diagnostic morphological and histological features of the botanical raw material used for the confirmation of authenticity.
- 4. Process for extraction and subsequent fractionation and purification:**
- 4.1. Quality specifications and test methods for starting material.
  - 4.2. Steps involved in processing.
    - (a) details of solvent used, extractive values, solvent residue tests or limits, physico-chemical tests, microbial loads, heavy metal contaminants, chromatographic finger print profile with phytochemical reference markers, assay for active constituents or characteristic markers, if active constituents are not known;
    - (b) characterisation of final purified fraction;
    - (c) data on bio-active constituent of final purified fraction;
    - (d) information on any excipients or diluents or stabiliser or preservative used, if any.
  - 4.3. Details of packaging of the purified and characterised final product, storage conditions and labeling.

**5. Formulation of phytopharmaceutical drug applied for:**

- 5.1. Details of the composition, proportion of the final purified fraction with defined markers of phytopharmaceutical drug per mill dose, name and proportions of all excipients, stabilisers and any other agent used and packaging materials.
- 5.2. Test for identification for the phytopharmaceutical drug.
- 5.3. Quality specifications for active and inactive phytopharmaceutical chromatographic finger print profile with phytochemical reference marker and assay of active constituent or characteristic chemical marker.

**6. Manufacturing process of formulation:**

- 6.1. The outline of the method of manufacture of the dosage form, along with environmental controls, in-process quality control tests and limits for acceptance.
- 6.2. Details of all packaging materials used, packing steps and description of the final packs.
- 6.3. Finished product's quality specifications, including tests specific for the dosage form, quality and chromatographic finger print profile with phytochemical reference marker and assay for active constituent or characteristic marker, if active constituents are not known.

**7. Stability data:**

- 7.1. Stability data of the phytopharmaceutical drug described at 4 above, stored at room temperature at  $40 \pm 2$  deg. C and humidity at 75%RH  $\pm$  5%RH for 0, 1, 2, 3 and 6 months.
- 7.2. Stability data of the phytopharmaceutical drug in dosage form or formulation stored at room temperature at  $40 \pm 2$  deg. C and humidity at 75%RH  $\pm$  5%RH for 0, 1, 2, 3 and 6 months, in the pack intended for marketing.

**8. Safety and pharmacological information:**

- 8.1. Data on safety and pharmacological studies to be provided.
- 8.2. Animal toxicity and safety data:
  - (a) 28 to 90 days repeat dose oral toxicity on two species of animals;
  - (b) *In-vitro* genotoxicity data (Amie's test and Chromosomal aberration test as per Schedule Y);
  - (c) dermal toxicity tests for topical use products;
  - (d) teratogenicity study (only if phytopharmaceutical drug is intended for use during pregnancy).

**9. Human studies:**

- 9.1. Clinical trials for phytopharmaceutical drugs to be conducted as per applicable rules and guidelines for new drugs.
- 9.2. For all phytopharmaceutical drugs data from phase I (to determine maximum tolerated dose and associated toxicities) and the protocols shall be submitted prior to performing the studies.
- 9.3. Data of results of dose finding studies performed and the protocols shall be submitted prior to performing the studies:

Provided that in the case of phytopharmaceutical drug already marketed for more than five years or where there is adequate published evidence regarding the safety of the phytopharmaceutical drug, the studies may be abbreviated, modified or relaxed.

**10. Confirmatory clinical trials:**

- 10.1. Submit protocols for approval for any specific or special safety and efficacy study proposed specific to the phytopharmaceutical drug.
- 10.2. Submit proposed protocol for approval for human clinical studies appropriate to generate or validate safety and efficacy data for the phytopharmaceutical dosage form or product as per applicable rules and guidelines.
- 10.3. Submit information on how the quality of the formulation would be maintained during the above studies.



**11. Regulatory status:**

- 11.1. Status of the phytopharmaceutical drug marketed in any country under any category like functional food or dietary supplement or as traditional medicine or as an approved drug.

**12. Marketing information:**

- 12.1. Details of package insert or patient information sheet of the phytopharmaceutical drug to be marketed.  
12.2. Draft of the text for label and carton.

**13. Post marketing surveillance (PMS):**

- 13.1. The applicant shall furnish periodic safety update reports every six months for the first two years after approval the drug is granted.  
13.2. For subsequent two years the periodic safety update reports need to be submitted annually.

**14. Any other relevant information:**

Any other relevant information which the applicant considers that it will help in scientific evaluation of the application.”

(F. No. X. 11014/2/2012-DFQC)

K. L. SHARMA, Jt. Secy.

**Note:** The principal rules were published in the Gazette of India vide notification No. F.28-10/45-H (1) dated the 21st December, 1945 and was last amended vide notification number GSR 826 (E), dated the 30th October, 2015.



### LEVELS OF EVIDENCE

The degree of importance of evidence is given in ascending order. For eg., Ia is considered to be highest level of evidence.

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

#### **Grading of recommendations:**

available criteria for recommendation of AYUSH intervention based on the level of evidences is given below. For e.g., availability of requirements as listed in Grade A gives a highest recommendation for the use of AYUH intervention.

Grade	Recommendation
A	(Evidence levels quality Ia, Ib) Requires at least one randomized controlled trial as part of the body of literature of overall good and consistency addressing the specific recommendation.
B	(Evidence levels IIa, IIb, III) Requires availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation.
C	(Evidence level IV) Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.

Source: <http://apps.who.int/medicinedocs/en/d/Jwhozip42e/6.3.html>

**TEMPLATE FOR MONITORING****DURING VISIT OF MONITORING TEAM**

1.	<b>Name of the Institute</b>	
2.	<b>Date of Visit of Monitoring Team</b>	
3.	<b>Category of the project (IMR / Collaborative)</b>	
4.	<b>Title of the Project</b>	
5.	<b>Name of the Principal Investigator</b>	
6.	<b>Name of the Co – investigator(s)</b>	
7.	<b>Collaborator (If applicable)</b>	
8.	<b>Budget sanctioned and date of sanction</b>	
9.	<b>No. of Installment received with amount and status of utilization (head wise)</b>	
10.	<b>Date of Initiation/Enrollment</b>	
11.	<b>Status of IEC /IAEC clearance</b>	
12.	<b>Status of CTRI Registration /CTRI Registration No:</b>	
13.	<b>OPD Register (Random checking of entries enrolled participants)</b>	



14.	<b>Status of Execution</b>	
15.	<b>CRFs in Original(random checking)</b>	
	<b>Randomly selected clinical /demographical information /investigations to be cross verified in CRFs &amp; E-format/ Original reports</b>	
16.	<b>Current stock /Whether trial drug is present in sufficient quantity</b>	
17.	<b>Storage conditions of trial drugs</b>	
18.	<b>Registers/files / receipts (technical/drug/accounts, etc) related to clinical / Pharmacological trial</b>	
19.	<b>Any other information</b>	
20.	<b>Expected period of completion of targets</b>	
21.	<b>At the time of monitoring the targets achieved as per deliverables\</b>	

<b>Investigators/Head of institute</b>	<b>Signature</b>	<b>Date</b>	<b>Name of monitoring committee</b>	<b>Signature</b>	<b>Date</b>
<b>PI</b>					
<b>Co-PI</b>					
<b>Head of the Institute</b>					



## DATA AND SAFETY MONITORING BOARD (DSMB) GUIDELINES

### I. Roles and Responsibilities

The Data and Safety Monitoring Board (DSMB) is an independent group of experts that advises NIDCR and the study investigators. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and 2) make recommendations to NIDCR concerning the continuation, modification, or termination of the trial. The DSMB considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study.

The DSMB is responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review, stopping guidelines, unmasking (unblinding) and voting procedures prior to initiating any data review. The DSMB is also responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it.

The DSMB should review each protocol for any major concern prior to implementation. During the trial, the DSMB should review cumulative study data to evaluate safety, study conduct, and scientific validity and integrity of the trial. As part of this responsibility, DSMB members must be satisfied that the timeliness, completeness, and accuracy of the data submitted to them for review are sufficient for evaluation of the safety and welfare of study participants. The DSMB should also assess the performance of overall study operations and any other relevant issues, as necessary.

Items reviewed by the DSMB include:

- Interim/cumulative data for evidence of study-related adverse events;
- Interim/cumulative data for evidence of efficacy according to pre-established statistical guidelines, if appropriate;
- Data quality, completeness, and timeliness; Performance of individual centers;
- Adequacy of compliance with goals for recruitment and retention, including those related to the participation of women and minorities;
- Adherence to the protocol;
- Factors that might affect the study outcome or compromise the confidentiality of the trial data (such as protocol violations, unmasking, etc.); and,
- Factors external to the study such as scientific or therapeutic developments that may impact participants safety or the ethics of the study.

The DSMB should conclude each review with their recommendations to NIDCR as to whether the study should continue without change, be modified, or terminated. Recommendations regarding modification of the design and conduct of the study could include:

- Modifications of the study protocol based upon the review of the safety data;
- Suspension or early termination of the study or of one or more study arms because of serious concerns about subjects' safety, inadequate performance or rate of enrollment;
- Suspension or early termination of the study or of one or more study arms because study objectives have been obtained according to pre-established statistical guidelines;
- Optional approaches for NIDCR and investigators to consider when the DSMB determines that the incidence of primary study outcomes is substantially less than



expected such as recommendations to increase the number of trial centers or extend the recruitment period; and,

- Corrective actions regarding a study center whose performance appears unsatisfactory or suspicious.

Confidentiality must always be maintained during all phases of DSMB review and deliberations. Usually, only voting members of the DSMB should have access to interim analyses of outcome data by treatment group. Exceptions may be made when the DSMB deems it appropriate. The reason and to whom the exceptions for access to interim analyses is granted will be documented in the Closed Session Report. DSMB members must maintain strict confidentiality concerning all privileged trial results ever provided to them.

The DSMB should review data only by masked study group (such as X vs. Y rather than experimental vs. control) unless or until the DSMB determines that the identities of the groups are necessary for their decision-making. Whenever masked data are presented to the DSMB, the key to the group coding must be available for immediate unmasking.

## II. Membership

The membership of the DSMB should reflect the disciplines and medical and dental specialties necessary to interpret the data from the clinical trial and to fully evaluate participant safety. The number of DSMB members depends on the phase of the trial, range of medical issues, complexity in design and analysis, and potential level of risk but generally consists of three to seven members including, at a minimum:

- Expert(s) in the clinical aspects of the disease/patient population being studied;
- One or more biostatisticians; and,
- Investigators with expertise in current clinical trials conduct and methodology.

*Ad hoc* specialists may be invited to participate as non-voting members at any time if additional expertise is desired. Some trials, depending on the population and nature of the intervention, may well be served by inclusion of a bioethicist on the DSMB, Steering Committee, or Advisory Panel.

NIDCR staff without direct involvement in study implementation and who meet other membership criteria may participate as *ex officio*, non-voting members. NIDCR staff serving in these positions must have a current confidential financial disclosure report on file with the Deputy Ethics Counselor, NIDCR.

Representatives of the manufacturer (industrial collaborator) of the test substance(s) or any other individual with vested interests in the outcome of the study are not eligible to serve on the DSMB although they may attend open sessions of the DSMB meetings.

### ***Conflict of Interest***

No member of the DSMB should have direct involvement in the conduct of the study. Furthermore, no member should have financial, proprietary, professional, or other interests that may affect impartial, independent decision-making by the DSMB. Letters of invitation to prospective DSMB and *ad hoc* members should include the following: "Acceptance of this invitation to serve on the xxx DSMB confirms that I do not have any financial or other interest with any of the collaborating or competing pharmaceutical firms or other organizations involved in the study that constitute a potential conflict of interest." In addition, all DSMB and *ad hoc* members will sign a Conflict of Interest certification to that effect at the time they are asked to participate. At the beginning of every DSMB meeting, NIDCR program staff or the DSMB Chair will reconfirm that no conflict of interest exists for DSMB members. Interests that may create a potential conflict of interest should be disclosed to the DSMB prior to any discussion. The DSMB will determine how to handle such potential conflict. The DSMB can require that a member with a potential conflict not vote or take other means deemed appropriate. NIDCR may





dismiss a member of the DSMB in the event of unmanageable potential conflict or appearance of conflict.

### ***Selection and Invitation to Participate***

The Program Official (PO) holds primary responsibility for the formation of the DSMB unless the Clinical Terms of Award for a grant or the Roles and Responsibilities negotiated for a protocol specifically identify this as the responsibility of the grantee. The PO (or grantee as specified) is responsible for developing the roster of potential DSMB members. Recommendations for proposed members are solicited from many sources. Study investigators and the industrial collaborators should have the opportunity to review the list of proposed members before the candidate's interest and availability are confirmed by the PO (or grantee as specified). The proposed roster of members must be submitted to the Director, Office of Clinical Trials.

### ***When is a DSMB Needed?***

A DSMB is indicated, from a practical perspective in the following circumstances:

- If the trial is intended to provide definitive information about effectiveness and/or safety of a medical or biobehavioral intervention
- If there are prior data to suggest that the intervention being studied has the potential to induce potentially unacceptable toxicity
- If the trial is evaluating mortality or another major endpoint, such that inferiority of one treatment arm has safety as well as effectiveness implications
- If it would ethically be important for the trial to stop early if the primary question addressed has been definitively answered, even if secondary questions or complete safety information were not yet fully addressed.

It is generally expected that a DSMB will be utilized in the following situations:

- All Phase III studies require a DSMB, with the exception of low-risk behavioral and nutritional studies.
  - For this discussion, "low-risk" refers to trials where subjects are expected to experience only minor sideeffects, and interim analyses are not crucial for the protection of the subjects
  - The involvement of a DSMB may still be requested for low-risk studies if the studies are exceptionally large, long term, and/or involve vulnerable subjects
- Phase II clinical trials which are multicenter and randomized require a DSMB, with the exception of low-risk behavioral and nutritional studies
- Phase II studies which are "high risk" require a DSMB
  - For this discussion, "high-risk" refers to trials of interventions associated with substantial side effects to subjects (e.g., side effects that could result in serious morbidity or death, or are irreversible), trials of diseases associated with high mortality or morbidity, and trials of highly experimental therapies (e.g., gene therapy)
  - As a general guideline, DSMBs are needed for clinical trials of diseases with high mortality or morbidity, for clinical trials involving high risks, and for large, multicenter clinical trials
- For some studies involving particularly vulnerable study participants (e.g., children or persons with impaired ability to consent), it may be beneficially to utilize a DSMB as an additional measure of subject protection

A DSMB is NOT generally expected in the following situations:



- Single-center open-label Phase I and II clinical trials generally do not need a DSMB since the local investigator will have access to all data. In these types of trials, the investigator could appoint an independent medical monitor to evaluate adverse events and make recommendations for continuing or stopping a trial
- A multicenter, high-risk Phase I clinical trial should not require a DSMB if there are very clear rules for stopping the trial. For example, a DSMB is generally not required for a classic open-label dose escalation trial with clear and objective criteria for halting the dose escalation when unacceptable side effects are observed. A DSMB is likely to be requested if the DSMP lacks objective criteria for continuing or halting the trial
- A DSMB may not be feasible for clinical trials that are expected to accrue too quickly to allow for a DSMB to be constituted and complete data and safety monitoring

#### NIH or other Federal Grants

- If you are considering utilizing the NC TraCS DSMB to monitor a clinical trial included in an NIH or federal grant, please submit a copy of your grant to the DSMB for review in advance of submitting the grant to the agency. The DSMB prefers to review research proposals prior to submission to a funding agency in order to determine whether the NC TraCS DSMB is the appropriate body to monitor the study
- The NC TraCS DSMB will provide guidance to the investigator regarding study stopping rules, appropriate study design, and the safety monitoring plan. If the TraCS DSMB agrees to provide oversight for the clinical trial, a letter of support will be written that describes the DSMB and their role in monitoring the study
- A copy of the NC TraCS DSMB Charter to be included with the grant application will be provided upon request.

Please note that all NIH funded clinical trials require a Data and Safety Monitoring PLAN; however, only some clinical trials require a Data and Safety Monitoring BOARD.

- Data and Safety Monitoring Boards (DSMBs) are specifically required for multi-site clinical trials with interventions that entail risk(s) to participants
- DSMBs are generally required for Phase III clinical trials
- A DSMB may be required for Phase I, Phase II or Phase III clinical trials if:
  - The clinical trial is blinded
  - The clinical trial involves high risk intervention(s), or
  - The clinical trial includes vulnerable population(s)

*Source: [National Institutes of Health (NIH) & National Institute of Dental and Craniofacial Research (NIDCR)]*



LIST OF SoPs

1. Writing, Reviewing, Distributing and Amending Standard Operating Procedures for IECs
2. Constituting an Ethics Committee
3. Confidentiality Agreements
4. Conflict of Interest Agreements
5. Training Personnel and EC Members
6. Selection of Independent Consultants
7. Procedures for Allowing a Guest or Observer
8. Categorization of Submitted Protocols for Ethics Review
  - a. Initial Full Committee Review of New Research Protocols
  - b. Expedited Review of Research Protocols
  - c. Exemption from Ethics Review of Research Protocols
9. Agenda Preparation, Meeting Procedures and Minutes
10. Review of New Medical Device Studies
11. Review of Resubmitted Protocols
12. Review of Protocol Amendments
13. Continuing Review of Protocols
14. Review of Final Reports
15. Review of Serious Adverse Events (SAE) Reports
16. Review of Study Completion Reports
17. Management of Premature Termination, Suspension, Discontinuation of the Study
18. Waiver of Written or Verbal/oral Informed Consent
19. Site Monitoring Visits
20. Dealing with Participants' Requests and Complaints
21. Emergency Meetings
22. Communication Records
23. Maintenance of Active Study Files
24. Archive and Retrieval of Documents
25. Maintaining Confidentiality of EC's Documents
26. Reviewing Proposals involving Vulnerable Populations
27. Review and Inspection of the EC
28. Audio Visual Recording of the Informed Consent Process



## ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

### Introduction

Essential Documents are those documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of GCP and with all applicable regulatory requirements. Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor, and monitor. These documents are also the ones that are usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected. The minimum list of essential documents that has been developed follows. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated (1) before the clinical phase of the trial commences, (2) during the clinical conduct of the trial, and (3) after completion or termination of the trial. A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable. Trial master files should be established at the beginning of the trial, both at the investigator/institution's site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files. Any or all of the documents addressed in this guidance may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies).

#### A. Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts.

Sl. No	Title of Document	Purpose	Located in Files of	
			Investigator	Sponsor Institution
1.	Investigator's brochure	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
2.	Signed protocol and amendments, if any, and sample case report form (CRF)	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	X	X
3.	Information given to trial subject:		X	X



	<ul style="list-style-type: none"><li>- Informed consent form (Including all applicable translations)</li><li>-Any other written information</li> <li>-Advertisement for subject recruitment (if used)</li></ul>	<p>To document the informed consent</p> <p>To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent</p> <p>To document that recruitment measures are appropriate and not coercive</p>	X	X
4	Financial aspects of the trial	To document the financial agreement between the investigator/ institution and the sponsor for the trial	X	X
5	Insurance statement (wherever required)	To document that compensation to subject(s) for trial-related injury will be available	X	X
6	<b>Signed agreement between involved parties, e.g.:</b> <ul style="list-style-type: none"><li>- Investigator/institution and sponsor</li><li>- Investigator/institution and CRO</li><li>- Sponsor and CRO</li><li>- Investigator/institution and authority(ies) (Where required)</li></ul>	To document agreements	X	X
			X	X (where required)
			X	X
			X	X
7	<p>Dated, documented approval/favorable opinion of IRB/IEC of the following:</p> <ul style="list-style-type: none"><li>-Protocol and any amendments</li><li>- CRF (if applicable)</li><li>- Informed consent form(s)</li><li>-Any other written information to be provided to the subject(s)</li><li>- Advertisement for subject recruitment (if used)</li><li>- Subject compensation (if any)</li><li>-Any other documents given approval/favorable opinion</li></ul>	<p>To document that the trial has been subject to IRB/IEC review and given approval/favorable opinion.</p> <p>To identify the version number and date of the document(s).</p>	X	X



8	Institutional review board /Institutional Ethics Committee composition	To document that the IRB/IEC is constituted in agreement with GCP	X	X (where required)
9	Regulatory authority(ies) authorization/approval/ notification of protocol (where required)	To document appropriate authorization/approval/ notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	X (where required)	X (where required)
10	Curriculum vitae and/or other relevant documents evidencing qualifications of investigator(s) and subinvestigators	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	X	X
11	Normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/or test(s) included in the protocol	To document normal values and/or ranges of the tests	X	X
12	Medical/laboratory/technical procedures/tests - Certification or - Accreditation or - Established quality control and/or external quality assessment or - Other validation (where required)	To document competence of facility to perform required test(s), and support reliability of results	X (where required)	X
13	Sample of label(s) attached to investigational product container(s)	To document compliance with applicable labeling regulations and appropriateness of instructions provided to the subjects		X
14	Instructions for handling of investigational product(s) and trial- related materials (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing, and disposition of investigational products and trial-related materials	X	X
15	Shipping records for investigational product(s) and trial-related materials	To document shipment dates, batch numbers, and method of shipment of investigational product(s) and trial related materials. Allows tracking of product batch, review of shipping conditions, and accountability.	X	X
16	Certificate(s) of analysis of investigational product(s)	To document identity, purity and strength of investigational		X





	shipped	products to be used in the trial.		
17	Decoding procedures for blinded trials	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment	X	X (Third party if applicable)
18	Master randomization list	To document method for randomization of trial population		X (Third party if applicable)
19	Pretrial monitoring report	To document that the site is suitable for the trial (may be combined with point no.20)		X
20	Trial initiation monitoring report	To document that trial procedures were reviewed with the investigator and investigator's trial staff (may be combined with point no.19)	X	X

### B. During the Clinical conduct of the Trial

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available.

	Title of Document	Purpose	Located in Files of	
			Investigator	Sponsor Institution
1	Investigator's Brochure updates	To document that investigator is informed in a timely manner of relevant information as it becomes available	X	X
2	Any revisions to: - Protocol/amendment(s) and CRF - Informed consent form	To document revisions of these trial- related documents that take effect during trial	X	X
3	Dated, documented approval/favorable opinion of institutional review board (IRB)/ Institutional Ethics Committee (IEC) of the following:  -Protocol amendment(s) - Revision(s) of:	To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favorable opinion. To identify the version number and date of the document(s)	X	X



	<ul style="list-style-type: none"> <li>- Informed consent form</li> <li>- Any other written information to be provided to the subject</li> <li>- Advertisement for subject recruitment (if used)</li> <li>- Any other documents given approval/ favorable opinion</li> <li>- Continuing review of trial</li> </ul>			
4	<p>Regulatory authority(ies) authorizations/ approvals/notifications where required for:</p> <ul style="list-style-type: none"> <li>- Protocol amendment(s) and other documents</li> </ul>	To document compliance with applicable regulatory requirements	X  (where required)	X
6	Updates to normal value(s)/range(s) for medical laboratory/technical procedure(s)/test(s) included in the protocol	To document normal values and ranges that are revised during the trial	X	X
7	<p>Updates of medical/ laboratory/technical procedures/tests</p> <ul style="list-style-type: none"> <li>- Certification or Accreditation or</li> <li>- Established quality control and/or external quality assessment or</li> <li>- Other validation (where required)</li> </ul>	To document that tests remain adequate throughout the trial period	X  (where required)	X
8	Documentation of investigational product(s) and trial-related materials shipment	(See the section-A.15)	X	X
9	Certificate(s) of analysis for new batches of investigational products	(See the section-A.16)		X
10	Monitoring visit reports	To document site visits by, and findings of, the monitor		X
11	<p>Relevant communications other than site visits</p> <ul style="list-style-type: none"> <li>- Letters</li> <li>- Meeting notes</li> <li>- Notes of telephone calls</li> </ul>	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	X	X
12	Signed informed consent forms	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each	X	



		subject in trial. Also to document directaccess permission		
13	Source documents	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	X	
14	Signed, dated, and completed case report forms (CRFs)	To document that the investigator or authorized member of the investigator's staff confirms the observations recorded	X (copy)	X (original)
15	Documentation of CRF corrections	To document all changes/additions or corrections made to CRF after initial data were recorded	X (copy)	X (original)
16	Notification by originating investigator to sponsor of serious adverse events and related reports	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance	X	X
17	Notification by sponsor and/or investigator, where applicable, to regulatory authority(ies) and IRB(s)/IEC(s) of unexpected serious adverse drug reactions and of other safety information	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s)/IEC(s) of unexpected serious adverse drug reactions and of other safety information	X (where required)	X
18	Notification by sponsor to investigators of safety information	Notification by sponsor to investigators of safety information	X	X
19	Interim or annual reports to IRB/IEC and authority(ies)	Interim or annual reports provided to IRB/IEC and to authority(ies)	X	X (where required)
20	Subject screening log	To document identification of subjects who entered pretrial screening	X	X (where required)
21	Subject identification code list	To document that investigator/ institution keeps a confidential list of names of all subjects allocated to trial numbers onrolling in the trial. Allowsinvestigator/ institution to reveal identity of any subject	X	
22	Subject enrollment log	To document chronological enrollment of subjects by	X	



		trial number		
23	Investigational product(s) accountability at the site	To document that investigational products(s) have been used according to the protocol	X	X
24	Signature sheet	To document signatures and initials of all persons authorized to make entries and/or corrections on CRFs	X	X
25	Record of retained body fluids/tissue samples (if any)	To document location and identification of retained samples if assays need to be repeated	X	X

### C. After Completion or Termination of the Trial

After completion or termination of the trial, all of the documents mentioned above in section A & B should be in the file together with the following:

	Title of Document	Purpose	Located in Files of	
			Investigator	Sponsor Institution
1	Investigational product(s) accountability at site	To document that the investigational product(s) have been used according to the protocol. To document the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor	X	X
2	Documentation of investigational product(s) destruction	To document destruction of unused investigational product(s) by sponsor or at site	X (if destroyed at site)	X
3	Completed subject identification code list	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	
4	Audit certificate (if required)	To document that audit was performed (if required)		X
5	Final trial close-out monitoring report	To document that all activities required for		X



		trial close-out are completed, and copies of essential documents are held in the appropriate files		
6	Treatment allocation and decoding documentation	Returned to sponsor to document any decoding that may have occurred		X
7	Final report by investigator/ institution to IRB/IEC where required, and where applicable, to the regulatory authority(ies)	To document completion of the trial	X	
8	Clinical study report	To document results and interpretation of trial	X (if applicable)	X

**Source:** Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance: ICH April 1996



## **GUIDANCE FOR THE INVESTIGATOR**

This section should provide an overall discussion of the nonclinical and clinical data, and should summarize the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials. The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that are based on previous human experience and on the pharmacology of the investigational product.

### **Investigator's Brochure (Example)**

#### **Title page-**

Sponsor's Name:

Project title:

Research number:

Details of the interventions:

Release date:

Date:

#### **Table of contents-**

Confidentiality statement (Optional)

Signature page (Optional)

1. Table of contents
2. Summary





3. Introduction
4. Physical, Chemical and Pharmaceutical properties and formulations
5. Non-clinical studies
  - 5.1. Non-clinical Pharmacology
  - 5.2. Pharmacokinetics and product metabolism in Animals
  - 5.3. Toxicology
6. Effects in Human
  - 6.1. Pharmacokinetics and product metabolism in Animals
  - 6.2. Safety and efficacy
  - 6.3. Marketing Experience
7. Summary of data and Guidance for the investigator
  - References on
    1. Publications
    2. Reports

The references should be found at the end of the chapter

Appendices (if any)

**PROFORMA**

Name Age Sex Religion Marital Status Educational status Socio economic status Occupation	Date of visit Registration no Address
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**Presenting complaints (प्रधानवेदना)**

The main complaints with which the patient approaches the doctor. It should be mentioned with the duration.

**Associated complaints (अनुबन्धवेदना)**

Groups of related symptoms provide diagnostic clues about pathologic processes and involved samprapti ghatak.

**H/o presenting complaints (अद्यतनिकवेदनावृत्तान्तः)**

**Onset:** A chronologic description provides the framework for characterizing the course of an illness. The physician should obtain a chronological report by asking when the problem first started and facilitate a continuing flow of information with questions such as "And then what happened? ... and then? ... and after that?"

**Bodily location:** for pain /skin lesions/ Swelling etc. The bodily location of pain or other discomfort should be defined as accurately as possible. Patient may have more than one pain and that multiple pains may indicate multiple disease processes. Ask the patient to characterize and differentiate each.

**Character:** In patients own words for pain/ itching/cough/skin lesions/ discharges etc. Most patients use analogies to describe the quality of a sensation.

**Spread/ radiation:** The patient may be encouraged to indicate the location and spread of symptom using hand gestures, which also indicate how large an area is involved

**Severity:** The severity can be measured by the quantity or intensity of the symptom. The intensity of pain can be estimated on a scale of 1 to 10 or compared to another pain the patient has experienced. Other examples of quantity include volume (for example, the quantity of sputum expectorated in a day), number (for example, the number of times the patient has lost consciousness), and the degree of impairment the patient suffers. Impairment or disability is best characterized in terms of the patient's usual daily activities, such as breathlessness with climbing stairs at home or chest pain while sweeping the floor. The patient's exact words are important." Try to use the patient's own vocabulary if possible.

Also can assess whether the daily routine/ Sleep/ job/ family life/ Social life (for mental disorders) etc are affected.

Eg: Khalli is a similar disease as viswachi and gridhrasi but with a greater severity.



**Timing:** Any pattern of appearance/ frequency/ Course/Pattern whether related to ritu kala in female etc

### Relieving/Aggravating factors

(उपशयः/ अनुपशयः) – आहार (Food article)  
विहार (Activities/regimen)  
औषध (medicines)  
देशः(Place)  
कालः( Season/ time of the day)

Mention the specific food articles, Activities/regimen, medicines, Place, Season/ time of the day with which/ in which the complaints are relieved or aggravated.

### H/O past illness (पूर्वव्याधिवृत्तान्तः)

A review of past medical problems and treatments not directly pertinent to the history of presenting complaints completes the past medical history. Any illness that made to visit doctor/ for a hospital stay/ to take time off the work .

Major elements of the past medical history are viz.childhood and adult illnesses, trauma, and drug sensitivities, findings in routine medical checkup etc.

*(e.g prior diagnosis of Kasa in a patient of Rajayakshma belongs with the history of presenting complaints, whereas a remote diagnosis of Mutrakrichra done in the past does not)*

### Family history (कुलजवृत्तान्तः)

Medical problems in family members should be reviewed with special attention to heritable disorders.

### Treatment history (चिकित्सावृत्तान्तः)

- ✓ Treatment
- ✓ Surgical
- ✓ Specify any adverse effects of any therapy undergone or medicine taken

This helps to assess the nidana such as Mithya upacahara/ mithya samsarjana etc in diseases and to analyse the treatment given and responses found in patient. An analysis of the previous treatment responses of the patients gives important clues regarding the personal features of the patient such as prakriti etc and state of the disease.

### Personal History (वैयक्तिकवृत्तान्तः)

It includes the daily activities of an individual which should be recorded in detail to rule out the various faulty life styles as the nidana of the disease and to know how far the individual is deviated from healthy life style. In ayurveda , faulty life style and dietetics (mithya ahar vihar)



are important etiological factors for most of the diseases and the individual can be interrogated for their daily activities in a sequence they are to be observed/ practised daily.

**Getting up in the morning:** (प्रातरुत्थानम्)

- ✓ Time
- ✓ Getting up : to the alarm/ on your own after enough sleep
- ✓ Feeling after getting up: energetic/ Tired/heaviness of the body/ body ache/

The time of getting up indicate the specific dosha activity predominant in that individual. For example getting up late in the morning around 8pm ie Sleshma kala would not facilitate the routine malapravritti which is a function of vata that can easily happen in vata kala before 6 am.

*Sukhena pratibodhanam* ie easy waking up is a characteristics of a healthy individual. If it does not happen , it may indicate the disease condition in the patient.

Individual if does not feel energetic, it indicate poor quality or quantity of sleep (*Nidra nasha*) or atinidra due to kapha vridhi.

**Bath:** (स्नानम्)

- ✓ How many times: -----times/ day -----times/ wk
- ✓ With hot water/ warmwater/ normal water/ cold water/ change water as per season
- ✓ Body bath alone/ head bath

If the individual does not take bath regularly, it affects the normal functioning of agni, the reproductive functioning, it can result in vitiation of rakta, sveda . It cause itching and skin diseases. Hot water is advised for body bath and if done with cold water it can result in vata/ kapha vridhi especially in vata/kapha prakriti individuals and patients with vata vyadhi.

*Head bath:* - -----times in a week

With hot water/ warmwater/ normal water/ cold water/change water seasonally

What do you use for washing head: shampoo/ Soap/ Herbal powder

If head bath is done with hot water, it can affect the health of eyes and hair and also can cause vitiation of pitta and rakta. If done with excessive cold water, vata and kapha vitiation can happen and according to season/ disease condition, warm water can be used on head. Avoiding head bath, can result in diseases like palitya darunaka, arushika, indriya daurbalya

*Time:*

- ✓ early morning/ noon/ evening
- ✓ Before evacuating bowel/ after evacuating bowel
- ✓ Soon after exercise/ food/ heat exposure

Taking bath in the early morning after evacuation of bowels can cause agni dipti. Bathing, before evacuating the bowel can further aggravate the condition of Ajirna and bathing after exercise or heat exposure can result in netra roga, sweda vaha sroto vikara, kushta etc.



### *Style of bath:*

- ✓ First water on body/ first water on head
- ✓ Taken afterअभ्यङ्गः/ taken withoutअभ्यङ्गः
- ✓ Uses: Soap/ moong dal powder/ Besan
- ✓ How body dried: Head first/ back first/ body first

### **Anoininting (अनुलेपनम्)**

Moisturizer/ Fairness cream/Coconut oil/Glycerin/Olive Oil

The results of various studies conducted to analyse the effects of long term use of moisturizers on skin suggest that long-term treatment with moisturizers on normal skin considerably reduces the skin hydration and may increase skin susceptibility to irritants.( Effect of long-term use of moisturizer on skin hydration, barrier function and susceptibility to irritants. Held E, Sveinsdóttir S, Agner T.Acta Derm Venereol. 1999 Jan; 79(1):49-51.)

The results can be analysed in ayurveda as follows. The skin reflects the status of rasa dhatu and rakta dhatu in the body and the healthy skin should be mridu, snigdha, rakta varna(Unctuous skin / Smooth clear skin).Any agent that reduces the snigdhatu can impart rukshataand kharata to skin causing vata vridhi which may affect the normal complexion, texture etc making it susceptible to kushta or skin diseases.

Most of the fairness creams contains topical steroids as The long-term risk associated include monomorphic acne, steroid atrophy, steroid rosacea, telangiectasia, perioral dermatitis, striae and other manifestations which have been collectively described as topical steroid damaged facies (TSDF).

This condition can be understood as the dushi visha janya vikara. These topical applications initially affect the rasa dhatu producing the various skin changes(Kohta, Mandala etc) and subsequently affect the deeper dhatus producing the other systematic manifestations.

### **Brushing :(दन्तधावनम्)**

- ✓ Daily once/ twice/ after every meal
- ✓ Using: Datun

Tooth paste: Sweet/ Salty/ Medicated

Tooth powder/Danta manjan Curn: Salty/ Pungent/ Sweet/ medicated

It is told that Sleshma ulbana dosha cause various mukha rogas, hence it is advised to use three Rasa ie katu, tikta, kashaya which are kapha hara for danta dhavana (eventhough Susruta mention madhura rasa)(रसत्रयेणहिअनेनमुखवैरस्यारोचकश्रेष्ठाद्यपनयाःसम्यक्सम्पद्यन्ते)). The adjuvants mentioned are also kapka mitigating. like,kushta,tejovati churna, (trivarga tritaya ie triphala, trikatu, triphala) are also having these rasa, honey and saindhava also used as these does the actions like kaha chedana and kapha vilayana helping in mukha/ danta shodhana action (Ca.ka.1/15). Avoiding danta dhavana / oral hygiene is specifically mentioned as a nidana of mukha roga (A.Hr.U.21/1, 2.)Daily two instances are mentioned where brushing is indicated ie every time after food and after waking up in the morning. If its not followed it can result in various tooth and oral diseases.



### **Tongue Scraping: (जिह्वानिर्लेखनम्)**

Yes/ no

With tongue cleaner/ brush

Eventhough modern medicine, does not stress upon the need of tongue 'scraping', in Ayurveda it has got greater significance as Jihva is the kapha sthana, so it should be scraped to remove the upalepa and to keep the normal character of jihva as tanu slender (Ca.Sa.8/51). In long term, it may affect the speech quality and the taste perception .

The biomedical studies also show that tongue scraping gives better result than tongue brushing in removing the bacterial load and dental plque.(Winnier JJ, Rupesh S, Nayak UA, Reddy V, Prasad Rao A. The Comparative Evaluation of the Effects of Tongue Cleaning on Existing Plaque Levels in Children. *International Journal of Clinical Pediatric Dentistry*. 2013; 6(3):188-192. Doi: 10.5005/jp-journals-10005-1216.)

*Any habit of applying medicated अञ्जन?*

*Any habit of applying oil on nostrils (नस्य in दिनचर्या): ----times/week: ----times/ month*

*Any habit of गण्डूषः: ----times in a week/ ----times in a month*

*Any habit of ताम्बूलः: ----times in a week/ ----times in a month*

*Ingredients used: Paan/ Supari/*

*Any habit of taking धूमः*

### **Oil Application:अभ्यङ्गः**

Applying oil: Head daily/----times in a week/ ----times in a month

Ear daily/----times in a week/ ----times in a month

Soles daily/----times in a week/ ----times in a month

Limbs daily/----times in a week/ ----times in a month

Whole body daily/----times in a week/ ----times in a month

Oil used: Gingely oil/ Mustard oil/ Coconut oil/ Olive oil/ medicated/Any other oil

अभ्यङ्गः After food/ without bowel evacuation/ after bath

Any adverse reaction after using any specific oil forअभ्यङ्गः?

### **व्यायामः(Physical exercise)**

- ✓ Regularly/ Occasionally
- ✓ Nature: Walking/ Playing badminton/ Cricket/ Jogging/ Aerobics/ Gymnasium
- ✓ After अभ्यङ्ग/ without अभ्यङ्ग
- ✓ Duration:
- ✓ Strenuous/ moderate/ Mild

### **Diet and Food habits (आहार)**

1. How many times you eat in a day (Major Meal)?

Thrice Daily/ Less than three times /Frequently/ varying, not constant





2. What kind of food you usually take?  
Heavy food / Light food/ Mixed, not specific
3. How do you rate your food quantity?  
Normal as compared to your peers /less always /Excess always/ Sometimes excess sometimes less-
4. Do you get hunger for the successive food time?  
Yes /No /Gets hunger before food time /Sometimes yes sometimes no
5. How do you enjoy the taste of food?  
Generally enjoy the taste during food time  
Appreciate the taste any time generally  
Usually not / sometimes yes sometimes no-
6. If at all indigestion happens, what kind of symptoms you get?  
Relieves with mild disturbances  
Heaviness, Salivation, Swelling of eyelids, Taste of food in eructation  
Giddiness, Thirst,Sourbelching,Burning sensation  
Abdominal colic,Distension of abdomen, Constipation
7. How is your indigestion usually relieved?  
With skipping 1-2 meals/ within 2-3 days with medicine/ By skipping 1 meal  
Varies every time
8. What is the nature of eructation you get?  
Clear  
With the taste of food taken/Burning sensation/Sour  
Pungent,rarely occurs.  
No Specific taste,But frequently occur with abdominal colic
9. How do you feel when you skip the meal?  
Can't skip the meal, if skips with mild disturbances  
Usually Skips the meal  
Can't skip the meal, troubles with headache,nausea,low energy, difficulty to concentrateetc  
Sometimes can skip the meal and sometimes cannot
10. What is the pattern of your digestion?  
Usually digest the food taken  
Takes longer time to digest even the wholesome food  
Digest even the incompatible food immediately



Sometimes digest the food and sometimes not

11. Which taste you usually prefer in your diet?

Not specific, likes to include all taste/Hot,Spicy,Sour/Sweet/It varies

**Routinely consumed food**

	Time	Ingredient	Quantity
Liquid			
Morn breakfast			
Lunch			
Eve snacks			
Dinner			
Any Other			

- ✓ Type of diet: Veg/ Non veg
- ✓ Vegetarian:
  - Grain: Rice/ Wheat/ Ragi/Jowar/Barley/Any other
  - Pulses: Green gram/ black gram/ Horse gram/Bengal gram/Any other
- ✓ Non Vegetarian
  - Regular/ Irregular
  - Once in a wk/ fortnight/ month/rare
  - Type: egg/ Chicken/ Mutton/ beef/ Pork/Any other

Habit of taking stale food?

Any sudden change in your routine food habits/ articles?

**Drinking Water**

- ✓ Source : Tap Water ( Filtered/ Non Filtered) / Ground water
- ✓ Type : Cold/ Chilled / Boiled and Cooled/ Medicated
- ✓ Quantity: How many glasses per day/ night?
- ✓ Habit of drinking large amount of water soon after waking up?
- ✓ Habit of drinking water and vomiting out on empty stomach each day?
- ✓ Dominant rasa:to be assessed by physician
- ✓ Dominant गुण:to be assessed by physician
- ✓ Dietary habits: समशन/ अध्यशन/ विषमाशन/ प्रमिताशन/ अनशन
- ✓ विरुद्ध involved: to be assessed by analyzing the food habits

देशविरुद्ध (place)

अवस्थानविरुद्ध (State of health)

कालविरुद्ध

क्रमविरुद्ध (sequence)

अग्निविरुद्ध

परिहारविरुद्ध



मात्राविरुद्ध (quantity)

सात्म्यविरुद्ध (wholesome)

दोषविरुद्ध

संस्कारविरुद्ध (mode of preparation)

वीर्यविरुद्ध (potency)

कोष्ठविरुद्ध

वीर्यविरुद्ध— fish + milk

संस्कारविरुद्ध— heated honey. Deep frying vegetables, Reheating oil and food

मात्राविरुद्ध— honey + cow's ghee mixed in equal proportion.

क्रमविरुद्ध— hot water after taking honey.

कालविरुद्ध— pungent substance in summer and cold substances in winter.

क्रमविरुद्ध— consuming curd at night. Taking मधुररस food or द्रव्य at the end of meals and तिक्त and कटुरसद्रव्य (food substances) at the starting of meals.

संयोगविरुद्ध— fruit salad or milk + banana.

परिहारविरुद्ध— consuming cold water immediately after having hot tea or coffee.

Banana+ milk

Fruit Salad

Milk Shake

Milk +Rice+ Salt

Curd at night

Plain Curd

Heated/ boiled curd

Refrigerated water after hot meal

Excessive water after taking meal

Cold/ Refrigerated water after snigdha ahara

Non veg food with honey/ milk/ black gram/

Sweet and sour fruits in a fruit chat

उपचारविरुद्ध (treatment)

पाकविरुद्ध (cooking)

संयोगविरुद्ध (combination)

हृदयविरुद्ध

संपद्विरुद्ध (richness of quality)

विधिविरुद्ध (rules for eating)

Curd+ Milk+Rice

Butter milk+ Milk+Rice

Moong Khichdi+Milk

Milk+ Fish



### पुरीषप्रवृत्ति (Bowel evacuation :)

- ✓ Feeling of urge:
  - Soon after waking up
  - After sometime without supplementation
  - After taking food/ liquid/ Solid
  - After medication
  - Varying/Other
  - Urge to evacuate immediately after or during a meal
- ✓ Frequency:- Daily-----times; -----times/week
  - After every meal
- ✓ Time required: -----minutes (time taken)
- ✓ Consistency: Pellets like very hard/ hard/ Banana like/ Semi solid/ watery/ Varying
- ✓ Symptoms associated with evacuation: pain/ वातप्रवृत्ति/ burning sensation/Itching
- ✓ Mixed with mucous: yes/ no/sometimes (mention the frequency)
- ✓ Mixed with blood yes/ no/ sometimes (mention the frequency)
- ✓ Presence of undigested material: yes/ no/ sometimes (mention the frequency)
- ✓ H/O worms/ presence of worms: yes/ no
- ✓ Frequency of worm infestation: -----times/ 6months
- ✓ Evacuation: Complete/ Incomplete/Unsatisfactory/ varying
- ✓ Color of stool:
- ✓ Odour of stool:
- ✓ Quantity of stool:
- ✓ Habit of suppressing the urge/ initiating the urge

It is very difficult to assess the nature of *agni* with from the nature of bowel habits. The following references were helpful to draw important conclusions. *Sabhaktā sānna anna pī itā purī a*, (faeces mixed with food articles) were found in *purī āv ta vāta kopa*<sup>1</sup>, *āmajatisāra*<sup>2</sup>, *graha i*<sup>3</sup> etc.

Faeces mixed with mucous is found in *kaphāv ta apāna vāta kopa*<sup>4</sup>, *kaphaja atīsāra*<sup>5</sup>, *kaphaja graha i*<sup>6</sup>, *kaphaja arśa*<sup>7</sup> etc. Unformed faeces (*asamhata*, *śithila*) are formed in *snehana samyak yoga*<sup>8</sup> and *kaphaja arśas*<sup>9</sup>. Hard faeces is found in *vāta v ddi*<sup>10</sup>, *vātaja atīsāra*, *udāvarta*, *vātikajvara*, *vātika arśas* etc. Dry faeces (śuška) are found in *viṭāvṛta vāta kopa*, *vātaja atīsāra*, *vātika grahaṇi*, *vātika gulma*, *udāvarta* etc. Faeces in excessive quantity are found in *pitta prakṛti*, *kardama visarpa*, *kaphaja arśa* etc.

<sup>1</sup>Ca.Ci.28/71

<sup>2</sup>Su.U.40/16

<sup>3</sup>A.H.Ni.8/27

<sup>4</sup>Ca.Ci.28/33

<sup>5</sup>Ca.Ci.19/7

<sup>6</sup>Ca.Ci.15/17

<sup>7</sup>Mā.Ni.5/23

<sup>8</sup>Ca.Sū.13/58

<sup>9</sup>Ca.Ci.14/173

<sup>10</sup>Su.Sū.15/31



Scanty faeces (*alpa*) is found in *vātaja graha*□*i*, *vātaja udāvarta*, *pā*□□*u*, *vātaja arśas* etc.

### मूत्रप्रवृत्ति: (Micturition)

- ✓ Frequency: -----times/day; -----times/ night
- ✓ Colour: White/ yellowish/ Yellow/ turbid/ Reddish
- ✓ Associated symptoms: Painful/ burning sensation/ Itching/ Scanty/Incomplete voiding/ Urgency/incomplete voiding/ Crystals in urine/ Semen with urine

### स्वेदप्रवृत्ति: (sweating)

- ✓ Sweating More sweat throught the year/ Summer season/ After physical exercise  
Compared to others: Excess/ Similar/Less
- ✓ Odour: Excess/ Moderate/ Irregular/Nil
- ✓ Stain on clothes: Y/N
- ✓ Stains clear after washing Yes/No
- ✓ Sweat especially on soles of palmand feet yes/No

### निद्रा: Sleep

- ✓ -----Hrs/ night Sound sleep/ Disturbed/ Reduced
- ✓ How many times do you wake up in the middle of the night
- ✓ How much time does it take to go back to sleep
- ✓ How time does it take to fall asleep after you get into bed at bedtime
- ✓ If disturbed:- (In initiation/ In middle/ end part of sleep)
- ✓ Day time job/ night Shifts
- ✓ -----Hrs/ day After lunch
  - Before food
- ✓ Dream habits: Excess/ Moderate/ Less
- ✓ Other complaints: Biting teeth/ Bed wetting/ sleep talking/ sleep walking

### (व्यसनम्)Addiction

S.No	Addiction	No.of times/day:/ Quantity	Since: ---- Months/ Years
1.	Smoking		
2.	Alcohol		
3.	Pan/Gutka		
4.	Tea/Coffee		
5.	Mobile Phone/ Computer/ Social Media	Hours spent in a day:	
6.	Others		



### आर्तववृत्तान्तः (Menstrual history)

- ✓ Menarche Age
- ✓ Regular/Irregular
- ✓ Interval:
- ✓ Flow ----Pads/day; Duration -----days
- ✓ Amount: Average/ Scanty/ heavy
- ✓ Colour:
- ✓ Consistency: thin/thick
- ✓ Clots: Excessive/moderate/Nil
- ✓ Stains on washing: Yes/No
- ✓ Foul smell:
- ✓ Other complaints: During/ Pre/Post
- ✓ H/O any related medication/Contraceptives
- ✓ Date of last menstrual period:
- ✓ Menopausal Age:

### वैवाहिकवृत्तान्तः (Sex and Marital history)

- ✓ Age of marriage
- ✓ Relationship with the spouse
- ✓ Family planning Children boys/Girls
- ✓ Any H/O disease to the spouse:

### Obstetrical history(प्रसववृत्तान्तः)

- ✓ Gravida
- ✓ Para
- ✓ Abortion
- ✓ Live birth/ Dead :- Female--- Male-----
- ✓ Mode of delivery: FTND/Preterm ND
- ✓ Forceps/ ventous
- ✓ C.S
- ✓ Abortion: Spontaneous/ Induced
- ✓ Last Delivery
- ✓ Last Abortion
- ✓ Have you followed?
- ✓ Garbhini paricarya, Yes/ No, If yes give details
- ✓ Sutika paricarya Yes/ No, If yes give details
- ✓ Paricharya after abortion: Yes/ No, If yes give details

### Occupational history(व्यापत्तिवृत्तान्तः)

- ✓ Type of job: Sedentary/ exhausting/Intellectual/Mental stress/ Ac/Hot/ Night Shifts/Computer work/Typing/ Teaching/ Police professional
- ✓ Work place:
- ✓ Posture while working:





- ✓ Working Hours:
- ✓ Travel: ----km/day Conveyance:-
- ✓ Attitude towards the job
- ✓ Relationship at work place
- ✓ Punishments if any
- ✓ Are you satisfied with your job? If not, what are the reasons?

### अङ्गप्रत्यङ्गपरीक्षा(In the order of दर्शन/ स्पर्शन/ प्रश्न)

1. अङ्गम्
2. ऊर्ध्वजत्रु
3. अन्तराधि
4. बाहु
5. सक्थि

#### I. अङ्गपरीक्षा

दर्शनम्	स्पर्श	संवेदनम्
काश्यम्	कठिन	अङ्गमर्द
कौब्जम्	खर	भङ्ग
नमनम्	क्लेद	ग्रह
संकोचम्	रौक्ष्य	गौरव
शोफम्	शीत	कण्डू
शोषम्	स्निग्ध	लाघव
आक्षेपम्	उष्णम्	स्तम्भ
कम्पम्		संसन

### स्रोतोपरीक्षा

#### दोषपरीक्षा

1. Check for वात/ पित्त/ कफ /रक्त vitiating आहार/विहार
2. क्षय&वृद्धि-लक्षण
3. प्रकोप-लक्षण (A.San.Su.19)
4. गत-लक्षण (A.San.Su.19)
5. साम-निराम-लक्षण (Ma.Ni.1, Madhukosha)
6. Involvement of आवरण ( Ca.Ci.28)



## दूष्य-परीक्षा (धातु and उपधातु)

1. क्षय
2. वृद्धि
3. प्रदोषज-लक्षण

## मलपरीक्षा

## इन्द्रियपरीक्षा

## नाडीपरीक्षा

## आतुर-बल-परीक्षा

1. प्रकृति
2. सार
3. संहनन
4. प्रमाण
5. सात्म्य
6. सत्व
7. आहार-शक्ति
8. व्यायाम-शक्ति

## व्याधि-परीक्षा

- ✓ सहज/जन्मोत्तर-कालज

If सहज,

1. मातृज
  2. पितृज
- ✓ निज /आगन्तु

If निज,

1. आमाशय
  2. पक्वाशय
- ✓ शारीर/ मानस/शारीर-मानस
  - ✓ उपसर्गज/ संसर्गज/ आकस्मिक

If आगन्तु

- 1, शस्त्रकृत
- 2, जन्तुकृत



- ✓ दोषज/ कर्मज/ both
- ✓ कालज/ अकालज
- ✓ जनपदोध्वंसजन्य
- ✓ अपतर्पणज/सन्तर्पणज

**निदानपञ्चकपरीक्षा (Enlist and analyze from history and examination)**

1. निदान
2. पूर्वरूप
3. रूप
4. उपशय

**संप्राप्ति with संप्राप्ति-घटक (Give conclusive inputs)**

1. दोष
2. दूष्य
3. स्रोतस्
4. स्रोतोदुष्टि-प्रकार
5. अग्नि
6. कोष्ठ
7. Involvement of आम
8. उद्भव-स्थान
9. सञ्चार-स्थान
10. व्यक्त-स्थान
11. रोगमार्ग
12. क्रियाकाल
13. व्याधिअवस्था
14. रोगप्रकृति
15. उपद्रव

**सापेक्ष-निदान/ संभावितरोग (Probable Diagnosis)**

**व्यवच्छेदक-निदान (Differential diagnosis)**

**व्याधिविनिश्चयः(Final Diagnosis)**

साध्यासाध्यता



## **EXPERTS INVOLVED IN DEVELOPMENT OF GUIDELINES AND CONSULTATIVE PROCESS**

### **Working group**

1. **Vd. (Prof.) K. S. Dhiman**  
Director General | Central Council for Research in Ayurvedic Sciences | New Delhi
2. **Dr. N.Srikanth**  
Deputy Director General | Central Council for Research in Ayurvedic Sciences | New Delhi
3. **Dr. Bharti**  
Assistant Director (Ayu.) | Central Council for Research in Ayurvedic Sciences | New Delhi
4. **Dr.B.C.S.Rao**  
Assistant Director (Ayu.) | Central Council for Research in Ayurvedic Sciences | New Delhi
5. **Dr. Sarada Ota**  
Research Officer (Ayu.) | Central Council for Research in Ayurvedic Sciences | New Delhi
6. **Dr. Sunita**  
Research Officer (Ayu.) | Central Council for Research in Ayurvedic Sciences | New Delhi
7. **Dr. Shruti Khanduri**  
Research Officer (Ayu.) | Central Council for Research in Ayurvedic Sciences | New Delhi
8. **Dr. Babita Yadav**  
Research Officer (Ayu.) | Central Council for Research in Ayurvedic Sciences | New Delhi
9. **Dr. Renu Singh**  
Research Officer (Ayu.) | Central Council for Research in Ayurvedic Sciences | New Delhi
10. **Dr. Kishore Kumar**  
Research Officer (Ayu.) | Regional Ayurveda Research Institute for Metabolic Disorders | Bengaluru
11. **Dr. Sakshi Sharma**  
Research Officer (Ayu.) | Central Ayurveda Research Institute for Cardiovascular Diseases | New Delhi

### **Members of National Consultation**

1. **Dr. H.M.Chandola**  
Former Director, CBPACS, New Delhi; Former Dean & Prof. Dept. of Kayachikitsa | IPGT & RAGAU | Jamnagar
2. **Dr. Hemlatha R**  
HOD | Clinical Research Protocol/Sr. DDG | National Institute of Nutrition (ICMR) | Hyderabad
3. **Dr. S. Syed Hissar**  
Scientist-C (Medical) | National Institute for Research in Tuberculosis (ICMR) | Chennai

### **Technical Assistance**

1. **Dr. Aarti Sheetal**  
Senior Research Fellow (Ayu.) | Central Council for Research in Ayurvedic Sciences | New Delhi









## **CENTRAL COUNCIL FOR RESEARCH IN AYURVEDIC SCIENCES**

**Ministry of AYUSH (Government of India)**

Jawahar Lai Nehru Bhartiya Chikitsa Evam Homeopathy Anusandhan Bhawan,  
No. 61-65, Institutional Area, Opp. "D" Block, Janakpuri, New Delhi-110058

Tele.: 91-11-28524457, Fax: 91-11-28520748

Email : [dg-ccras@nic.in](mailto:dg-ccras@nic.in), Website : [www.ccras.nic.in](http://www.ccras.nic.in)