Regional workshop on clinical research methodologies in traditional medicine for the WHO South-East Asia Region

Report of the regional workshop

Jamnagar, Gujarat, India
9–11 September 2019
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## Contents

<table>
<thead>
<tr>
<th>Acknowledgements</th>
<th>Page iv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preface</td>
<td>Page v</td>
</tr>
<tr>
<td>Acronyms and abbreviations</td>
<td>Page vi</td>
</tr>
<tr>
<td>1. Background</td>
<td>Page 1</td>
</tr>
<tr>
<td>2. Opening session</td>
<td>Page 1</td>
</tr>
<tr>
<td>3. Objectives</td>
<td>Page 2</td>
</tr>
<tr>
<td>4. Summary of workshop proceedings</td>
<td>Page 2</td>
</tr>
<tr>
<td>4.1 Introduction of participants and nomination of Officebearers</td>
<td>Page 2</td>
</tr>
<tr>
<td>4.2 Session 1: WHO Guidelines &amp; SEA Region Member States’ challenges and experience with TM research</td>
<td>Page 3</td>
</tr>
<tr>
<td>4.2 Session 2: Research methodology in traditional medicine – guidance and examples</td>
<td>Page 9</td>
</tr>
<tr>
<td>4.3 Session 3: Research methodology design and gaps</td>
<td>Page 12</td>
</tr>
<tr>
<td>4.4 Session 4: Research methods for clinical trials</td>
<td>Page 15</td>
</tr>
<tr>
<td>4.5 Session 5: Research methods for clinical trials for TM procedure-based therapies</td>
<td>Page 16</td>
</tr>
<tr>
<td>4.6 Session 6: Research methods – observational studies in TM and designing research proposals</td>
<td>Page 19</td>
</tr>
<tr>
<td>4.7 Session 7: Research methods – biostatistics and information technology in TM research</td>
<td>Page 20</td>
</tr>
<tr>
<td>4.8 Session 8: Proposed SEARO guidelines for methodologies on research and evaluation of traditional medicine</td>
<td>Page 21</td>
</tr>
<tr>
<td>4.9 Session 9: Summary of the workshop themes and recommendations</td>
<td>Page 23</td>
</tr>
<tr>
<td>5. Conclusions</td>
<td>Page 28</td>
</tr>
</tbody>
</table>

## Annexes

| 1. Opening address by Dr Poonam Khetrapal Singh, WHO Regional Director for South-East Asia | Page 29 |
| 2. Agenda                                           | Page 31 |
| 3. List of participants                            | Page 32 |
Acknowledgements

This report was drafted by Dr Suzanne Grant, Senior Research Fellow, Western Sydney University, Sydney, Australia, together with Dr Mandip Goyal, Associate Professor, Department of Kayachikitsa, and Dr Swati Khandale, Assistant Professor, Department of Kriya Sharir, IPGT&RA, Jamnagar, Gujarat, India, under the guidance of a team led by Mr Manoj Jhalani, Director, Department of Health Systems Development, and Dr Kim Sungchol, Regional Adviser for Traditional Medicine at the WHO Regional Office. Our special thanks to all the experts for their valuable contribution.
Preface

This report provides the proceedings from the traditional medicine (TM) research workshop for the WHO South-East Asia (SEA) Region conducted in Jamnagar, India, in September 2019. The meeting of these Member States provided an important opportunity to reflect upon, demonstrate and develop their research capacity and skills while evaluating the previous WHO guidelines and highlighting their main achievement and shortfalls for improvement.

This report provides a brief introduction to the current TM research capacity and activity of each of the Member States, along with valuable details of research-related issues discussed at the meeting. Opportunities for future collaboration between the Member States of the SEA Region were considered at the meeting and are also reported in these proceedings. High-quality research, specifically on TM, is critical to ensuring that the TM provided in countries of the South-East Asia Region, and globally, is safe and effective, and that opportunities for TM to improve global health and well-being are pursued.

I take this opportunity to extend my sincere thanks to all the participants, including international experts, who contributed to the productive meeting. I hope this meeting report will add value to all efforts in TM research and will be able to lead to further discussions to contribute more significantly towards the development of traditional medicine.

Dr Kim Sungchol, Regional Adviser for Traditional Medicine, Regional Office for WHO South-East Asia, New Delhi, India
### Acronyms and abbreviations

<table>
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<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
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<tr>
<td>AYUSH</td>
<td>Ayurveda, Yoga, Unani, Siddha, Homoeopathy</td>
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<td>ASU</td>
<td>Ayurveda, Siddha, Unani</td>
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<td>CCRAS</td>
<td>Central Council for Research in Ayurvedic Sciences</td>
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<td>DHARA</td>
<td>Digital Helpline for Ayurveda Research Articles</td>
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<td>GAP</td>
<td>good agricultural practice</td>
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<tr>
<td>GCP</td>
<td>good clinical practice</td>
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<tr>
<td>HMPC</td>
<td>Committee on Herbal Medicinal Products</td>
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<tr>
<td>ICD-11</td>
<td>International Classification of Diseases, 11th Revision</td>
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<tr>
<td>ICT</td>
<td>information and communication technologies</td>
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<td>IPGT&amp;RA</td>
<td>Institute for Post Graduate Teaching and Research in Ayurveda (India)</td>
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<tr>
<td>ODA</td>
<td>official development assistance</td>
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<tr>
<td>OTC</td>
<td>over-the-counter</td>
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<tr>
<td>PV</td>
<td>pharmacovigilance</td>
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<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
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<td>SEARO</td>
<td>South-East Asia Regional Office (of WHO)</td>
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<tr>
<td>TCM</td>
<td>traditional Chinese medicine</td>
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<tr>
<td>T&amp;CM</td>
<td>traditional and complementary medicine</td>
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<td>TM</td>
<td>traditional medicine</td>
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<td>WHO</td>
<td>World Health Organization</td>
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1. **Background**

Traditional medicine in South Asian countries has a rich heritage of usage. For millions of people in South Asia, traditional medicine represents the only available therapy for addressing health concerns. Around 80% of the world’s population rely on traditional medicine for some part of their health care. Traditional medicine is commonly individualized, varies from country to country, and is used to treat or prevent disease and chronic illness and improve quality of life. Traditional medicines often have a long history of use and safety and effectiveness studies have not been part of this landscape.

Many governments have recognized the role of traditional medicine and developed national policies and strategies to protect public health and maximize the potential contribution of traditional and complementary medicine (T&CM) products, practices and providers to primary health care. Member States in the South-East Asia Region have demonstrated a continued, strong commitment to policy, law, regulation and national infrastructure for T&CM. Ten Member States of the Region have established a national policy, programme, office and expert committee for T&CM. The use of T&CM among populations is also strongly acknowledged in the Region.

Traditional medicine provides many potential therapeutic healing options for chronic diseases and conditions that are difficult to treat using Western medicine. However, the global acceptance of traditional medicine is hampered by the lack of research data and Member States expressed a high level of interest in receiving guidance for research and evaluation of T&CM related to safety, quality and efficacy.

This regional workshop was designed to provide practical guidance on research methodology and discuss research issues and gaps. Under the technical guidance of WHO, the workshop brought together senior officials and experts in research and traditional medicine from the Member States, WHO, research and teaching institutions and government bodies.

The workshop was held over three days and was conducted in English. The sessions were divided into three parts:

1. An opening session of speakers from Australia, Hungary, the People’s Republic of China and India, followed by presentations from Member States on key issues, challenges, gaps in clinical research in their respective country.
2. Keynote speeches on research methodology for observational studies, clinical/interventional studies and for traditional procedures from experts of traditional medicines.
3. A session for group discussion that included four different topics for 4 groups on collaborative research on TM.

2. **Opening session**

On behalf of Dr Poonam Khetrapal Singh, Regional Director of the WHO South-East Asia Region, Dr Manisha Shridhar, Acting Director for Health Systems Development, delivered her message.

In her welcome address, the Regional Director observed that the South-East Asia Region has rich experience with traditional medicine usage by the Region’s population being between 70% and 95%. During the past two decades, the use of traditional medicine has expanded globally and gained significant popularity. She noted that the dramatic
increase in people with noncommunicable diseases (NCD) such as heart disease, cancer, diabetes, mental disorders and other chronic diseases was one of the drivers. For these diseases, and for many other conditions, traditional medicine has much to offer. Research needs to address important concerns around safety, efficacy and quality. The different therapeutic approaches and research methodologies between Western and traditional medicines present a considerable challenge.

To overcome these challenges, the Regional Director noted, WHO has conducted several meetings and congresses and developed a series of guidelines, including the General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine, developed in 2000.

Dr Poonam Singh expressed satisfaction that the WHO Traditional and Complementary Medicine Strategy 2014–2023 will support Member States in promoting safe and effective use of traditional medicine through regulation and research.

She hoped that this workshop will allow Member States to strengthen clinical research capacity in traditional medicine and also provide health authorities and researchers with clearer objectives and directions for future research.

The full text of the Regional Director’s message is available in Annex 1.

3. Objectives

The objectives of the meeting were introduced by Dr Kim Sungchol, Regional Adviser for Traditional Medicine at the WHO Regional Office.

**General objective**

The general and overall objective was to promote the development and strengthening of the research capacity in traditional medicine in the Member countries of the South-East Asia Region. An additional objective was to discuss the WHO Guidelines for clinical research in traditional medicines (2000) and to deliberate on the need to revise these guidelines to reflect new developments in the field of clinical research and trans disciplinary culture.

Specific objectives were to:

- improve clinical research capacity in T&CM;
- discuss recent advances in T&CM research, including different clinical research methodologies;
- enable Member countries to share their challenges and achievements in clinical research in T&CM; and
- identify key common challenges, opportunities and possible solutions to enhance regional collaboration and improve research capacity in T&CM.

4. Summary of workshop proceedings

4.1 Introduction of participants and nomination of Officebearers

The participants introduced themselves. Professor M.S. Baghel from India was elected Chairperson for the workshop. Dr Anchale Chuthaputti (Thailand) was elected as co-Chairperson. Dr Suzanne Grant (Australia), Dr Kalpesh Panara (India) and Dr Swapnil Chaudhari (India) were elected as Rapporteurs for the workshop.
After the election of the Chair, co-Chair and Rapporteurs, Dr Kim, Regional Adviser, TM, provided a brief background of TM in the WHO South-East Asia Region. Professor Hitesh Vyas outlined the programme of the three-day regional workshop.

4.2 Session 1: WHO Guidelines & SEA Region Member States’ challenges and experience with TM research

Professor Tamas Paal, of the University of Szeged in Hungary, noted that the aim of the WHO General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine, published in 2000, was to prove that clinical research on traditional medicine is possible and provide evidence for efficacy for local and global consumers, regulators and Western health professionals. However, Professor Tamas said that the guidelines are now dated and require revision.

Professor Paal emphasized the differences between traditional medicine and Western medicine approaches in diagnosis and treatment, which result in difficulties with applying research methodology. The placebo and control groups, which are important parts of randomized controlled trials (RCTs), are not easy to replicate in traditional medicine trials. Differences he spoke specifically of included the following:

➢ A traditional medicine doctor prescribes an individualized, often multidimensional, programme according to a patient’s need. This may include a mixture of herbal medicine(s), acupuncture, special diet, lifestyle modifications, yoga, Tai-chi or Qigong and Panchakarma, and not the same mixture for every patient.

➢ A traditional medicine doctor undertakes a traditional medicine diagnosis. This is not reflected in current clinical trials where the treatment is only based on Western diagnosis and not individualized.

➢ Traditional medicine treatment also depends on the patient’s will and motivation. Randomization often eliminates preferences for treatment.

The requirement for proof of efficacy may depend on the nature and level of indications. For example, Levels IIb up to Level IV are needed for minor and prophylactic indications.

Professor Paal reflected that while RCTs comprise Level I evidence, if a placebo-controlled RCT is not feasible, other research approaches to consider include:

➢ single case design,

➢ evaluating the effectiveness of the “black box” of TM; the diagnosis, treatment and its components are delivered as they would be in typical clinical practice,¹

➢ observational studies, and

➢ case reports or case series (the patient is their own control group).

Professor Paal mentioned that the European Union accepts traditional use without clinical proof (HMPC monograph - Level IV proof). However, in the United States of

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¹ In this research approach, the “black box” refers to the multimodal delivery of TM; the treatment and all of its components are delivered as they would be in the usual clinical situation. No component is isolated and studied independently. This allows the effectiveness of traditional medicine to be determined either within its own theoretical framework or within that of conventional medicine. However, it is difficult to know which component of the intervention is exerting the main effect – the combination of the therapies, the extra attention, the patient-practitioner relationship or something else not considered. Similar to “whole system research”, see: Ijaz, N., et al., Whole systems research methods in health care: A scoping review. The Journal of Alternative and Complementary Medicine Research, 2019. 25(S1): p. S21–S51
America and other countries, only double-blind RCTs (Level Ia/Ib proof) are accepted. The RCT needs to have adequate patient numbers, the end-point difference is to be significantly (not only statistically, but clinically) better for the verum, and the trial is certified to be conducted under good clinical practice (GCP) conditions; thus the WHO Guidelines are hardly used.

Controlled trials to date have been conducted on mostly herbal medicines, the use of which is closest to the conventional therapy. However, this evidence may not necessarily reflect traditional clinical practice. In (almost) all studies, treatment was based on the Western diagnosis only. Professor Paal recommended that research should focus on personalized, multidimensional features of traditional medicine. Further, studies of poor quality are continuously entering into the corpus of literature. Most of these studies are carried out on small samples. To address these issues, He referred to three important reviews on providing clinical proofs from traditional medicine. He suggested that the in revised guideline:

- avoid generalized statements and repeated content;
- increase the focus beyond herbal medicine to all traditional medicine;
- take note that trans disciplinary research is increasing and, therefore, needs to be incorporated;
- address quality issues such as standardization and details for plant extracts and species used in research;
- include controls and placebo, which suit TM;
- include TM diagnosis, which may be converted to modern medicine. The researcher should consider all aspects of a disease from the perspective of both systems; and
- address the complex treatment protocols of TM that contain herbal medicines, diet, exercise, lifestyle advice, and procedure-based therapies such as Panchakarma, yoga, cupping and acupuncture. Research protocol designs should consider this as a treatment package without omitting a single component.

**Key challenges:**

- How can traditional medicine diagnosis be converted into Western diagnosis?
- How can the personalized features of traditional medicine be adequately reflected in research?

**SEA Region Member States: Experiences in TM research**

**Bangladesh:** Dr Khandaker Sagir Ahmed Director, Directorate General of Drug Administration (DGDA), Dhaka observed that Bangladesh lacked experienced clinical researchers for randomized clinical trials of traditional medicines. To date, there has been

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2 Statistical significance indicates the reliability of a study’s results; clinical significance reflects its impact on clinical practice.  
6 Transdisciplinary research is defined as research conducted by investigators across different disciplines, integrating and synthesizing content, theory and methodology from any discipline area to help address research questions.
an ethnomedical survey of TM plants used and traditional medicine practised, but very few clinical studies have been carried out. With only two clinical studies on TM in Bangladesh to date, there is also a lack of infrastructure to support such studies. Dr Ahmed recommended that clinical research-building capacity be prioritized and scientific research on TM strengthened. He also suggested that adequate financial support needs to be provided and skills built through collaboration with established, experienced clinical researchers and organizations on projects, and by obtaining research grants.

**Bhutan:** In his presentation, Dr Phuntsog Wangadi, Drungtsho, Department of Traditional Medicine Services, Ministry of Health, in Thimphu referred to the geobiological diversity and richness of Bhutan. However, he said it was difficult for Bhutan to contribute to research in traditional medicine due to lack of research infrastructure.

**Democratic People’s Republic of Korea:** In his presentation, Dr Nam Kung Jin, Section Chief, Academy of Koryo Traditional Medical Science, Pyongyang, outlined the research capacity in TM in Democratic People’s Republic of Korea. This included the Academy of Koryo Medical Science, Academy of Medical Science, Korean Koryo Herbal Medicine Institute, Pyongyang, DPR Korea, and separate medicinal plant and animal institutes. Around 142 clinical research projects have been undertaken during 2015–2018, across a range of health conditions. Research results are communicated in national publications, conferences, tele health lectures and workshops. Research is published largely in national Koryo journals with over 1000 articles written between 2015 and 2018. Examples of projects using different research methodologies, including RCTs, were outlined.

**India:** Dr Narayanam Srikanth, Deputy Director-General, Central Council for Research in Ayurvedic Science (CCRAS) Dwarka, New Delhi outlined the TM research schemes and budget allocations in India. Research facilities and government support for TM in India are comprehensive. The market size and potential of Ayurveda are recognized as considerable. He presented current research on TM showing the growth of 71 clinical research projects underway since 2015. Prioritized research areas include diabetes, hypertension, obesity, reproductive and child health, skin diseases, pain, neurological and degenerative disorders, vector-borne diseases and quality of life in cancer.

Capacity-building in research has been through the data management systems established for researchers, research methodology and scientific writing. Over 27 000 publications are lodged on the AYUSH research portal, with nearly 5000 publications on clinical research, and over 11 000 on pre-clinical research. There are 895 publications on Levels Ia and Ib and 1369 on Levels Ia–III, with 710 publications in PubMed indexed journals. Systematic reviews of Ayurveda are being undertaken for 25 selected conditions. Some whole system and complex research studies have been undertaken, e.g. those on osteoarthritis and rheumatoid arthritis. Local health traditions have been actively investigated for validation of claims and generation of evidence.

Data management has been developed considerably with the National AYUSH Morbidity and Standardized Terminologies Electronic Portal (NAMASTE Portal), an AYUSH informatics initiative for centralized collection of morbidity statistics pertaining to various systems of medicine under the Ministry of AYUSH. Other initiatives include the testing of Ayurvedic diagnostic methods (Ayur Prakriti portal), an assessment of Ayurvedic lifestyle

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7 Apex Research Councils exist for each speciality: Ayurveda, Unani, Homeopathy, Siddha and Yoga & Naturopathy (CCRAS, CCRUM, CCH, CCRS, CCYN); National Institutes: All India Institute of Ayurveda (AIIA), Institute for Post Graduate Teaching & Research in Ayurveda (IPGTRA), NIA, NIS, NEIAH, NIN, NIUM, NIH, MDNIY
practices across India, and publication of guidelines for research and development in Ayurveda (drug, safety and clinical evaluations).

Recommendations for research-building collaboration included using biology to understand Ayurveda and TM, development and validation of research methods for TM, collaboration across and within countries, and enriching the TM pharmacopeia by sharing the understanding of common medicinal plants across Member States.

Indonesia: Dr Ina Rosalina, Director for Traditional Medicine Ministry of Health in Jakarta, referred to Indonesia as having the second largest mega-biodiversity in the world, including a large number of indigenous plant species, many of them medicinal. TM research is supported by the R&D Institute of Medicinal Plants, and 13 centres for the development and application of TM, and other allied government bodies.

Research covers epidemiological studies on usage, and on efficacy and safety. Her presentation covered the need for studies on TM to include health outcome measures that incorporate patient-reported outcomes (PROs) and the practitioner and patient point of view. During her presentation, she highlighted the clinical research undertaken in Indonesia from 2010 to 2018, including single arm-controlled studies and RCTs in hypertension, obesity, arthritis, diabetes, and allergies. Challenges include insufficient availability of raw materials, lack of technical and financial support, and lack of acceptance of TM by conventional medical practitioners.

Dr Rosalina suggested that areas of collaboration in the SEA Region may include the development of a database on herbal and medicinal plants, joint research, exchange of information and experience in indigenous medicine, and standardization of medicinal plants.

Maldives: Mr Mohamed Zaid, Vice-President, Maldives Allied Health Council, Malé, indicated that Maldives had inadequate research capacity in traditional medicine. There has been no clinical research on TM in Maldives, although some student theses do exist. He advocated for financial allocation to TM research from official development assistance (ODA) and national budgets, to build research capacity for traditional practitioners and create awareness among undergraduate and postgraduate students so that they undertake traditional medicine research.

Myanmar: Dr Khin Phyu Phyu, Director (Research), Department of Medical Research, Yangon, presented the research activities being undertaken by the Pharmacology Research Division within the Department of Medical Research, which conducts research on safe and effective utilization of TM in the existing health-care system. The division’s research covers basic (toxicology, phytochemical, pharmacognosy), experimental and clinical research on traditional medicine. There are optimum facilities for herbal medicine testing; standardizations and tests have been conducted for 48 TM formulations.

Since 2015, 11 clinical trials have been undertaken in TM and diabetes, fever, diarrhoea, hypertension, analgesia and cholesterol. Collaborative clinical research has been carried out on stroke, pain and spondylosis. The University of Traditional Medicine in Mandalay, Myanmar has established review and protocol boards with 42 clinical studies undertaken since 2015 in the areas of women’s health, pain, hypertension, diabetes, and other musculoskeletal disorders. Results are locally presented. Study designs are quasi-experimental and RCT. There are limited publications in international or PubMed indexed journals.

Nepal: Dr Siddharth Kumar Thakur, Chief, National Ayurveda Research and Training Centre, Government of Nepal, Kirtipur, outlined that TM research capacity in Nepal is
supported by the Nepal Health Research Council (NHRC), the National Ayurvedic Research and Training Centre (NARTC), the Ayurveda Campus (Institute Of Medicine, Tribhuvan University) and the Nepal Academy of Science and Technology (NAST) Lalitpur, Nepal.

Most research activity is focused on phytochemical and physical parameters of medicinal plants. The planned focus is on NCDs such as diabetes, cancer, rheumatoid arthritis and lifestyle disorders. Publications in indexed journals are less than 50 papers in the last five years. Recommendations for building research capacity included collaborative research, funding, networking, research knowledge, culture and skill building, and better governance capacity.

Thailand: Dr Anchalee Chuthaputti, Director, Technical and Planning Division Committee, and Member, Department of Thai Traditional and Alternative Medicine, Thailand outlined the various research facilities that conduct traditional medicine research with government financial support. In 2015–2018, 152 clinical studies have been conducted with 45 publications. Publications are both in Thai TM journals as well as 23 articles in PubMed indexed journals. Health conditions include musculoskeletal issues, cancer, diabetes, stroke, chronic obstructive pulmonary disease or COPD, and postpartum care and recovery.

Research capacity has been built through the provision of training in research methods and the establishment of a TM Ethics Committee. Dr Chuthaputti cited some examples of clinical studies, including RCTs on a standardized TM formula for dysmenorrhea. Key challenges include the ethics of providing a placebo, difficult to maintain blind testing participants and research on cancer patients being permitted for Stage IV patients only. Recommendations for building capacity included regional-level training in clinical research methodologies for the trainers; Member States taking turns to host a biennial regional conference on clinical research; and countries conducting an annual conference for the presentation of their TM research, which will provide a platform for researchers and TM practitioners to discuss and develop their pursuit.

Timor-Leste: Ms Perpetua Ana Mery Estela Laot, Trainers and Research Officer, Institute National Health, Dili, noted that there is no specific law for TM and no funds either. No research activity has been conducted till date.

Common issues and challenges

Member States face the following common issues:

1. TM is delivered, evaluated and interpreted through the perspective of Western medicine and Western medicine research methodologies.
   - TM regimens focus on health promotion, prevention and control of illnesses using the synergistic effect of multiple interventions. There are difficulties in conducting research on complex, holistic and personalized intervention of TM.
   - RCTs have low feasibility in TM research and limited application in TM (personalized versus standardized).
   - There are difficulties in bridging advanced science and technology with the core concepts of TM.

2. Systematic reviews of TM frequently conclude with recommendations for an improvement in the quality of research.
   - Research methodologies for TM are difficult to execute and blinding.
Regional workshop on clinical research methodologies in traditional medicine for the WHO South-East Asia Region

- There is lack of appropriate research methods for TM to generate evidence.
- Research is often of poor quality due to lack of standardization and small sample sizes.

(3) Practice, research and training in TM remains fragmented.
(4) There is lack of resources (research infrastructure, funds, manpower, quality drugs, etc.) and inadequate support from respective governments in some countries.
(5) There is lack of integration and implementation of TM in health-care delivery in terms of recognition and national legislation (country-specific).
(6) Regulatory systems need to be strengthened to ensure:
  - safety, quality and efficacy of TM products and services; and
  - quality control of herbal/mineral/metallic traditional medicines/formulas.
(7) Pharmacovigilance needs to be considered for safety:
  - Over-the-counter (OTC) TM drugs may be misused by people.
  - Non reporting of drug-herb and drug-TM products interactions;
  - There is a need for safety pharmacology studies.
(8) There is considerable skepticism and prejudice from some population groups towards TM.
(9) There is lack of well-functioning health information systems to monitor TM system performance.
(10) Reporting guidelines for TM are lacking.
(11) Ethical issues such as incorrect findings, fabricated and fraudulent data, poorly written scientific reports or studies that cannot be reproduced, can collectively lead to erosion of the quality and importance of the science.
(12) There is lack of publications in indexed journals.
(13) There are few exclusive journals that support TM research.

Recommendations for clinical research capacity-building across SEA Region Member States

In summary, the following options were offered by Member States on the development of research capacity through regional collaboration:

(1) Improving research quality by:
  - conducting collaborative research drawing on the clinical research infrastructure and the experience of researchers across countries to build skills in protocol development and research methods, and to obtain research grants.
  - opportunities for networking to build research culture and skills. This may be accomplished through a biennial regional conference where research is presented and researchers and practitioners are able to learn from one another.

(2) Development and validation of TM models for diagnosis and treatment to use in research.

(3) Improving quality of TM by:
- quality control of medicinal raw materials and finished products,
- improving safety by recording possible interactions between drug-herb and herb–herb,
- ensuring standards for herbal products.

(4) Setting up a database of medicinal plants that provides for an exchange of information, indications and experience in such plants that are common across Member States of the SEA Region.

(5) Development of specific ethical guidelines for TM research.

4.2 Session 2: Research methodology in traditional medicine – guidance and examples

There were presentations on the People Republic of China’s experiences in traditional Chinese medicine (TCM) research (Professor Darong Wu), the use of the Delphi method in research (Dr Grant), and the transformation of an idea into a research project (Dr Manoj Nesari).

Research in traditional Chinese medicine in China

Professor Darong Wu of the Guangzhou University of Chinese Medicine, Guangzhou, shared the experience of research in TCM in the country. More than 90% of the urban and rural Chinese population seek TCM at least once in their lifetime. TCM is highly accepted, recognized and implemented by the Central government of China, and has been included in the Constitution. Most Chinese medicinal therapies are covered by medical insurance in the country. The Chinese government encourages doctors with biomedical training to learn TCM, and most TCM doctors in China, especially those who work in hospitals that have inpatient departments, have an educational background in biomedicine. Professor Wu explained three different models of care for the integration of TCM in China.

(1) In disease-based models, biomedical diagnosis is conducted in clinical areas such as cardiovascular disease, neurological disease, oncology, kidney disease, digestive disorders, respiratory disease, etc. Internal treatments, such as Chinese patent medicine, and other than external therapies, such as acupuncture, are widely adopted in biomedical hospitals either for inpatient or outpatient services. In some cases, the consumption of Chinese patent drugs in biomedical hospitals is even higher than that in TCM or Integrative Medicine (IM) hospitals.

(2) In combined model of disease and Chinese medicine diagnosis, both biomedical- and TCM-pattern diagnoses are considered. This approach is more widely adopted in TCM/IM hospitals.

(3) In the symptom-based model, a biomedical diagnosis for inpatient is necessary, but not for outpatient. In some cases, there is a fixed treatment with or without high-level evidence, which is promising in a number of situations such as pain, fatigue, nausea, etc.

Dr Wu discussed the difference between hierarchical models of evidence and a circular model. The hierarchical model of evidence includes: i) case studies, ii) retrospective or prospective case series, iii) cohort study with historical and concomitant non-randomized controls, iv) open-label randomized controlled studies, and v) blinded, placebo-controlled RCTs. She noted that those which offer the most internal validity are considered the most reliable evidence.
However, this hierarchy, founded on a pharmacological model of therapy, is not suitable for complex and non-pharmacological interventions such as healing, acupuncture and surgery. In a circular model of evaluation, more than one research method may be used to answer questions on effectiveness and safety.

**The use of the Delphi method in traditional medicine research**

The second keynote speech was delivered by Dr Suzanne Grant of the Western Sydney University, Sydney. She noted that in Australia, two in three people use complementary therapies each year, and 42% do so to prevent or manage chronic conditions. Dr Grant provided a short introduction to the National Institute of Complementary Medicine (NICM) at the Western Sydney University.

The NICM Health Research Institute conducts three core research activities: preclinical R&D (chemical identification, stability testing, bioactivity of herbal medicines, medicinal cannabis lab); clinical trials, hospital and specialist collaborations, and systematic reviews; research translation and policy contributing to clinical guidelines; and work with Therapeutic Goods Administration (TGA).

Dr Grant then conducted a workshop on using the Delphi method in TM research. The Delphi method is a systematic approach to consensus development by using repeated question-and-answer analyses. It is a structured process using a panel of experts and a series of questionnaires or “rounds” to gather information that are continued until “group” consensus is reached. The Delphi technique is characterized by: (i) anonymous group interactions and responses, (ii) multiple rounds of questioning, and (iii) the provision of feedback to the group.

Dr Grant used three examples of the Delphi method for traditional medicine: to develop consensus for a yoga intervention, and for an acupuncture intervention, and to determine priorities for complementary therapies in cancer care. In summary, the key steps in each example for using the Delphi method Dr Grant mentioned were:

1. **Defining the question** (objective). For example, to arrive at an expert consensus on the best yoga intervention for people with anxiety and depression.
2. **Find the experts** (inclusion criteria). What is the level of expertise or knowledge or credentials needed? How many (small number will limit anonymity)?
3. **Define consensus**. This should be predefined at the outset; there is no fixed agreement on what this should be. It may be as little as agreeing on 50% or as high as 100% agreement on all topics.
4. **Round One**. This first round may often have broad questions or statements according to the different components that are being explored. For example, in a yoga intervention, it may be how long should a session be for someone with anxiety? How frequently should the practice be? What postures and meditation techniques? Maintain a balance between using scales (e.g. Likert where there is a numeric rating for how strongly they agree or disagree with a statement) for

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responses and keeping it open-ended. Draw on existing research as the basis for Round One.

(5) **Rounds Two and Three.** These rounds are where the responses from Round One are ranked and the panel is asked to respond with agreement or disagreement. Rounds Two and Three are often run using a questionnaire and there is less room for open-ended responses. Rounds can continue beyond three, if needed.

(6) Address non-responders by using reminders, engaging personally at the outset to bring ownership to the task, and setting tight deadlines so that the study doesn’t drag on.

Some of the advantages of the Delphi method are that it is not constrained by geographical location; can be anonymous or quasi-anonymous; gives equal weighting to each participant; is useful when strong personalities dominate; and helpful where very diverse backgrounds and expertise could result in inter-group disagreements that could impair group functioning.

Some of the disadvantages are that the rationale for responses cannot be explored and there cannot always be adequate diversity in the expert panel. Adequate diversity of the expert panel may also make consensus difficult. Consensus should not be the primary goal, and where many panellists have diverging viewpoints, this can be an important finding.

**Transforming an idea into a research project**

The third keynote speech of the second session was delivered by Dr Manoj Nesari, adviser, Ministry of AYUSH, India. He covered the full scope of research in TM that includes clinical management, diagnostic tools and biomarkers, reverse pharmacology and fundamental research.

Dr Nesari put forth a summary of idea-generation methods. Ideas are generated from experience, previous knowledge, and facts about an object of knowledge. When two things happen in succession, they can either be seen as an anomaly or if the two things happen with some regularity, this may provide the ground for hypothesis.

A TM researcher may get ideas from reviewing existing practices; challenging accepted ideas; looking for conflicting views; investigating geographical variation; freeing the imagination; building on experience; being alert about new ideas; harvesting literature, journal club, and meetings; being skeptical about prevailing beliefs; carefully observing patients; using teaching experiences; forgetting formal designs; and thinking outside the box.

When transforming the idea into a project, consider exactly the knowledge gap that you want to fill. Is it about aetiology, pathogenesis or about prognosis? What should change for the benefit of a particular group of patients? What is the study design needed? Do we have the capacity? Can it be funded? If the practical problem is too large or research question too unfeasibly grandiose, it may be wise to settle for a less ambitious aim.

Dr Nesari observed that TM research is placed at different levels in different countries of the SEA Region, but some of the challenges in TM research of Member States include:

- ignorance about TM among biomedical and basic scientists/policy-makers;
- lack of confidence among TM scientists;
- ignorance among TM researchers about latest technological advances; and
- compromises in research design.
Dr Nesari stated that thinking about research problem is a strongly iterative process. The study design and the research question may change along the way. He concluded that hypotheses are not generated by data, they are proposed by scientists.

4.3 Session 3: Research methodology design and gaps

Main features and gaps of research methodology in traditional medicine

In this third session, Professor K.S. Dhiman, Director General, Central Council for Research in Ayurvedic Sciences (CCRAS) highlighted the current AYUSH initiatives and issues in TM research. He defined “Traditional Medicine” as the health practices, approaches, knowledge and beliefs incorporating plant-, animal- and mineral-based medicines, spiritual therapies and manual techniques applied individually or in combination to treat, diagnose and prevent illnesses or maintain well-being. The basic tenets of traditional medicine are holistic and personalized approaches to both diagnosis and treatment.

Current research areas of AYUSH were highlighted including:

(1) Basic or fundamental research
   - The development of parameters to assess the fundamental principles of key Ayurvedic concepts such as Panchmahabhoota (five basic elements that constitute everything in the universe), Tridosha (three functional energies of the human body), Agni (responsible for digestion and metabolism), Dhatu (tissues), Ojas (responsible for building tolerance or immunity), Srotas (circulatory system), Ama (the products of digestion that can trigger pathogenesis) and the therapeutic, potential and biological effect of drugs related to their properties (Rasa, Guna, Virya, Vipaka and Prabhava).
   - Undertaking the validation of other principles related to collection of drugs (season, time, habitat, etc.).
   - Undertaking research and development of tools for Ayurveda diagnosis; protocols for clinical research; and standardizing therapeutic procedures such as Panchakarma, Ksharasutra, Kriyakalpa, Agnikarma and bloodletting.

(2) Literature: Initiatives include the survey and collection of manuscripts and rare books and their translation and publication; the retrieval of ancient classics, manuscripts, medico-historical investigations; and developing e-books.

(3) Drug development: A variety of initiatives are underway:
   - An ethnomedicine survey of medicinal plants/cultivation and collection practices.
   - Revival of ancient agricultural techniques and use of Miyawaki method for medicinal plant forests.
   - Assessment of pharmacodynamics and pharmacokinetics of drugs, pharmacognosy studies and reverse pharmacology.
   - Conducting safety, toxicity and drug interaction studies.
   - Standardization and quality assurance related to TM drugs.
   - Developing experimental models, dosage forms, cell line studies, shelf life, quality issues, etc.

(4) Clinical research: Studies include using a range of primary research studies for validating classical formulas and therapies, using reverse pharmacology for new drug leads and exploring indications for classical formulas in clinical trials.
Professor Dhiman provided a comprehensive summary of the differences between TM and contemporary science.

<table>
<thead>
<tr>
<th>Areas that differ</th>
<th>Contemporary science</th>
<th>Traditional medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basic principles</strong></td>
<td>Cell-molecular biology, focus on the physiological (reductionist)</td>
<td>Focus on physiological, psychological, behavioural and spiritual aspects</td>
</tr>
<tr>
<td><strong>Approach</strong></td>
<td>Disease-focused, symptom-oriented and standardized</td>
<td>Holistic and individualized approach</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>Well-defined diagnosis, which is uniform and valid throughout the world</td>
<td>Diagnosis is non-standard, considers stage of the disease, constitution and external, internal, diet and lifestyle factors</td>
</tr>
<tr>
<td><strong>Tools for diagnosis</strong></td>
<td>Valid and reliable tools for diagnosis (laboratory, radiology, etc.)</td>
<td>Non-standard and no SOPs for uniform diagnosis. Relies on examination techniques such as inspection, palpation and interrogation</td>
</tr>
<tr>
<td><strong>Drugs</strong></td>
<td>Developed through rigorous R&amp;D with standard procedures</td>
<td>Guided by traditional use. Components, mode of use, methods of preparation, dosage, indication, etc. vary across the country</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>Fixed universal dosage</td>
<td>Varies with constitution, nature of disease, geographical location, season, etc.</td>
</tr>
<tr>
<td><strong>Availability</strong></td>
<td>Usually available</td>
<td>Availability as per geographical location</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>Evidence-based</td>
<td>Practice-based</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Documented Adverse Drug Reaction/Adverse Events</td>
<td>Documented data are lacking</td>
</tr>
<tr>
<td><strong>Drug action</strong></td>
<td>Well-charted pharmacodynamics and pharmacokinetics</td>
<td>Compound formulation based on traditional use and drug qualities suited for the individual presentation</td>
</tr>
<tr>
<td><strong>Treatment principle</strong></td>
<td>Symptom/system- and pathogen-oriented uniform treatment principles</td>
<td>Type and amount of treatment are individualized and dependent on the unique presentation of the patient, stage of disease, constitution, digestion</td>
</tr>
<tr>
<td><strong>Mode of treatment</strong></td>
<td>Disease-based, may be medical/surgical treatment or lifestyle</td>
<td>Dependent on the examination, but may include a combination of a range of therapies – yoga, herbal, lifestyle, procedure-based, counselling</td>
</tr>
<tr>
<td><strong>Research</strong></td>
<td>Well-developed, specifically for Western medicine</td>
<td>Lack of standard research methodology to suit TM</td>
</tr>
</tbody>
</table>

Professor Dhiman noted that research methods designed for Western medicine do not take into account the individualized, complex diagnosis and approach of traditional medicine, and as such, do not strengthen traditional medicine. There is a fundamental gap in linking the concepts between the two systems. Specifically, when Western medicine research methods are used for traditional medicine, the focus is typically on one aspect of the TM (rather than on seeing TM as multidimensional), the mechanism of action of the herbal medicine, symptom- or disease-oriented, and does not use TM diagnosis.

In summary, Western research methods are not being able to examine the complex Ayurvedic parameters used in clinical practice and responsible for outcomes. Different responses to therapy by the patient will depend upon various factors such as Prakriti (constitution of the body based on Tridosha), extent of the disease, cause of the disease and so on, prompting further tailoring of treatment. However, the absence of evidence is not the evidence of ineffectiveness.

Professor Dhiman provided insights into pharmacological studies on safety in TM. In particular, consider the concentration of active or toxic compounds and other chemicals.
that varies in different parts of the plant, for different harvest seasons, and when extracted, with different methods. Additionally, the geography, soil composition and its contaminants, year-to-year variations in soil pH, water, weather conditions and other growth factors have significant effects on the therapeutic properties and safety of medicinal plants.

Key problems conducting clinical trials in traditional medicine relate to the lack of standardization around dosage, diagnosis, TM/Ayurvedic concepts, lack of quantifiable outcomes for TM/Ayurvedic parameters, and a lack of appropriate reporting guidelines for TM/Ayurvedic interventions. Research designs meant for evaluating complex treatments are better suited to TM, e.g. pragmatic trials, whole system research and pharmaco-epidemiological studies. Many initiatives are underway by CCRAS to assist in meeting these challenges, including development of standardized parameters for Ayurveda (e.g. Prakriti assessment scale, Ayurvedic health assessment scale, assessment tools for Agni, Kosttha).

Professor Dhiman noted that the publication of incorrect findings, fraudulent data, poorly written scientific reports or studies that cannot be reproduced leads to the erosion of quality. He concluded that the way forward for traditional medicine research is to generate evidence on TM medicine and approaches to form a baseline for more rigorous studies; use assessor blinding to reduce bias; and adopt whole system research designs that are better suited to the mind-body approach of Ayurveda.

Roadmap for clinical research methodology in traditional medicine

The objective of this workshop by Dr Girish Tillu, Savitribai Phule Pune University, Ganeshkhind, Pune, India was to outline clinical research methods. He presented the circular model of evidence, with a focus on using a collage of research methods rather than the hierarchical model of evidence that emphasizes RCTs. Dr Tillu noted that there have been considerable developments in methodology through Complementary and alternative medicine (CAM) initiatives such as AYUSH and CAMbrella, along with a range of international platforms (Cochrane, WHO Groups, EQUATOR network, publication guidelines such as COPE, WAME, etc., trial registries). Developments in data science, OMICs and systems biology have implications for research methodology.

Challenges in traditional medicine research include evaluating TM through the perspective of Western medicine; practice, research and training of TM remain fragmented; and bringing together science and technology with the core concepts of traditional medicine. TM research quality needs improvement as indicated by the outcomes of systematic reviews.

1. Foundations of clinical research:
   - Key concepts in causal association;
   - choosing outcome measures using quality-of-life measures (e.g. Pramana Pareeksha), patient reported outcomes, safety, and comparing outcomes in real-life clinical settings (comparative effectiveness research); and
   - reporting research in scientific publications (using standards such as those on the EQUATOR network), synthesizing evidence (Cochrane systematic reviews and meta-analysis), using informatics for T&CM (such as the National AYUSH Morbidity and Standardized Terminologies Electronic Portal) and coordinating efforts for implementation of research.

2. Research methods and clinical trials

Dr Tillu covered general steps in undertaking research:
Defining the research question; selecting the research design (e.g., observational, experimental, RCT, field research and community research); developing the components of the design (e.g., sampling, randomization, blinding, etc.); statistical concepts (e.g., variability, confounders, bias and validity) and designs (equivalence and non-inferiority).

For a clinical trial, the first step is formulating a clear research question; this should cover PICOS (participants, intervention, control, outcomes and settings). The design of the study needs to be appropriate for the question. It may be an RCT, but may also be more widely a black-box approach or whole system research, pragmatic trials, ethnographic design.

To answer the research question, outcome measures need to be selected; these may include quality of life, patient reported outcome measures and AYUSH concepts. Safety in the study should always be assessed in a clinical trial.

Attempts should be made to reduce bias (see PROBE: prospective randomized open label blind evaluation). When the research protocol is being developed, the statistical approach should also be determined.

Dr Tillu expanded on observational research methods and whole system research methods. He also referred to specific guidelines and regulations that can help to avoid "research waste".

4.4 Session 4: Research methods for clinical trials

Professor M.S. Baghel, Former Director, IPGT & RA, Jamnagar, India, started his presentation discussing the crisis in Ayurveda and traditional medicine. The reduction of the whole system of TM in research to single practices, such as herbalism or massage therapies, without the fundamental principles, is a crisis. Further, most scientific studies have yielded negative results, warranting a serious reconsideration of the research approach. It is unlikely that a “magic drug” will emerge from the Materia Medica of traditional medicine; the system of TM was not based on a single drug, but on a holistic approach to balanced health rather than the eradication of a single disease.

The research aims and objectives of clinical research in TM should be to:

- increase the knowledge of TM system;
- complete the information that has been lost or is incomplete;
- better explain the mechanism of action of TM;
- understand if the synergy with modern biomedicine and science can lead to broader advancements in research leading to better health-care strategies; and
- create evidence that is acceptable to biomedical researchers, doctors, academics, policy-makers, industry and consumers.

Professor Baghel noted that clinical research is still needed to validate the classics of TM; to establish dose, duration, indication and side-effect profile of any given drug; to find treatment modalities for diseases to standardize treatment procedures for therapies; and to find out the mechanism of action.

Problems faced in planning clinical research on traditional medicine include understanding fundamental principles and terminologies of TM, selecting the appropriate research model, the type of participants, the diagnostic approach and the assessment criteria to be used. TM research has a high dependency on subjective criteria.
To overcome these problems, Professor Baghel suggested that research institutions make it mandatory to include research training in topics of medical ethics and research methodologies; preparation of research protocols; the use of biostatics in research; and assessment of outcome measures. He also recommended that publication of research findings be made mandatory.

Considerations for planning research on TM:

➢ The individualized, holistic and integrative approach of TM involving body, mind, and spirit.
➢ Borrow technical tools and biomedical assessments (laboratory values, etc.) from modern biosciences, but apply them judiciously.
➢ Outcome measures should include quality of life and disease status as per TM concepts.
➢ Evaluating efficacy under controlled conditions such as a control or placebo, homogeneous samples, blinding, etc. may not be possible in most clinical studies of traditional medicine, but randomization and standard protocols can be used.

Research design applicable for clinical trials in TM:

➢ Pragmatic trials testing “real life” treatments.
➢ Trials that investigate the effectiveness of the “black box” or whole system research of traditional medicine are possible. For example, one can consider an RCT of the whole treatment of Ayurveda for rheumatoid arthritis where placebos were used for six components of the intervention.\(^\text{11}\)
➢ Studies that are open, single-arm, where there is a group of subjects with a specified indication and managed systematically with a specified therapy to measure outcomes.
➢ Single-case studies are adaptable to the clinical needs of the patient and the therapeutic approach of the practitioner, but lack generalizability. But these are useful for developing and testing research hypotheses, in chronic and less common diseases, and refining clinical techniques.

In general, all studies should comply with guidelines such as good clinical practice (GCP), good agricultural practice (GAP) and good manufacturing practice (GMP) and include standard operating procedures (SOPs) that accurately describe and ensure consistency in the trial drugs. Concluding, Professor Baghel recommended that the WHO TM guidelines be revised and the role of traditional medicine in global health care should be considered. He also suggested that there may be a need for a set of ethical guidelines for TM.

4.5 Session 5: Research methods for clinical trials for TM procedure-based therapies

Professor Anup Thakar’s, Director IPGT & RA, Jamnagar, Gujarat presentation covered SOPs\(^\text{12}\) for procedure-based therapies in Ayurveda, including the types of formulations used in these procedures and safety issues.


\(^{12}\) SOPs provide a set of ‘how to’ instructions: what to do, how to do it, when to do it and how to document the completion of the activity. SOPs define best practice and are a critical element of a clinical trials practice in ICH GCP.
Ayurveda uses a range of procedures as part of treatment, including Vamana (therapeutic emesis), Virechana (therapeutic purgation), Anuvasana Basti and Astahapana Basti (therapeutic enemas) and Nasya (therapeutic nasal drop procedure). The procedures involve three main stages:

1. Pre-operative (procedure) – preparation of materials.
2. Main procedural stage – administration of the therapy.
3. Post-operative care, such as post therapy dietetics.

Professor Thakar emphasized that SOPs play an important role in evaluating safety and efficacy. They provide a set of detailed instructions and ensure reproducibility and consistency from site to site, thereby confirming the reliability of the data as a whole. SOPs also make it easy for the research team to carry out trials in compliance with standards.

SOPs have been developed for several Ayurvedic procedures (such as massage and therapeutic enema). The SOPs cover the materials and equipment, manpower, step-by-step flow of the main procedure, duration, indications, dose, apparatus, etc.

Professor Thakar also called for the development of SOPs for formulations to ensure quality. These SOPs should cover:

1. Raw material standardization, aspects such as:
   - organoleptic (colour, odour, taste, etc.);
   - botanical (macroscopic, microscopic);
   - physical (moisture content, ash values, etc.);
   - chemical (qualitative such as high-performance thin layer chromatography (HPTLC), radioactive contamination, etc.); and
   - biological (microbial contamination, toxicology, pharmacological, etc.).

2. In-process standardization, aspects such as:
   - reference for the specific formulation;
   - accurate references from relevant classics;
   - development of SOP of manufacturing process of drug;
   - how particular instruments or methods are to be used;
   - various Parikshas (tests) of the drug that are to be carried out during its preparation. For example, one can consider the Tantumavam (thread like consistency) in Avaleha (confectionary) preparation – it should have a thread-like consistency, when pressed between two fingers; and
   - atmospheric conditions during the preparation of the drug – for example, the time period for fermentation process varies according to season.

3. Finished goods standardization, aspects such as:
   - standardization of the final product in such a way that the prepared medicine meets this fixed standard;
   - following the guidelines set out in the Ayurvedic Formulary of India Part 1 & 2; and
   - following good manufacturing practices.

Some formulations that are used for therapeutic procedures in Ayurveda include medicated oils, herbal juices, Kalka (medicinal paste), decoctions, Ksheera Kashaya (milk decoction), Churna (powder), Avalehas (confectionaries), medicine for different Dhara and
different Potalies (poultices). SOPs for Shashtika Shali Pinda Sweda (poulance), and Takardhara (procedure wherein a stream of medicated buttermilk is poured on the targeted body part) are good examples of preparations of formulations in Panchakarma.

Safety issues along with contraindications for different procedures need to be considered.

Professor Thakar outlined several research designs that are suitable for efficacy evaluation of therapeutic procedures, including black box design, ethnographic design, focus group discussion, and observational design. He noted other considerations for assessing efficacy:

➢ Select appropriate outcome measures, determine if quantitative and qualitative outcome measures or both are needed. Which are the primary and secondary outcomes?
➢ Ensure that the sample is representative enough to enable generalization. Justify the sample size and ensure that it is of an adequate size to detect any clinically important differences between the study groups.
➢ Describe inclusion and exclusion criteria.
➢ Consider the usefulness of randomization in traditional procedures research. In many situations, randomization may lose the integrity of the principles of TM.
➢ Reduce bias by blinding the assessor.
➢ Evaluate “quality of life” in cases where cure cannot be provided.
➢ Note potential limitations due to variability of treatment by a single practitioner (intra-practitioner variability) and groups of practitioners (inter-practitioner variability).
➢ Study design should take into account seasonal variations that are important to some TM systems, which affect the individual constitution, and the availability and therapeutic efficacy of herbs.

In conducting research on therapeutic procedures, the following should be considered:

➢ Standardize all instruments used for procedures, e.g. Basti Netra (nozzle for enema), Nadi Swedana Yantra (a type of instrument for sudation) and Gokarna (a type of vessel) for nasal therapy.
➢ Standardize measurements for all instruments, the type of material used for making instruments and look for cost-effective, eco-friendly and lightweight materials.
➢ Document sterilization techniques.
➢ Ensure safe disposal methods for disposable instruments.
➢ Modify equipment and procedure appropriately, e.g. tradition vs current technology – for example, machines for procedures such as Shirodhara and Sarvangadhara; the combined use of modern techniques like infra-red, traction, etc., along with traditional therapeutic procedures.
➢ Standardization of procedures such as depth and the amount of pressure applied in different massages. Surface electromyography (EMG) may be used to measure muscle activity levels at baseline and after each pressure levels.
4.6 Session 6: Research methods – observational studies in TM and designing research proposals

**Observational studies in TM**

Dr Supriya Bhalerao, Associate Professor, IRSHA, Pune, India delivered a presentation on the types of observational studies, advantages and disadvantages of observational study design. Dr Bhalerao noted that the current statistics of research on TM suggest that most of the research effort is related to plant pharmacology. There is little effort to develop a drug from this research that may address various unmet medical needs in India.

Dr Bhalerao elaborated on case control and cohort studies. Non-interventional, observational studies have the following advantages:

➢ findings on therapeutic or prophylactic treatments are collected under routine conditions;
➢ there is no influence on the unique doctor-patient relationship with respect to indications, the selection of and carrying out the treatment; and
➢ may be conducted with or without a control group.

Well-designed, high-quality observational studies can increase the level of evidence on the efficacy of traditional medicine. They enable TM intervention to be studied in a natural setting without the restrictions imposed by blinded RCTs. Decision-making in clinical practice is typically a mix of evidence-based medicine (systematic reviews and meta-analyses), clinical experience, patient need, patient and practitioner preference and peer group advice. The results of observational studies may be considered more representative of clinical practice and have high external validity.

**Designing research proposals in TM**

Dr Galib, Associate Professor, All India Institute of Ayurveda, New Delhi, India, outlined the need for TM research to increase evidence on efficacy, ensure safety, identify treatments for emerging diseases, understand mechanism of action and standardize treatment procedures for global acceptance. Many of the problems faced in designing research for TM include:

➢ assessment criteria of patients in TM;
➢ understanding of TM terminology and fundamental principles;
➢ incorporating the variations of disease according to Dosha and the different disease phases in TM;
➢ administration (time) of drugs; and
➢ considering the role of diet and lifestyle.

Other difficulties may include skepticism and prejudice and access to inadequate research infrastructure and support in some countries. This could be aided by some governments framing policies to support and guide TM research, and health information systems to monitor traditional medicine and TM research activities.

The research protocol in TM should include components that cover the examination of the disease itself (TM stage, etc.) along with the patient. Dr Galib concluded with the following suggestions:

➢ develop disease-specific protocols with validated assessment criteria according to the signs and symptoms of disease;
Regional workshop on clinical research methodologies in traditional medicine for the WHO South-East Asia Region

➢ undertake frequent research capacity-building and training in research methods and drug regulation;
➢ assess the need for exclusive journals that support TM research;
➢ involve biostatisticians in TM research; and
➢ ensure the establishment of a regional, independent clinical trial registry portal for the registration of clinical trials of traditional medicine. This will help to disseminate information about research on TM.

In addition, pharmacovigilance is important and any drug interactions or adverse events should be reported. This has already started with the Ministry of AYUSH.

4.7 Session 7: Research methods – biostatistics and information technology in TM research

Professor Pawan Kumar Godatwar, National Institute of Ayurveda (NIA), Jaipur delivered the session on bio-statistical approaches in TM research.

Dr Godatwar outlined the need for ensuring validity and reliability in TM research studies. This means that the measures used are accurate and consistent for what is being assessed. The use of inferential statistics allows us to make generalizations from the study sample for the wider population. He elaborated on the use of statistics such as:

➢ summarization of data (a data mining concept);
➢ estimation of normal limits at 95% confidence intervals;
➢ using comparison and association of data;
➢ using correlation and regression analysis to understand relationships between study variables; and
➢ sample size calculations.

He noted that a result from a study may be statistically significant, but may not be clinically significant. Statistical significance provides an indication of the reliability of the study results, while clinical significance reflects its impact on clinical practice. With the help of biostatisticians, experts of TM can define exact sets of statistical tools that are best suited for analysis of parameters on the basis of TM fundamentals or principles.

Technology can be used for statistical analysis, including software options such as SPSS, SAS, Epistat, Statgraf, Spida, EXCEL, Epi-info. Dr Godatwar recommends Graphpad software, www.graphpad.com (Instat for beginners, Prism for advanced users). Graphpad offers a user-friendly, stepwise guide, that ensures quick results, makes it possible to import data from Microsoft EXCEL and produces graphs.

Dr Godatwar made the following recommendations on data management and storage for TM:

➢ create TM disease registries;
➢ establish record linkages;
➢ incorporate ICD with traditional medicine terminologies; and

13 The Ministry of AYUSH in India has developed a portal named National AYUSH Morbidity and Standardized Terminologies Portal (NAMSTP). The portal (http://namstp.ayush.gov.in/#index) provides Standardized Terminologies & Morbidity Codes for Ayurveda, Siddha and Unani systems of medicine along with WHO ICD-10/11 codes meant for dual coding and morbidity reporting for Yoga, Naturopathy and Homoeopathy systems.
➢ ensure central storage of data on specific TM health programmes and from government surveys.

Information technology has changed the conduct of clinical research by removing some of the constraints of speed, cost and distance from the researcher. For example, the evidence-based research portal (http://ayushportal.nic.in/) provides searchable information related to AYUSH research at a global level. The Digital Helpline for Ayurveda Research Articles (DHARA) (http://www.dharaonline.org/Forms/Home.aspx) is an online index of articles on Ayurveda published in research journals worldwide.

Dr Godatwar recommended that institutions recognize and meet their responsibilities to develop and support policies, services and standards for information technology, and provide accessible, expert help in learning and using information technology. This would be facilitated by:

➢ establishing career paths for IT positions;
➢ implementing mechanisms for the evaluation, merit (peer) review and dissemination of software useful in the conduct of research;
➢ researchers working in collaboration with vendors to establish standards for simplified and consistent user-machine interfaces;
➢ network administrators should provide simple user interfaces and addressing schemes, add gateways to other networks, improve system reliability and capacity, and provide online help, such as guides to services and mail addresses of individuals who can answer questions;
➢ Information service providers should create simplified common standards for accessing and querying information sources, and eventually provide unified access to information; and
➢ software vendors, research and professional groups should create programme libraries and make them accessible through the networks.

Dr Godatwar recommended that institutions should develop an interconnected national information technology network that can be used by all qualified researchers. This has been done for Ayurveda in India with the establishment of the digital database, DHARA, and the AYUSH portal.

To facilitate implementation of previous recommendations and to focus attention on the opportunities and impediments associated with research uses of information technology, Dr Godatwar suggested the establishment of a user’s group at the national level to oversee and advise on the evolution and use of information technology in support of clinical research.

4.8 Session 8: Proposed SEARO guidelines for methodologies on research and evaluation of traditional medicine

Dr Girish Tillu presented a summary of the original purpose of the WHO Traditional Medicine Guidelines (2000), which were to:

➢ harmonize the use of certain accepted and important terms in traditional medicine;
➢ summarize key issues for developing methodologies for research and evaluation of traditional medicine;
➢ improve the quality and value of research in traditional medicine; and
provide appropriate evaluation methods to facilitate the development of regulation and registration in traditional medicine.

Since the Guidelines were published, the WHO Traditional Medicine (TM) Strategy 2014–2023 has been developed. Goals of the strategy are:

- harnessing the potential contribution of TM to health, wellness and people-centered health care; and
- promoting the safe and effective use of TM by regulating, researching and integrating TM products, practitioners and practice into health systems, where appropriate.

The WHO TM 2014–2023 Strategy survey of Member States highlighted such key issues as lack of research data (the most common difficulty faced by Member States), the need for technical guidance on research and evaluation of T&CM safety, quality and efficacy (the greatest need expressed by Member States) and the need for capacity-building activities.

Strategic actions for Member States highlighted from the WHO Traditional Medicine Strategy 2014–2023 included:

- Promote research and development, innovation and knowledge management.
- Encourage knowledge generation, translation and dissemination by establishing a comprehensive and inclusive approach to T&CM research and development, including quality and cost-effectiveness.
- Develop a national research agenda that acknowledges and includes various types of research models
- Develop and share appropriate methods and criteria for evaluating the safety, efficacy and quality of T&CM products and assessing the value of T&CM practice.
- Develop research methodologies consistent with T&CM theories and practice.
- Build up the capacity and capability for international research.
- Support international research collaboration on T&CM.

The focus of the SEA Regional Traditional Medicine Guidelines should be on empowering TM researchers to use appropriate research methods. The proposed structure for the revised guidelines is as follows:

- Background: needs, problems, challenges, context, developments
- Definitions: glossary/terms/explanation
- Methodology:
  - Literature, fundamental, in vitro, in vivo, in silico,\(^\text{14}\) clinical, community, etc.
  - Conceptual evaluation to quality control
  - Various methods, inputs, best practices, case studies
  - Selection and research designs, pros and cons, application etc.
  - Research and publication ethics.

\(^{14}\) In silico studies are performed on computer or via computer simulation.
Annexure: related documents, scales, further readings, resources links, etc.

The proposed process for revising the guidelines is as follows:

- WHO collaborating centre will appoint an expert group and assign responsibilities;
- WHO SEARO to coordinate activities;
- collaborative exercise;
- group member contribution expected with timely commitment; and
- group advises WHO to adopt the guidelines.

4.9 Session 9: Summary of the workshop themes and recommendations

Rapporteurs Dr Swapnil Chaudhari, Dr Kalpesh Panara and Dr Suzanne Grant provided a summary of the themes from the workshop and recommendations.

Summary of the research methodology themes

A recurrent theme throughout the workshop was how to undertake high-quality research that reflects the complex whole system nature of TM. Key points and recommendations were:

Clinical trial research methods

1. Shift the research methodology focus from “reductionism” to “whole system” and from “disease” to “health promotion and prevention”.
2. In clinical research, include both the examination of the disease (according to TM principles) as well as the patient.
3. Include studies that allow for individualized treatment.
4. When comparing TM with Western medicine, the emphasis should perhaps be on comparing the whole traditional healing system, rather than a single component.
5. Defining the research question and intervention can be helped using experts with techniques such as the Delphi method.
6. Avoid “research waste”.
7. Remember that it may take a large sample size to reach not only statistical, but also clinical significance.
8. Research designs suited to TM clinical research include black-box approach, n=1 trials, ethnographic design, pragmatic trials, adaptive trials and whole system personalized pragmatic trials (protocol-driven trials, decision tree, analysis of outcomes).
10. Assess safety in clinical research – use a safety index.

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**Patient reported outcome measures (PROMs)** are questionnaires that help patients to report on outcomes relating to their health.
(11) Where possible, reduce bias, e.g. use the prospective randomized open label blind evaluation (PROBE) design for intervention studies; blind the assessor.

(12) Involve a biostatistician in TM research at the outset and determine the statistical approach for analysis.

Observational research methods

(1) This research can be undertaken in clinical practice, using case reports, case series, cohort studies, case control studies, patient registry data (with TM diagnosis), documentation in clinical practice and electronic health records.

(2) Big data – the National AYUSH Morbidity & Standardized Terminologies (NAMASTE) Portal provides information about standard terminology and codes for recording data, morbidity and treatment outcomes in Ayurveda.

(3) Clinical documents can become clinical data with analyses and this can generate research questions and evidence.

Quality publication

(1) To generate evidence for TM research, published reports in good indexed journals are very essential as without quality evidence, claims cannot be accepted.

(2) Guidelines for reporting specific TM may need to be developed; current reporting guidelines are available for framing and writing up research (EQUATOR).^16

(3) There is a need to start one indexed journal for TM research from each Member State.

Summary of general research recommendations:

Training

To build research capacity, conduct regular training for researchers in:

- medical ethics and research methods,
- preparation of biomedical and TM research protocols,
- use of biostatistics in preparation of projects and evaluation of trials, and
- assessment of outcome measures.

Collaboration

- Build economies of scale and assist countries with no research infrastructure through collaborative research on topics and diseases that are of mutual concern through a bilateral mechanism, such as signing MoUs.
- Facilitate collaborative research, exchange of knowledge and skills and sufficient networking within the Region.
- Strengthen transdisciplinary traditional medicine research, including research between TM and WM researchers and countries.

^16 The EQUATOR (Enhancing the Quality and Transparency of Health Research) Network is an international initiative that seeks to improve the reliability and value of published health research literature by promoting transparent and accurate reporting and a wider use of robust reporting guidelines. [https://www.equator-network.org/about-us/](https://www.equator-network.org/about-us/)
Funding and governance
➢ Sufficient funding is required for TM research.
➢ Respective governments should frame policies to support TM research and undertake guiding and monitoring activities.

Safety
➢ Generate evidence on safety of TM medicines and approaches.
➢ Register and study of drug interactions/pharmacovigilance.
➢ Develop ethical guidelines for conducting TM research.

Research on therapeutic procedures
➢ Develop standard operating procedures for all instruments and preparations used for procedures.

Data management
To develop standardization and data management systems that facilitate access to evidence-based traditional medicine practice and research, the following initiatives are suggested:
➢ Patient and disease registries for TM treatment outcomes, use consistent terminology for TMs and relate to ICD-10 disease codes (standardization).
➢ Collect data of specific TM health programmes.
➢ Central repository for data from TM-related government surveys.
➢ Develop an independent clinical trials registry for TM for respective countries/SEA Region.

Technology
➢ Use new diagnostic tools and biomarkers and integrate technology with TM where feasible, e.g. pulse examination gadgets, which might be useful for standardization and research methodology.

Recommendation for revision of WHO–TM clinical research guidelines
Dr Tamas Paal pointed out that WHO 2000 guidelines for research in TM are quite old and these need to be revised in many respects. Guiding principles recommended were:
➢ Reduce vague words and terms to bring precision.
➢ Generalized statements and repeated content can be avoided.
➢ The focus has been on herbal medicine in the guidelines and not on traditional medicine.
➢ The rising quest and demand for TM lead to evidence demand.
➢ Transdisciplinary research is increasing, so this component needs to be incorporated in the present guidelines.
➢ Update to include research methods on the “black box” approach, whole system research and the Delphi technique.
Group discussions

Following these presentations, Member countries worked in groups to discuss four topics. Four groups were announced by the Chairperson for the group discussions. Each group appointed a chair and rapporteur from among its members to present a report at the end of the discussions.

Group 1: Collaborative research in TM

Professor Anchalee Chuthaputti of Thailand, was the chairperson and Dr Mohamed Zaid of Maldives was the rapporteur. Dr Zaid presented their recommendations on collaborative research in TM. This group prepared and presented a three-year workplan and timeline for conducting regional collaborative research on traditional medicine for selected diseases. They also sought help from WHO-SEARO for financial support, technical support, training or capacity-building, knowledge sharing and logistic support.

Group 2: Development of guidelines in TM research and collaboration

Dr Khandaker Sagir Ahmed of Bangladesh was the chairperson and Dr Shyam Babu Yadav of Nepal was the rapporteur. Dr Ahmed presented the following recommendations:

➢ National Ethical Guidelines for the SEA Region Member States may be included as a separate section for TM research. The WHO Regional Office may introduce the advocacy necessary for the need to have a set of separate guidelines on ethics in the context of TM.
➢ The registration system of clinical trials is diverse in different Member countries. WHO SEARO may provide advocacy on the need for clinical trial registry in all Member States.
➢ Each Member State should be required to maintain a research database separately for TM.
➢ Pre-clinical safety requirement of TM approaches and procedure-based therapies should be rational in order to meet the requirement in the context of TM in the SEA Region.
➢ It would be beneficial to set up a mechanism for international cooperation and collaboration for TM research by each Member State to strengthen research and capacity-building.
➢ It would be beneficial to evolve a system such as a research management information system to guide research scholars on various aspects of research (sample size, design, etc.).
➢ All Member States would benefit from establishing portals to document health statistics for TM like the NAMASTE portal in India.

Group 3: Limitations of collaborative research

Dr Khin Phyu of Myanmar was the chairperson and Dr Phuntso Wangdi of Bhutan was the rapporteur. Dr Wangdi presented the challenges for collaborative research:

➢ Member States have different priority areas (non communicable/communicable diseases).
➢ Member States may have differences in TM philosophy or fundamental principles.
➢ Member States are at different levels of expertise and have different training needs (human resources).
➢ Differences in country policies such as intellectual property and Biodiversity Act/guidelines may limit sharing.
➢ Administrative procedures may be different (e.g. drugs, data, samples).
➢ There is a lack of funding available for undertaking collaborative research.
➢ Member States have different levels of availability for personnel, which results in time constraints.
➢ Publications and contributions for authorship would need to be determined on each collaborative piece of research.
➢ Member States have different knowledge levels of modern medicine and TM.

Group 4: Inter-TM Research (AYUSH-Korean-Chinese-other TM) collaboration

Dr Asim Ali Khan of India was the chairperson and Dr Dorji Gyeltshen of Bhutan was the rapporteur. Dr Dorji Gyeltshen presented their recommendations:
➢ Priority research areas for collaboration include cancer, diabetes and mental health. Some Member States would need survey for the prevalence of the diseases mentioned above and the usage of different TM drugs being used for treatment.

This may involve WHO as the coordinating center. An expert group consisting of Members from different countries needs to be established. These expert groups may collaborate on research topics and diseases. Developing common research protocols and supporting each other are necessary.
➢ Identify and reform the policies that will support interdisciplinary activities and research – Institutional Review Board (IRB)/ Institutional Ethics Committee (IEC)/ research ethics board (REB).
➢ Develop research facilities, training and infrastructure.
➢ The outcomes of these collaborative activities would be:
  - High-impact publications;
  - High-quality research;
  - Development of research facilities; and
  - Mutual understanding of strengths and weaknesses of different systems of traditional medicine in the Region.

Group visit

On the third day of the workshop, participants visited the Institute for Post Graduate Teaching & Research in Ayurveda (IPGT&RA) at the Gujarat Ayurved University in Jamnagar.

Participants were divided into two groups and visited the IPGT&RA hospital outpatient department (OPD), the Panchakarma department, the university library, the Ayurvedic manuscriptology, Ayurveda pharmaceutical (Rasashastra and Bhaishajya Kalpana) museum, the medicinal plant (Dravyaguna) museum and lastly, the Rasayana Kuti.

The library of the institute has impressive manuscript collections and is home to valuable literature related to Ayurveda and allied sciences. The total number of manuscripts in the library is about 7350, many of them are related to the Ayurveda system of medicine.
Participants visited the IPGT&RA Hospital and Facilities. The hospital houses eye/ENT OT, labour room, children's procedure room, physiotherapy, modem diagnostics (X Ray, USG, ECG, etc.), along with Ayurveda facilities to undertake traditional medicine procedures such as Panchakarma, Ksharasutra, Kriyakalpa, and Trigarbha Kuti. The hospital runs 15 outpatient departments per day and more than 1000 patients visit the hospital daily. All the medicines provided to patients are being manufactured by the pharmacy of the Gujarat Ayurveda University.

Both groups met at the Rasayana Kuti building. The institute’s director explained to them the details about Kuti, its importance in the Rasayana (rejuvenation) therapy in Ayurveda and so on. Rasayana Kuti is a treatment offered in entire isolation from the outside world, along with ensuring complete rest for the sensory points in the body.

All participants were impressed seeing the benefits of Ayurveda treatment in a real hospital environment.

5. Conclusions

At the end this session, Dr Kim delivered concluding remarks along with recommendations to WHO for enhancing collaboration in traditional medicine research and research capacity-building. It is also recommended that the WHO 2000 General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine be revised.

The valedictory programme started with the speech delivered by Professor M.S. Baghel, following which Dr Manisha Sridhar thanked everyone. At the end of the workshop, vote of thanks was delivered by Professor Anup Thakar.

The Regional Workshop on clinical research methodologies in traditional medicine for the WHO South-East Asia Region made the following conclusions:

1. There is a need to revise the TM research guidelines (2000) to meet current knowledge and advances.
2. Single-arm clinical trials may be adopted to overcome challenges of blinding and placebo group.
3. Whole body system researches may be adopted.
4. Observational studies should be carried out covering large sample sizes/populations.
5. SOPs for procedures and formulations should be designed and practised uniformly.
6. A wise use of statistics and technology may boost the evidence-based clinical research methodology.
7. Lessons learnt from this workshop will contribute to an overall improvement in research methodology in traditional medicine.
Annex 1

Opening address by Dr Poonam Khetrapal Singh,
WHO Regional Director for South-East Asia
at the WHO South-East Asia Regional Workshop on
clinical research methodologies in traditional medicine

It is with great pleasure that I welcome you all to this regional workshop. I also would like
to thank our honourable guests and participants for sparing their valuable time to attend
this meeting.

I would like to take this opportunity to speak briefly about traditional medicine in the
South-East Asia Region, and issues with regard to research in the area of traditional
medicine. As you know, all the Member States in our Region have a long history and rich
heritage of traditional medicine, which is widely used as a means of health-care delivery or
as complement, particularly in the remote and rural areas. Therefore, all 11 countries have
national policies on TCM. Nine countries have formal training and education systems for
TCM practitioners and these countries have TCM practitioners formally employed in the
public sector at the different levels of health system to varying degree, and six out of them
have co-located TCM and conventional medicine services in their health-care delivery
systems at some or all levels of health facility.

According to the recent information of the WHO South-East Asia Region, 70% to 95%
of the population in this Region are using traditional medicine and 10% to 40% of OPD
services in the public health sector are related to traditional medicine service.

During the past two decades, the use of traditional medicine has expanded globally
and gained popularity. It has not only continued to be used as a means of primary health
care of the people in developing countries, but has also been used in the developed
countries where conventional medicine is predominant in the national health-care system.

One of the reasons for the global expansion of traditional medicine is the dramatic
increase in the number of patients with non-communicable diseases such as heart disease,
cancer, diabetes and mental disorders, among other things, due to the widespread adoption
of unhealthy lifestyle, rapid unplanned urbanization and demographic ageing. For these
diseases and for many other conditions, traditional medicine has much to offer in terms of
health promotion, disease prevention and management.

Now, with this global expansion in the use of traditional medicine, safety and efficacy
as well as quality of care of traditional medicines have become important concerns for both
health authorities and the public, and research becomes more and more important in
proving their efficacy and safety.

Currently, the scientific approach to plant-based traditional medicines is often to
purify them into a single component and to try to explore or to prove its pharmacological
actions, its safety and efficacy through in vitro pharmacological studies or clinical trial and
research. This is simply modern drugs discovery in plants. However, many traditional
medicines usually include complex mixtures of plants or extracts in accordance with
traditional medicine theories that support the use of combined/mixed medicinal materials
and traditional procedure-based therapies, such as Panchakarma, yoga, acupuncture,
moxibustion, cupping, Tuina, Taiji, Qigong, etc. for the purpose of promoting a balanced
environment in the body and stimulating/boosting own body defence system against
pathogens. These theories are rarely known by modern scientists and, due to differences in
approaches to health between traditional and conventional allopathic medicines, evaluating and conducting research on traditional medicine presents a great challenge and difficulty to all concerned.

In order to overcome these challenges, since the early 1990s, WHO has developed a series of guidelines. These include guidelines for the assessment of herbal medicines developed in 1991, a guideline for evaluating the safety and efficacy of herbal medicines developed in 1993, a guideline for clinical research on acupuncture developed in 1995, WHO QOL (quality of life) user manual developed in 1998, and, most importantly, the guidelines titled General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine developed in 2000.

Moreover, in several WHO meetings and congresses during the past decade, the Organization urged Member States to share their best practices and experiences in research and development of traditional medicine that provide the evidence base for the safety and efficacy of traditional medicine and to develop the appropriate protocols for clinical study on efficacy and safety of traditional medicine.

The WHO Traditional and Complementary Medicine Strategy: 2014–2023 has set up the goal to support Member States in promoting safe and effective use of traditional medicine through regulation and research.

In other words, research and development in traditional medicine is part of WHO’s global strategy and plan of action on public health, innovation and intellectual property adopted at the World Health Assembly as well as one of our regional traditional medicine programme priority areas identified at the regional workshop in October 2015.

In response to the global demands and requests for traditional medicine and the research challenges it faces, this meeting is timely indeed.

Validation of the efficacy and safety of traditional medicines requires special research methodologies, rather than the simple application of modern medicine research methodologies.

I hope this workshop will provide opportunity to share country experiences and to learn new development so as to lead to strengthened research capacity for Member States with good recommendations for further strengthening clinical research capacity in traditional medicines through regional collaboration, while providing health authorities concerned and researchers with clearer objectives and directions for future research in traditional medicine.
Annex 2

Agenda

(1) Opening session
(2) Introduction to WHO General Guidelines for Methodologies on Research and Evaluation
(3) Challenges, achievements and gaps in traditional medicine research in SEA Region countries
(4) Research methodology in traditional medicine: Guidance and examples
(5) Research in traditional medicine: Project lifecycle and a roadmap
(6) Research methodology for clinical trials: Design, whole system research, patient reported outcomes, quality of life
(7) Research methodology for traditional procedures
(8) Research methodology for observational studies
(9) Research biostatistics
(10) Group work: Scope and fields for collaborative research activities in traditional medicine
(11) Closing session
Annex 3

List of participants

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Regional workshop on clinical research methodologies in traditional medicine for the WHO South-East Asia Region

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Regional workshop on clinical research methodologies in traditional medicine for the WHO South-East Asia Region

Report of the regional workshop

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