

## Study Protocol

### **Efficacy of Ayurveda Interventions specifically on weight gain in the Management of Protein Energy Malnutrition in Children: A Systematic Review Protocol**

#### **ABSTRACT**

**Background:** In India, Protein Energy Malnutrition (PEM) remains a significant and challenging public health issue despite implementing different nutritional policies over the period. It is also accompanying with aggravated risk of all-cause morbidity, as well as fatality. Ayurveda mentions about various nutritional disorders such as *karshya*, *balashosha*, *phakka*, *yakshma* which are having similar symptomatology and treatment approach as that of the PEM. Several clinical studies have been conducted and some are under trial but systematic review is still pending to explore an effective treatment modality to combat PEM in Children. **Aim:** A systematic review to evaluate the efficacy of Ayurveda Interventions specifically on weight gain in the Management of Protein Energy Malnutrition in Children.

**Materials and methods:** A systematic review which will evaluate published clinical work of Ayurveda treatment modalities specifically for weight gain in the management of PEM in children that will involve “The randomized controlled trials (RCTs), multiple-arms clinical trials, quasi-experimental trials, observational studies (case series and case reports) through databases like PubMed, COCHRANE, AYUSH Research Portal, DHARA; Google Scholar; etc. and Ayurveda compendia to fetch complete available literature.” **Observations and**

**Discussion:** The work of selection of the studies, data extraction, and synthesis will be taken up. Established guidelines for study selection, quality assessment, and narrative synthesis will be followed. Risk of bias assessment will be performed. A protocol will be designed that will ensure transparency for the completed review. Results of the study will be elaborately synthesized. The data will be presented in percentage, count and frequency; and if we find the data to be sufficiently homogeneous then meta-analysis will be carried out.

**Conclusion:** The results obtained from this systematic review will be useful in identifying the evidence-based efficacy of Ayurveda interventions on weight gain in the Management of PEM. It will also provide substratum for future research studies for generating good-quality evidence that can be helpful to design new health policy to combat PEM effectively.

**Keywords:** PEM, children, weight gain, *Karshya*, Systematic review protocol.

**Introduction:** Protein-energy malnutrition (PEM) (International Classification of Diseases 10: E44), remains a significant and challenging public health problem among paediatric age group in developing country like India in spite of implementing different nutritional policies to

overcome it. The global scenario estimates that 161 million children under five-year of age are suffering from malnutrition and this condition is worsening in India which is densely populated and a developing country [1]. According to latest National Family Health Survey 4 (NFHS-4), it has revealed that in India 7.5% of the under 5 children are severely wasted, 38.4 % are stunted & 35.7% are underweight, representing 31% and 43% of all the developing world's burden, respectively [2]. Millions of children are affected by malnutrition, some get disabled while for some it turns out to be life threatening. It often causes many diseases and disability in the survivors and restricts millions of children from conquering their growth, development and fullest of intellectual capabilities [1,2].

The World Health Organization (WHO) defines PEM as range of pathological conditions arising from coincidental lack in varying proportions of proteins and calories, occurring most frequently in infants and young children, and commonly associated with infection [3].

The Government of India has been putting in incredible efforts under the various nutritional programs like ICDS, (<https://icds-wcd.nic.in/guide.aspx>) [4], VDC, etc. for malnourished children. Due to these efforts a decrease in the cases of malnourished children has been seen over the years, but still India has highest burden of PEM as compared to other developing countries.

Emaciated clinical condition of malnutrition closely resembles to *karshya* [5-6], *balashosha*, *kuposhanajanyavyadhi*, *phakkaroga*, *shosha* [7], *yakshma* as mentioned in the classical texts of *Ayurveda* alongwith their management. Hence the same line of treatment can also be followed for the management of PEM [8]. In all the above specified conditions common pathophysiology is mainly vitiation of *vata* dosha [9], *agnimandya*, accumulation of *ama* and *rasavaha srotorodha* resulting in *uttarottara dhatukshaya*. To manage it the drugs which have *vatashamaka*, *amapachaka*, *deepana*, *brimhana*, *srotoshodhana*, *dhatu poshaka* and *rasayana* properties should be used, which will provide nourishment to the dhatus, and ultimately beneficial in treatment of PEM [10].

Under nutrition is a condition developed due to loss of nutrients, lack of supplementation and absorption of food and other contributing factors such as poverty, ignorance and false beliefs, low birth weight, poor personal hygiene, low availability of health care facilities, repeated infections like, pneumonia, diarrhea, anorexia, low food intake, inadequate breastfeeding, delayed complementary feeding etc. [11] Under nutrition also refers to malnutrition and is classified into 3 groups, Underweight, Stunting and Wasting. Underweight means low- weight –for- age, Stunting denotes low-height-for-age and wasting means low-weight-for-height. PEM-protein energy malnutrition among children in developing country like India remains a challenging public health problem in spite of implementing different

nutritional policies to overcome it [12]. It is also associated with increased risk of morbidity, as well as fatality due to different diseases in children. Increasing incidences and by observing consequences of children affected with PEM, it has been a serious problem, affecting their growth & development. Ayurveda also explains various nutritional disorders where management principles are Deepana, Pachana and Brumhana [13].

However, till date, no comprehensive systematic review has been undertaken to assess the quality of studies published and clinical efficacy of Ayurvedic treatments. Hence, the present systematic review is undertaken to explore the role of Ayurveda interventions specifically for weight gain in the management of PEM in children.

**Review Question:** Are Ayurveda interventions effective specifically on weight gain in the Management of Protein Energy Malnutrition in Children?

**Objectives:**

- To evaluate the efficacy of Ayurveda interventions in the Management of Protein Energy Malnutrition in Children
- To evaluate the effect of Ayurveda Interventions specifically on weight gain in children suffering from PEM.
- If a large number of clinical trials with homogenous data are available, meta-analysis will be performed

**Materials and Methods:** This systematic review protocol has been designed following the PRISMA-P (preferred reporting items for systematic review and meta-analysis protocol) statement guidelines.[14].

This systematic review will be performed using the principles of The Cochrane Handbook for Systematic Reviews of Interventions,[15]. Patients will not be enrolled in any phase of the study.

**Inclusion Criteria:**

- The review will include “randomized controlled trials (RCTs), controlled clinical trials (CCTs), parallel-group trial, and multiple arms clinical trial, case-series, case reports. Postgraduate and PhD dissertations and other unpublished clinical data if it contains sufficient data for critical evaluation.”
- There will be no restriction with respect to language, if the study is in any other language other than English, then original authors will be contacted, or an attempt will be made to find a translation of the manuscript. Before the final analysis, search will be rerun & further studies will be reanalysed for inclusion.

**Exclusion Criteria:**

- Non-randomized controlled trials, quasi randomized controlled trials & trials that do not offer detailed results will be excluded from the study.

**Type of Participants:** Studies with participants of both sex between 6 months to 6 years having classical signs and symptoms of *karshya*, *balashosha*, *phakka*, *yakshma*, *kuposhanajanya vyadhi* as explained in various classical texts of *Ayurveda* & Protein Energy Malnutrition will be included. Studies including Patients having PEM with Grade I and Grade II as per the WHO standards (MAM and Uncomplicated SAM) will be included [16].

**Type of Interventions:** Ayurveda treatment advised for *karshya*, *balashosha*, *phakka*, *yakshma*, *kuposhanajanyavyadhi* as per the classical text of Ayurveda precisely in the form of *Samshamana* and/or *Shodhanakarma* line of treatment. In this study, Ayurveda treatment which mainly comprises of any internal or external application of herbal, mineral, poly-herbal, Herbo-mineral drug: single or compound, described in classical Ayurveda literature or a novel drug with ingredients described in Ayurveda texts.

**Type of Comparators:**

Ayurveda treatment with any form of drug, respective dosage form, dose, schedule, treatment other than Ayurvedic interventions, or combination of both i.e., Ayurvedic and non-Ayurvedic interventions, conservative treatment, placebo/ sham therapy, waitlist controls, no treatment.

**Types of Outcomes**

**Primary Outcomes**

- Improvement in cardinal features of *karshya*, *balashosha*, *phakka*, *yakshma*, *kuposhanajanya vyadhi*/PEM specifically on weight gain.
- Consequent shift/transition of children from SAM to MAM to normal category.

**Secondary Outcomes**

- Improvement in Laboratory parameter such as Serum protein values.
- Improvement in other anthropometric Parameters
- Improvement in morbidity specifically, time to recovery, hospitalizations during the treatment phase.
- Number of participants withdrawn from the clinical study due to ineffectiveness or adverse event of treatment.

**Data Sources:** List of electronic databases that will be searched: "Medline via PubMed, Cochrane Library (Cochrane Central Register of Controlled Trials), INDMED database, AYUSH Research Portal (Government of India). Manual search in central and departmental

libraries of Institute for Post Graduate Teaching & Research in Ayurveda(IPGT&RA)and Ayurveda Research Database by Prof MS Baghel.” References gathered from the manuscripts searched through electronic database; and a thorough snowballing of the studies will be carried out to extract all possible data. Author or Authors will re-evaluate the search before the final analyses is made and further studies will be reanalysed for inclusion.

**Search Strategy:** An Attempt will be made to search all relevant clinical trials available online and off-line published till date. The list of electronic database that will be searched online through databases like “PubMed, COCHRANE, AYUSH Research Portal (Govt. of India), DHARA, Google Scholar, CAM databases, HerbMed, Scholarly exchange, Free Medical Journals data base, official publications (journals) of various Indian societies / associations, NISCAIR project register, IndMED, for ongoing trials- clinical trial registry of India- ctri.nic.in, Baghels thesis list- researches in *Ayurveda*, ARD, Conference proceedings/ reports/ compendia and hand searches to fetch complete available literature which will include selected journals of Ayurveda including the Journal of Research in Ayurveda and Siddha, Journal of Ayurveda, Ancient Science of Life, Journal of Drug Research in Ayurvedic Sciences, and AYU (an International Quarterly Journal of Research in Ayurveda)” to aid the electronic search. Later the bibliographic references of all the trials included will be reviewed to identify other studies relevant to weight gain in children suffering from PEM. Authors of the trial studies and experts in the field will be contacted as and when required.

The key terms will be searched relating to or describing the intervention “Ayurved,” “Ayurveda” in combination with search term describing condition of the disease “*balashosha*”, “*karshya*”, “*kuposhanajanyavyadh*”, “*phakkaroga*”, “*shosha*”, “*yakshma*” “PEM.” Specific filters will be used to search terms in database search by adaptation. The following search algorithm will be adopted [“AYUSH” OR “Ayurvedic medicine” OR “Medicine, Ayurveda” OR “Ayurved” OR “Ayurveda” OR “Ayurvedic” OR “Ayurvedatherapy” OR “Ayurvedaintervention” OR “Ayurvedic drugs” OR “Ayurveda Herbs” OR “Ayurveda Plants” OR “Ayurvedic Formulation” OR “Ayurveda Panchakarma” OR “ Basti” OR “*Santarpana*” OR “ *Brimhana*” OR “*Rasayana*” OR “CCRAS” OR “INDIAN TRADITIONAL MEDICINE”, OR “*Kaumarbhritya*” OR “*Balaroga*”] AND [“PEM” OR “pem” OR “Protein Energy Malnutrition” OR “CHILDREN” OR “CLINICAL TRIAL” OR “WHO” OR “IMMUNO-MODULATOR” OR “INDIAN ACADEMY OF PAEDITRICS” OR “Weight gain in Children” OR “ Anthropometry” OR “ Serum Protein” , OR “Z Score” OR “SAM” OR “MAM” OR “ICDS” OR “SUPPLEMENTARY NUTRITION PROGRAMME”] as title/abstract/keyword.

### **Data Collection and Analysis**

Data Management - Once the data is extracted from all the available sources, it will be kept secured. A copy of the data will be stored in an external data storage device and to google drive. Only authors of the present systematic review will be permitted to access the data.

Selection of Studies: Three of the review authors (SK,RR,BR), will be ear-marked to assess titles and/or abstracts of studies reanalysed using the search strategy and those collected from other additional sources. After excluding duplicates from eligible articles, full-text articles will be screened thoroughly to determine whether they fit into the inclusion and exclusion criteria as stated above. Any contradiction faced to decide the eligibility of particular studies will be resolved through discussion with reviewer (HH). If any of the essential data is found missing/or incomplete/unclear or to be sought from particular study, trial author will be contacted via e-mail or telephone for getting exact details. If records are unable to be obtained from the concerned author, the study will be discarded. Discarded/excluded studies will be documented with justified reasons for their omission. The selection process details for the study will be shown in Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.

#### Data Extraction/Collection

Three reviewers (SK, RR, BR) will do screening for the eligibility of the searched studies individualistically based on inclusion and exclusion criteria. PICO format will be followed to extract data from the included studies. If the available data is incomplete or unclear, the corresponding author of the clinical trial will be contacted to get the exact information or for further clarification.

**Risk of Bias (Quality) Assessment:** The study methodology of included randomized controlled trials (RCTs) will be assessed by using revised tool available online (RoB 2) for the assessment of the risk of bias of randomized trials [17]. A pre-defined algorithms will be followed to assess five domains of each study, i.e., randomization process, deviations from specified interventions, deleted outcome data, measurement of the primary and secondary outcome, and selection of the enlisted results. In case of any disagreement, it will be resolved by discussion.

**Data Synthesis:** meta-analysis will be done if sufficient studies are found homogenous with studies related to weight gain in children suffering from PEM. For dichotomous data, risk ratio will be used with 95% confidence interval the treatment effect will be measured by calculating the mean difference for continuous outcomes measure. For trials with Heterogeneity, it will be assessed by statistical chi-square test and using the I<sup>2</sup> statistic. Heterogeneity will not be considered if I<sup>2</sup> < 50%, whereas significant heterogeneity can be considered if I<sup>2</sup> ≥ 50%. Random-effects model will be used if significant heterogeneity is

observed in clinically meaningful studies for combination of studies. Fixed-effects model will be used in case of insignificant statistical heterogeneity. Meta-analysis will be conducted using available software tools to minimize the errors. If meta-analysis is not possible due to unavailability of homogenous trial, results will be summarized as systematic qualitative synthesis [18].

**Ethical Clearance:** Formal ethical assessment and approval is not required for this review, as no intervention will be carried out on individual or confidential participant.

**Result:** (PRISMA) guidelines will be followed for Reporting of the results of systematic reviews and meta-analyses. Further publication will be done in an indexed, open-access peer-reviewed journal. Presentation will be delivered at various national and international symposiums to ensure wider propagation of the study.

**Discussion:** After thorough search it was found that, no systematic review has been carried out to study the effectiveness of Ayurveda intervention in children suffering from PEM specifically on weight gain. In 2018, 40% children were underweight (Severe 14%, Moderate 26%) and 34% were stunted (severe 13%, moderate 21%). Prevalence was higher among boys in Wardha district, Maharashtra of India, also boys were more stunted than girls (boys 40%, girls 28%) [19]. Many studies aimed to reduce the percentage of PEM (*Karshya*) among pre-school children. Illiteracy, poverty of family and variable food habits, changes in diet, life style of present era of pre-school children are some common causative factors of *karshya* [11]. The symptoms of PEM are much similar to that of *Karshya* as both have malnutrition as a root cause. Ayurveda states that excessive nutritional supplement without proper digestive capacity can also lead to malabsorption of nutrients by suppressing the appetite [20]. Previous studies provide insight on the importance of *Deepana* and *brumhana* effect of Ayurveda interventions rather than only providing nutritional supplements [21].

The present best available management followed in nutritional programmes launched by Government of India is standard diet therapy including feeding of energy dense and protein rich food [4]. The recovery with diet is gradual, with minimal significant change in morbidity [22,23]. Thus, it is the need of the hour to standardize and implement an effective management protocol having prompt recovery which can help children suffering from *karshya*, *balashosha*, *kuposhanajanya vyadhi*, *phakkaroga*, *shosha* and PEM without leading to any further complications. In the recent years multiple studies have been conducted in the field of Ayurveda on PEM and significant results have been found in terms of efficacy. Anabolic, bioavailability enhancer, good source of energy and having micronutrients (Nutritive values are 200.6 cal/100 g) immunomodulator, anti-infective, nootropic appetizer and *Rasayana* and these pharmacological actions which are essential in breaking pathogenesis of PEM [24-25].

Ayurveda interventions are safe, cost effective, palatable with add on effect of appetizer as compared to only diet therapy. So, it is expected for speedy recovery due to better absorption[26].

This systematic review will draw an inference for evidence-based effectiveness of Ayurveda treatment and will help to generate database to explore further areas of research. The proposed protocol can be used as a substratum for regenerating same results in a scientific manner for the systematic review of PEM in children. We will be strictly adhering to PRISMA-P guidelines while executing the systematic review[14].

The systematic review publication will be a torch bearer to researchers for further studies. An awareness module can be prepared to prevent *Karshya, balashosha, phakka, yakshma, kuposhana janya vyadhi* and PEM. If the outcome is promising then Ayurveda interventions can be publicized as cost effective, conservative, additive and palliative management for not only chronic but in cases of secondary malnutrition such as CKD, CHD etc., module can be used.

**Conclusion:** The results obtained from this systematic review will be useful in identifying the evidence-based efficacy of Ayurveda interventions on weight gain in the Management of PEM. It will also provide substratum for future research studies for generating good-quality evidence that can be helpful to design new health policy to combat PEM effectively.

#### **COMPETING INTERESTS DISCLAIMER:**

**Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors**

#### **NOTE:**

~~The study highlights the efficacy of " Ayurveda " which is an ancient tradition, used in some parts of India. This ancient concept should be carefully evaluated in the light of modern medical science and can be utilized partially if found suitable.~~

**No need to add this note as it is a false statement**

## References:

1. UNICEF W, Bank W. Joint child malnutrition estimates. 2014.
2. Wankhade K. Urban sanitation in India: key shifts in the national policy frame. *Environment and Urbanization*. 2015 Oct 1;27(2):555–72 p.
3. Parthasarathy A, Menon PSN, Nair MKC. *IAP Textbook of Pediatrics*. Jaypee Brothers Medical Publishers; 2019. 1634 p.
4. <https://icds-wcd.nic.in/guide.aspx> [Internet]. [cited 2021 Mar 5]. Available from: last accessed on 11<sup>th</sup> Oct.2021,4 pm
5. *Sushruta Samhita, Sutrasthana15/48*. Ambika datta Shastri, editor. Chowkhamba Sanskrit Sansthan, Varanasi; 2008. 64 p.
6. *CharakaSamhita,Sutrasthana,21/15*. Y.G. Joshi, editor. 4th ed. vaidyamidra prakashana, Pune, 2009. 271p.
7. *Sushruta Samhita, Uttarantra, 41/10*. Ambika datta Shastri, editor. Chowkhamba Sanskrit Sansthan, Varanasi; 2008. 245 p.
8. *Charaka Samhita, Sutrasthan, 21/29-34*. Y.G. Joshi, editor. 4th ed. vaidyamidra prakashana, Pune,; 2009. 273 p.
9. Rathi R, Rathi B. Management of childhood Protein Energy Malnutrition through Ayurvedic interventions. 2017 Jun 14; 5:196–202 p.
10. OP Ghai, editor-Vinod k Paul.Essential Paediatrics, chapter 5, seventh edition, CBS publishers and distributors New Delhi; 2009, page no. 62.
11. Dongre AR, Deshmukh PR, Sinha N, Garg BS- Acute childhood morbidities in rural Wardha, *Indian J Med Sci*, Vol 63, No.8, Aug 2009; 345-353
12. Khedekar S, Rathi RB, Rathi BJ. A Randomized comparative study on efficacy of *Krishnadi* granules as an adjuvant with ICDS guidelines in management of Protein Energy Malnutrition in preschool children-A protocol Study. *WutanHuatanJisuanJishu*. Dec.2020:XVI(XII):901-910
13. *Sharangadhara Samhita*, Prof.K.R.Srikantha Murthy, 6<sup>th</sup> Edition, Chaukhamba Orientalia, Varanasi, 2006 : p 44
14. Shamseer L. Preferred reporting items for systematic review and and explanation meta-analysis protocols (PRISMA-P) 2015: elaboration. *BJM*; 2015.
15. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. *Cochrane Handbook for Systematic Reviews of Interventions*. John Wiley & Sons; 2019. 726 p.
16. OP Ghai, *Essential Pediatric* editor Vinod K Paul and ArvindBagga, chapter no 7, Nutrition, CBS Publishers &Distributors Pvt Ltd. page no .93-95.

17. Eldridge S, Campbell M, Campbell M, Drahota-Towns A, Giraudeau B, Higgins J, et al. Revised Cochrane risk of bias tool for randomized trials (RoB 2.0): additional considerations for cluster-randomized trials. 2016.

18. Medicine I of, Services B on HC, Research C on S for SR of CE. Finding What Works in Health Care: Standards for Systematic Reviews. National Academies Press; 2011,p. 267<sup>1</sup>

19. Nithya DJ, Bhavani RV. Dietary diversity and its relationship with nutritional status among adolescents and adults in rural India. Journal of biosocial science. 2018 May;50(3):397-413.

20. Kashyap, Kashyap Samhita, chikitsa Sthan gulma adhyaya 8/11, P V Tewari, editor. Delhi: Chowkhamba Sanskrit Pratishthan ;1988

21. Vagbhat, Ashtang Hridya, sutrasthan, chapter 14, shloka 19. Srikantha Murthy, editor. Chowkhamba Krishnadas Academy;2006.

22. Bhavprakash, Bhavmishra, Madhyam, chapter 40 Karshyadikar, shloka 3, BulusuSitaram, editor. Varanasi, ChowkhambaOrientailia 2010.

23 Bhutada R, Rathi R, Dasar D. Immunity boosting diet during Covid 19. IJRPS11(SPL)(1), 832-838

24 J. Krutika, S. Tavhare, K. Panara, P. Kumar, A. Nishteswar. Studies of Ashwagandha (Withania somnifera Dunal). International Journal of Pharmaceutical & Biological Archives 2016; 7 (1): 1- 11

25 Rathi R, Rathi B, Shrihari S, Rajput D. Management of childhood Protein Energy Malnutrition through Ayurvedic interventions. Journal of Indian System of Medicine. 2017 Jul 1;5(3):196

26 Masram P, Patel KS, Kori VK, Rajgopala. A Critical Review on Pharmacodynamics of Paushtic biscuits in the management of Karshya. Int J Res in alter Med 2014; 1(4):79-90