NHSRC

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Compendium of

Health Technology Assessments

An evidence-based approach
to technology-related policy making in health care

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to technology-related policy making in health care

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National Health Systems Resource Center, New Delhi and Healthcare Technology Innovation Center- IIT Madras in technical collaboration with WHO Country Office for India have conducted three fellowship programmes on Health Technology Assessment yearly over the last three years. The participants from each program are required to do a project work and submit it to the HTA secretariat. The reports in this compendium are HTA projects completed by the participants of past fellowship programme. Although, more assessments are underway, the technologies chosen are those for which data was appropriate and adequate, and an initial assessment was undertaken. The selection of topic was made based on interest of candidates and availability of technical resources and data pertaining to respective technologies. Effort has been made to exclude bias, if any. Interpretation of results of analysis rest with the readers and reports may be considered only as directional guidance. The assessments performed here are based on current available evidence from scientific literature and incase during the process of assessment or in future, more evidence gets added, the conclusions of the assessments may change. It is also necessary to have contextual requirements be applied to make technology application more practical and feasible. The technical assessments do not suggest use of any specific brand or trademark associated with any technology.

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सत्यमेव जयते
डॉ विश्व मोहन कटोच
एम डी, एफ एन ए एससी, एफ ए एम एस, एफ ए एससी, एफ एन ए
सचिव, भारत सरकार
(स्वास्थ्य अनुसंधान विभाग)
स्वास्थ्य एवं परिवार कल्याण मंत्रालय एवं
महानिदेशक, आई सी एम आर
Dr. Vishwa Mohan Katoch
MD, FNASc, FAMS, FASc, FNA
Secretary to the Government of India
(Department of Health Research)
Ministry of Health & Family Welfare &
Director-General, ICMR

भारतीय आयुर्विज्ञान अनुसंधान परिषद
(स्वास्थ्य अनुसंधान विभाग)
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
वी. रामलिंगस्वामी भवन, अंसारी नगर
नई दिल्ली - 110 029 (भारत)

Indian Council of Medical Research
(Department of Health Research)
Ministry of Health & Family Welfare
V. Ramalingaswami Bhawan, Ansari Nagar
New Delhi - 110 029 (INDIA)

FOREWORD

Health Technology Assessments have become increasingly useful, providing evidence on clinical benefit, cost effectiveness, social, legal and regulatory insights leading to identification and uptake of appropriate and safe technologies such as bio-pharmaceuticals, medical devices, implants, drugs and therapeutic practices.

National Health Systems Resource Centre (NHSRC), New Delhi has been playing a key role in conducting HTAs for various interventions. In terms of capacity building NHSRC and Health Technology Innovation Center- IIT Madras has been jointly conducting one week fellowship programs in which more than 200 professionals have been trained over last two years. This is by far, a pioneering work in the country in the domain of Health Technology Assessments. Several important themes on which HTA has been conducted includes – Use of Mammography; Modalities of mechanical ventilation; Handheld Ultrasonography; Home based dialysis; Role of multi-vitamin in ante-natal period; Non-pneumatic anti shock garment for prevention of obstetric hemorrhage, Smart cane for the blind, Diagnostic test for thalassemia, Use of oxygen concentrators, Indigenous heart valve, Mobile eye surgical unit, Diagnostic accuracy of magnetic resonance imaging technologies, among others. These themes cover a wide range of areas important for selection of evidence based technologies and have a crucial role to play in attainment of Universal Health Coverage. I complement the team of researchers who have achieved this success in establishing and propagating health technology assessments in India.

The results published in this compendium should be taken as directional guidance and if required more context specific evaluation should be done by health agencies and units which can adopt the technologies duly assessed in this report. I hope NHSRC would continue to pave the way forward in bringing the evidence based methodology of HTA to the forefront in practice and decision making. Department of Health Research, Ministry of Health & Family Welfare is in the process of establishing regulatory mechanism in Govt. for institutionalizing such efforts. We consider NHSRC a valuable partner and assure our enduring support in this endeavor.

(V. M. Katoch)

Tele. : (Off.) +91-11-26588204, 26589620; Fax (Off.) : +91-11-26588662, E-mail : secydhr@icmr.org.in; dg@icmr.org.in

Preface

I am pleased to introduce the 'Compendium of Health Technology Assessments (HTA) Assessments - An evidence-based approach to technology-related policy making in health care'. The report highlights the most essential health technologies required today for responding to India's disease burden. Jointly developed by the National Health Systems Resource Centre (NHSRC), New Delhi and the WHO Country Office for India, the compendium is a step towards filling the technology gap in the public health sector.

The purpose of this report is also to highlight the contribution that HTA can make to promote informed technology-related policy-making in health care, and perhaps inclusion of HTA in our health systems, particularly in developing and emerging countries.

This compendium is an outcome of the fellowship programme organized by NHSRC and WHO India in 2012-2013. I would like to especially acknowledge NHSRC's role as a premier body in assessing HTAs for various health care interventions.

HTA assessment is essential for evaluation of clinical benefit, cost effectiveness, ethical and regulatory aspects leading to identification and uptake of safe and appropriate technologies.

It is heartening to note that more than 200 professionals have been trained over the last two years under the HTA fellowship programmes under the aegis of the Healthcare Technology Innovation Centre (HTIC), a joint research and development initiative of the Indian Institute of Technology (IIT Madras) and Department of Biotechnology (DBT), Government of India.

To address the unmet need for affordable and accessible healthcare technologies in the country, this fellowship brings together engineers, researchers, healthcare professionals, industry experts, and government to form a vibrant and fertile innovative ecosystem for HTA.

The outcome of the last HTA fellowship programme was to develop assessment reports on 12 specific technologies; these are part of this compendium. These technologies have the potential to play an important role in improving public health, enhancing the quality of life and advancing the agenda of universal health coverage.

I hope that the reports in this compendium will serve as a useful source for directional guidance and can be used by health agencies for more context specific evaluations. I again congratulate NHSRC in bringing the evidence-based methodology of HTA to the forefront and in practice.

Nata Menabde
WHO Representative to India

Acknowledgement

Health Technology Assessment (HTA) has been used as an input to evidence based policy framework in healthcare across several countries. The comprehensiveness with which an HTA process evaluates a healthcare technology includes clinical effectiveness, cost-effectiveness, legal, ethical and social dimensions. Universal Health Care being the cornerstone of health policy framework requires robust assessments to prioritize uptake of healthcare technologies in a cost –effective and comprehensive manner.

National Health Systems Resource Center has been undertaking pioneering work in HTA for several technologies as well as in capacity building. As a part of this effort fellowships training programs have been organized in collaboration with Healthcare Technology Innovation Center, Chennai and the WHO Country Office for India. The experience has been enriching and outcome outstanding. A series of HTA reports have been compiled for greater understanding of healthcare technologies. As we continue to move forward in this direction, it is much appropriate to congratulate and acknowledge the team of researchers, whose efforts find fulfillment in the form of this report.

The assessments were conducted under overall supervision of Jitendar Sharma, Head-Division of Healthcare Technology, NSHRC and reviewed by Prakesh Shah, Professor Departments of Paediatrics and Institute of HPME University of Toronto; Shankar Prinja, Assistant Professor, Health Economics PGIMER Chandigarh - School of Public Health; Madhur Gupta, Technical Officer, WHO Country Office for India and Mohanasankar Sivaprakasam, Director, HTIC-IIT Madras. We are thankful to the contributors of assessment reports, which include Kavita Kachroo, Akriti Chahar, Meenu Sharma, Thaigainathan, Siraja Nair, Yugandhar Pothula, Binoy S. Babu, Vatsal Chhaya, Mohammed Ameel, Shailesh Sharma, and Aparamita Singha. Secretarial assistance of Manju Bisht and Amit Arora is gratefully acknowledged. We hope the compendium would be useful in technology identification, uptake and promote greater access to evidence based technologies.

Dr. Sanjiv Kumar

Executive Director

Executive Summary

Health Technology Assessment (HTA) could be utilized in three prominent ways. First is for evaluating a technology that is being considered for uptake into practice –at the level of healthcare facility or in regional/ national health programs. Second, is for evaluating impact of a technology that has already been adopted. Third is to inform better designing of a technology itself- a process known as early HTA. As a methodology HTA could be either comprehensive or a rapid assessment. Generally, an HTA covers all necessary elements that could have a role in technology application and its impact, including clinical efficacy, cost effectiveness, legal, social and ethical dimensions. The HTA process adopted in this compendium includes all the above themes. It additionally includes a health systems integration model in which the possible pathways of technology adoption have been suggested. The technologies reviewed in this compendium along with few specific suggestions that evolved as outcome of assessments are summarized below:

a. **Non-pneumatic anti-shock garment (NASG):** Maternal mortality has been a long standing challenge to health systems. Any technology that could have a positive impact on reduction in maternal mortality is a welcome and much awaited answer. Post-partum hemorrhage (PPH) contributes to 29.8% of all maternal deaths. Evidence shows that use of NASG could reduce PPH associated maternal mortality by 59% leading to saving of 8424 lives in current Indian scenario. At current cost of technology (Rs.3000 equivalent to $30 approx.) it leads to a cost of Rs.1424.5 per life saved. Being an extremely cost effective intervention, it is suggested that NASG be made a part of device kit for Ambulances based emergency care services.

b. **Handheld Ultrasonography (HHUS):** As a diagnostic technology, handheld ultrasonography gives values of positive likelihood ratio and negative likelihood ratio of 17 and 0.095 respectively which favour its use as a supportive technology for clinical diagnosis. Cost/test using HHUS device is one fifth of what could be for a traditional ultrasonography machine primarily due to difference in equipment costs. Concern is however, the decline sex-ratio is India and increasing sales of HHUS devices. India brought in place an Act prohibiting pre-natal detection of sex (PNDT Act). Hence to promote compliance of technologies capable of determining sex, it is suggested that HHUS should not be allowed for unregulated sale. Given the current circumstances where Drug Regulator in India does not regulate all medical devices, it is suggested that HHUS be provided with an inbuilt GPS/GPRS systems to track location of its use and be registered at the PNDT cell to eliminate any misuse of HHUS technology.

c. **Oxygen therapy in COPD patients and use of oxygen concentrators:** 'Primary and secondary prevention in COPD and bronchial asthma, with provision of follow up care in patients put on treatment by specialists' again being assured under the National Health Mission calls for wider look in selection of technologies for long term oxygen therapy- a much required intervention in COPD patients. Given the inadequate infrastructure of oxygen gas pipelines and dependency on oxygen cylinders, assessment of oxygen concentrator – electrically powered oxygen delivery mobile equipment was performed to explore it's appropriateness as a supplement to piped oxygen systems in facilities that have piped systems and as a substitute in those that do not have any existing oxygen supply systems. It is an encouraging finding that use of oxygen concentrators could reduce mortality by 30% compared

to conventional oxygen therapy. The use of concentrators could also leads to a cost saving of Rs.8/per patient/per day in patient population that requires long term oxygen therapy.

d. **Home hemodialysis systems:** It is reported that number of new cases of End stage renal disease (ESRD) is 2, 20, 000 whereas deaths due to ESRD is 2, 00, 000 per annum. One of the reasons is that only 55,000 patients which is only 25% of patient population. The supply if hemodialysis in India (including public and private facilities) is about 1.65 Crore (1 Crore= 100 Lakhs, 1 lakh =100, 000) and the demand is to the tune of 3.432 Crore per year. 52% being the shortage in supply and clustering of existing dialysis facilities in urban areas provides a way for identification of other potential technologies. One such is home based hemodialysis and technologies that enable it. Primarily due to reasons of infections, evidence shows that home based hemodialysis could reduce mortality by 35% compared to hospital based hemodialysis. It could also bring greater access to 1, 65, 000 patients suffering from ESRD and current have no access to dialysis. At Rs.63, 800 per QALY gained (less than 1 GDP per capita per QALY gained) home based hemodialysis could be a very cost effective intervention to provide greater access of dialysis to ESRD patients.

e. **Diagnostic Tests for Thalassemia:** Several technologies being available for diagnosis of Thalassemia, it is important to know the respective specificities as well as comparative cost effectiveness. Reverse Dot Blot Hybridization method is, based on evidence assessed in this report, the optimal method. Using this technology, if screening is done, the cost of treatment: prevention ratio would be 4:1, thereby making a strong case for well-planned thalassemia screening program.

f. **Smart cane for visually challenged:** White cane used by visually challenged gives a sense of obstacle that is placed horizontally. Smart cane is designed to help users detect obstacles above knee-level and can detect them up to a distance of 10 ft. The innovative device consists of an ultrasound device mounted on an ordinary white cane. As per the results of pilot studies, Smart cane gives reduction collision index by 93.53% compared to 4.67% given by traditional white cane. Empirical evidence suggests that it is twice more cost effective a technology than white cane.

g. **Auto-disposable syringes:** It is estimated that 3-4 billion syringes are used annually in India with 7.8 million persons suffers from diseases due to unsafe injections. Thus 0.195% of all injections lead to infections due to unsafe practices. There is a role of auto-disposable injections that could be explored to reduce needle stick injuries among healthcare workers as well as transmission among patient groups. Cost difference between the two technologies being very small, introduction of auto-disposable syringes could lead to a very positive cost-effectiveness ration. The market availability of auto-disposable syringes in all sizes and needle gauges needs to be explored.

h. **Iron fortification of drinking water:** Evidence on the subject is available from clinical studies since 1994, and a meta-analysis of available evidence shows that Hemoglobin in non-fortification group is lower by 0.79mg/dl compared to fortification group. The coverage of this intervention could however cost Rs, 1 lakh/per state/day. Solubility of iron is also a challenge and excess amount of iron in body could result in serious health conditions. It is therefore suggested that controlled trials and more evidence is required before considering iron fortification of drinking water as a public health intervention.

i. **Role of multi-micronutrient (MMN) in ante-natal period:** Pharmacologically, a multi-micronutrient pill has iron, folic acid along with several other minerals such as zinc, vitamins B complex, C and D. The evidence from studies analysis in this report suggests that if MMN be provided in ante-natal care instead of Iron-folic acid, risk of low birth weight in new born could be reduced by 14%. Given that 35% of neo-natal deaths are characterized with low birth weight, a reduction of 14% in low birth weight population could lead to an aversion of 6742 to 33, 712 neo-natal deaths at different levels of MMN coverage among the target population. India being a leader in generic drug manufacturing,

cost of MMN may be the same or slightly higher than current cost of IFA. It could be cost-effective intervention if MMN be provided instead of just IFA in ante-natal programs.

j. **Magnetic Resonance Imaging (MRI):** MRI is considered as a superior alternative to radiography for visualization of lesions and vasculatures and also safer since ionizing radiations is not used in MRI, unlike radiography and CT imaging. There are however, complex judgments involved in selected the appropriate type of MRI among what is available. Market has witnessed introduction of MRI, progress to 1.5 Tesla MRI and thereafter 3.0 Tesla and so on. Positive likelihood ratio of 16 and negative likelihood ratio of 0.38 suggests that the specificity of 1.5T MRI is quite appreciable and decision to upgrade to higher versions of MRI such as 3.0T may not necessarily find substantial evidence in common health facilities, unless the purpose is medical research. Given the substantially higher costs of MRIs with increase in magnetic field, it is suggested that although research institutions may opt for MRI with magnetic field greater than 1.5T, for most government medical colleges, district hospitals and any project of government under PPP mode with private providers of MRI services, 1.5 Tesla MRI would suffice patient requirements.

k. **Use of Mammography for breast cancer screening:** Annual screening of female population above 30 years of age could reduce breast cancer associated mortality by 29% mainly due to early detection of breast cancer and subsequent early treatment pathways. The cost effectiveness is about Rs.19520/- per life year gained which is an excellent social return on investment on this technology. It is however, pertinent that annual screening of target population in India cannot be achieved by limited existing mammography infrastructure and there requires to be at least one mammography unit in every Community Health Center (CHC) to meet the annual work load and once this infrastructural capacity has been achieved, Primary Health Centers (PHCs) could be considered for installation of mammography infrastructure. To bridge the skill gap in reading of images, pathways of Tele-radiology should be considered. 'Screening for breast cancers' (27% of all cancers in India) is an assured service under the National Health Mission and mammography could be a technology of choice.

The assessments performed here are based on current available evidence from scientific literature and incase during the process of assessment or in future, more evidence gets added, the conclusions of the assessments may change. It is also necessary to have contextual requirements be applied to make technology application more practical and feasible

CHAPTER 1

Non-Pneumatic Anti-Shock Garment (NASG)

A) Introduction:

Maternal mortality is a crucial health issue. For the improvement of public health in India, innovative and cost-effective technologies are being progressively undertaken under National Rural Health Mission. One such mechanism is "Emergency Response Systems "under which emergency transport is provided to patients free of cost. A sizable portion of beneficiaries of this system are maternal cases.

There exist recommendations from World Health Organization (WHO) on Active Management of Third Stage Labour (AMSTL).One of the point from the same recommendations is use of "NASG". Non-pneumatic anti shock garment is a stretchable device based on Neoprene. **Neoprene or polychloroprene** is a family of synthetic rubbers that are produced by polymerization of chloroprene. Neoprene exhibits good chemical stability, and maintains flexibility over a wide temperature range. It is used in a wide variety of applications, such as laptop sleeves, orthopaedic braces (wrist, knee, etc.), electrical insulation, liquid and sheet applied elastomeric membranes or flashings, and automotive fan-belts.

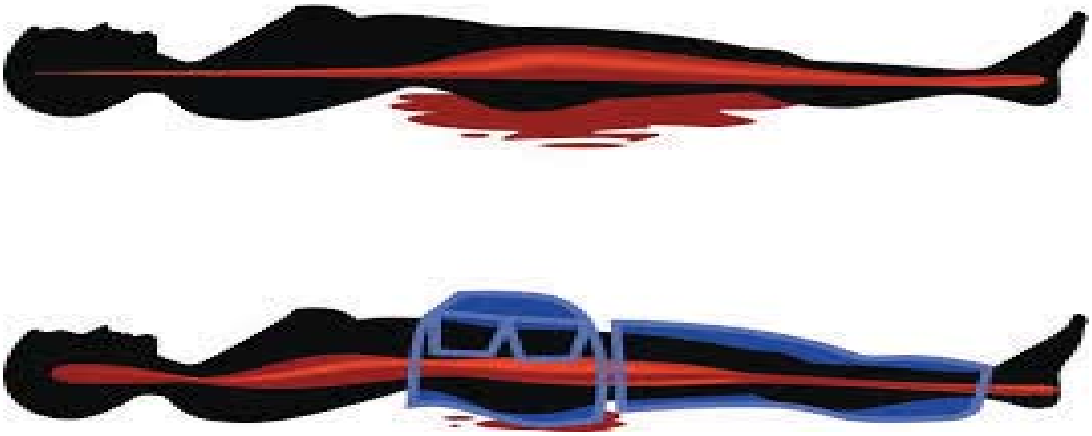
B) NASG as an intervention:-

NASG has 9 articulated segments that are wrapped sequentially around the legs, pelvis and abdomen and fastened with Velcro. The foam ball over the abdomen is provided for additional compression so as to pressurize aorta to affect blood flow. NASG works on simple physics principle of circumferential counter pressure. When pressure will be applied using NASG to compressed areas, blood flow from these areas will be diverted in direction of heart, lungs and brain, thereby reversing the obstetric shock symptoms. Thus, it serves the purpose of stabilizing the woman during the transport to reach a facility where it is possible to receive further treatment.

The health technology assessment on NASG includes gathering and analysing evidence on clinical efficacy, safety, cost-effectiveness, feasibility along with social and health system integration possibilities.

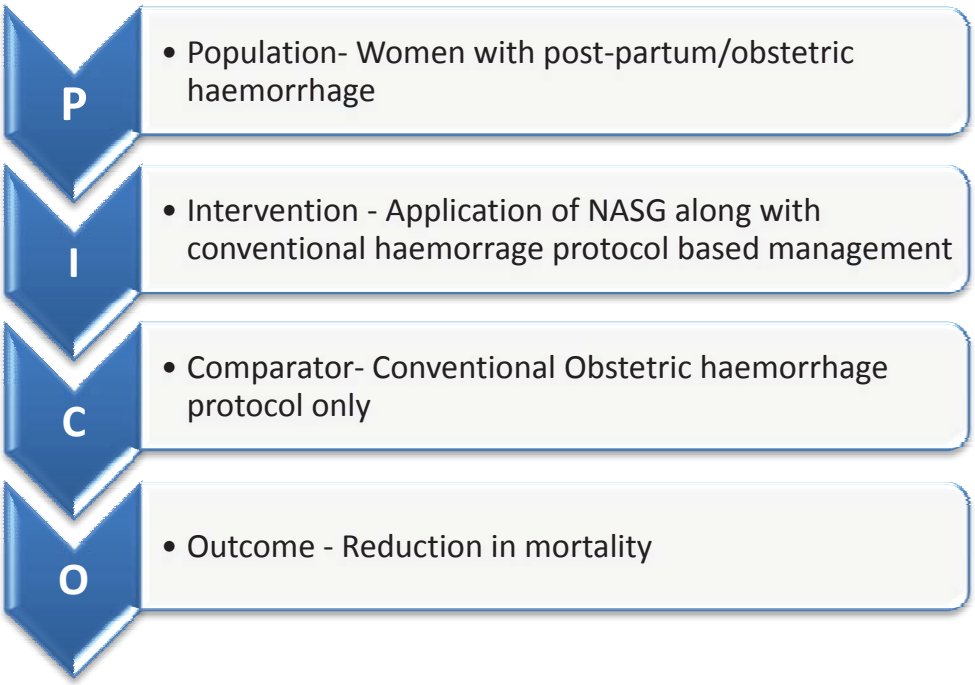
C) Problem Statement:

Postpartum Haemorrhage (PPH) is commonly defined as a blood loss of 500 ml or more within 24 hours of giving birth. Due to excessive blood loss, hypovolemic shock occurs resulting in fatal situation for mothers. Obstetric shock/ Hypovolemic shock is the pathophysiological condition which occurs due to inadequate perfusion of organs resulting from blood loss. Due to insufficient availability of oxygen for satisfying the tissues' oxygen demands, further impairment occurs. This condition worsens with multiple organ dysfunction syndromes. There is an utmost clinical need of an intervention that will control the blood loss before the patient reaches a health facility for appropriate care delivery. As shown in the picture below:-



D) Systematic review of studies on NASG:

PICO search strategy was used for formulation of research problem for this review.



Final Research Problem after combining PICO components:

Does application of Non-pneumatic anti shock garment reduces mortality in women with post-partum/obstetric haemorrhage in addition to conventional Obstetric Haemorrhage protocol based management?

Search Strategy based on PICO model

Type of studies to be searched:

Original research articles from journals mentioning effect of Non-pneumatic anti-shock garments were included with scientific study design (pre-NASG / NASG intervention trial) was considered for review. However, while primary search and screening, statistical aspects like blinding, randomisation were not considered due to nature of intervention.

Participants/Population:

Female participants with any stage of pregnancy with signs of obstetric haemorrhage and are prone to risk of having obstetric shock and thereby to fatality.

Intervention:

- Application of conventional obstetric haemorrhage protocol management. (control or Pre-intervention group)
- Application of NASG following to conventional obstetric haemorrhage protocol management.
- (For NASG group)

Outcomes:

1. Maternal Mortality
2. Blood loss measured in drape.

Inclusion criteria and exclusion criteria

Inclusion criteria:

- Women at any stage of pregnancy and diagnosed with obstetric haemorrhage with recorded blood loss in pre-specified limit mentioned in WHO obstetric haemorrhage diagnosis criteria.

Exclusion criteria:

- Women with antepartum haemorrhage

Electronic database search:

We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, MEDLINE, PUBMED Science Direct, and SCOPUS for relevant studies. We also conducted secondary referencing by manually reviewing reference lists of key articles and searching citations by using Web of Science. We also conducted specific searches for primary studies published more recently than the included systematic reviews and meta-analyses. Types of studies included during search were: Randomized controlled trial, observational analytical studies, Case control and cohort studies.

Other database search:

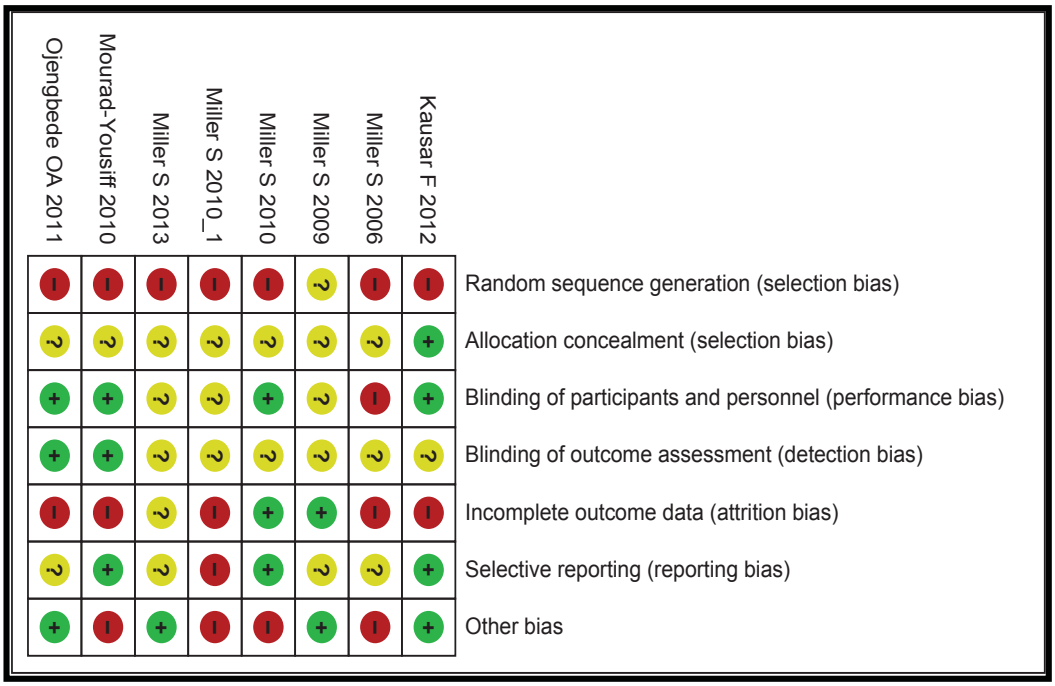
National Health Systems Resource centres' Public Health Administration department was contacted and policy briefs available from PATH FINDER – product distributor were also considered.

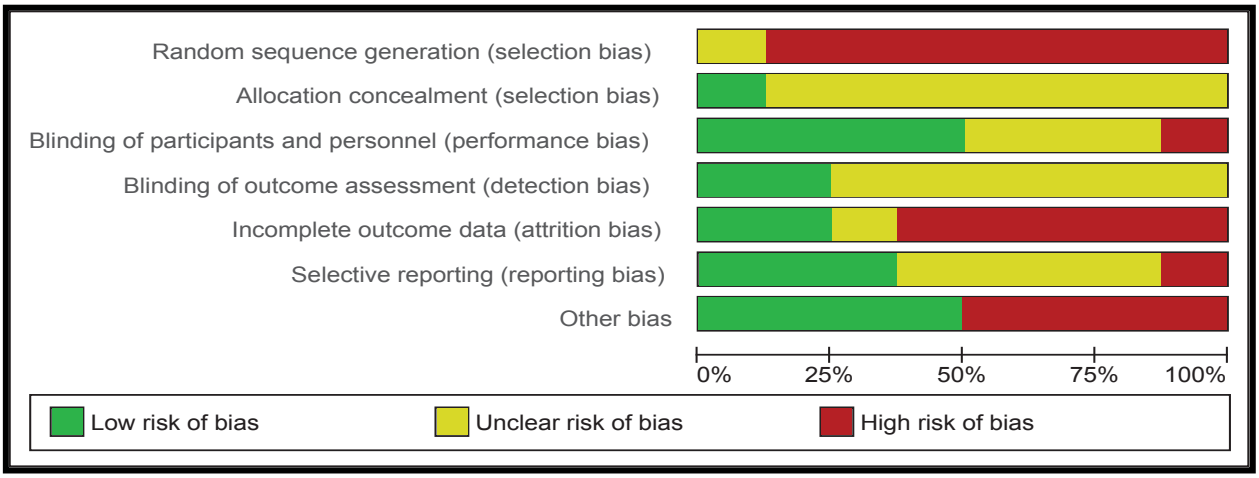
Key-words :

The key words used were "management of post partum haemorrhage", "obstetric anti shock garment", "non-pneumatic anti-shock garment", "non-pneumatic anti-shock garments in low resource settings", "NASG for post partum haemorrhage", "effectiveness of NASG" and "safety and NASG".

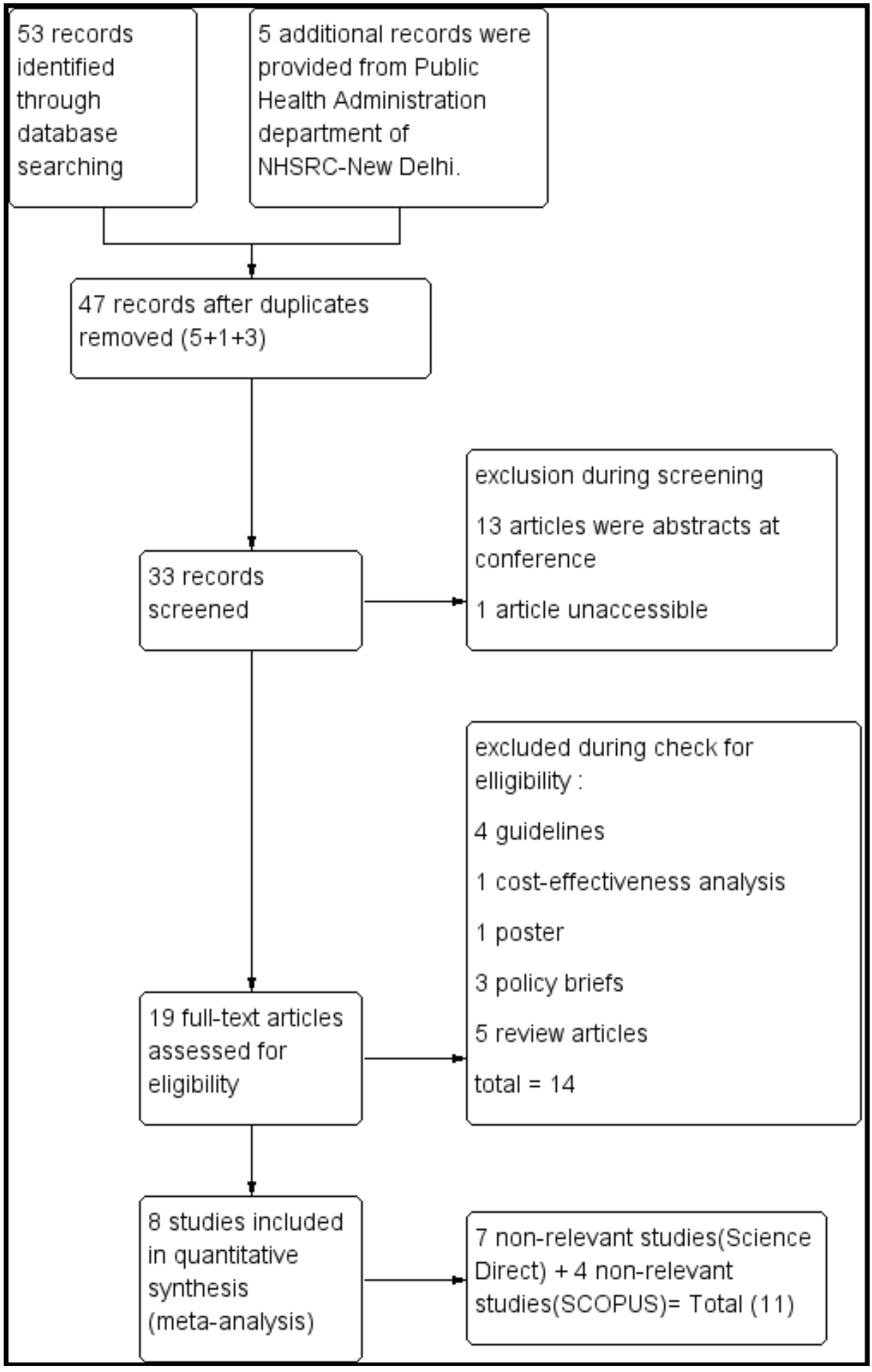
E) Risk of Bias Assessment for included studies:

For methodological quality assessment, Cochrane Review Manager's Risk of Bias Table method was used. Findings of the same are as given





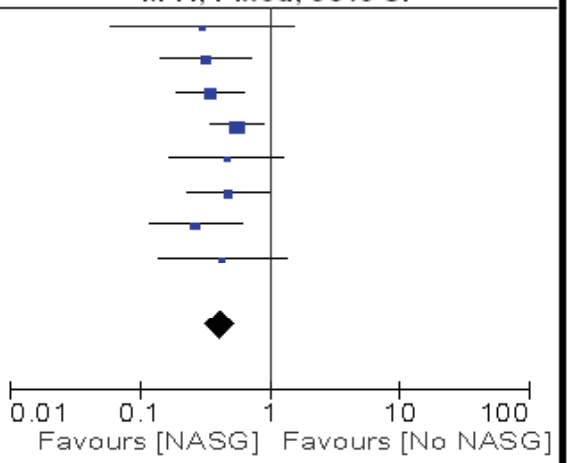
F) Study flow diagram:



Forest Plot showing Maternal Mortality

Study or Subgroup	POST-NASG Events	Total	PRE-NASG Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Miller S 2006	2	206	5	153	3.3%	0.30 [0.06, 1.51]	2006
Miller S 2009	7	86	21	83	12.3%	0.32 [0.14, 0.72]	2009
Mourad-Yousiff 2010	16	511	31	343	21.3%	0.35 [0.19, 0.62]	2010
Miller S 2010_1	29	835	38	607	25.3%	0.55 [0.35, 0.89]	2010
Miller S 2010	6	558	10	432	6.5%	0.46 [0.17, 1.27]	2010
Ojengbede OA 2011	10	174	21	174	12.1%	0.48 [0.23, 0.98]	2011
Kausar F 2012	8	354	19	224	13.4%	0.27 [0.12, 0.60]	2012
Miller S 2013	4	405	11	475	5.8%	0.43 [0.14, 1.33]	2013
Total (95% CI)		**3129**		**2491**	**100.0%**	**0.41 [0.32, 0.53]**	
Total events	82		156				

Heterogeneity: Chi² = 3.71, df = 7 (P = 0.81); I² = 0%
Test for overall effect: Z = 6.68 (P < 0.00001)



As per Forest Plot:-

Risk ratio of meta-analysis is less than 1; this means intervention is more effective than the control.

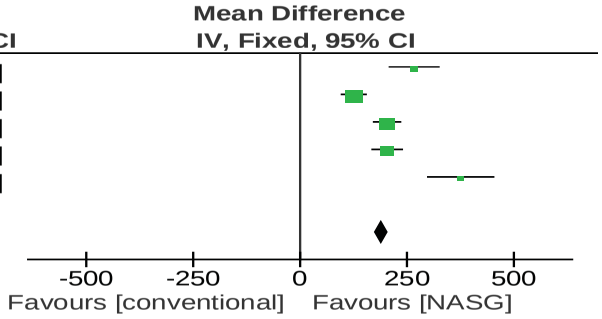
RR for death in NASG group to Pre-intervention group (only standard obstetric haemorrhage protocol based management) is 0.41.

This means NASG intervention reduced the risk by 59% of what it was in control group (Pre-NASG group).

Forest Plot showing Measured blood loss in drape (ml)

Study or Subgroup	Pre-NASG Mean	SD	Total	NASG Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Miller S 2009	340.4	248.2	83	73.5	93.9	86	8.4%	266.90 [209.94, 323.86]
Miller S 2010	378.9	234.3	432	253.2	205.3	558	34.9%	125.70 [97.80, 153.60]
Miller S 2010_1	443.5	346.1	607	240	199.4	835	28.9%	203.50 [172.82, 234.18]
Mourad-Yousiff 2010	424.3	302.3	343	220.5	144	511	23.1%	203.80 [169.46, 238.14]
Ojengbede OA 2011 (1)	470.6	404.6	114	94.9	110.9	174	4.7%	375.70 [299.62, 451.78]
Total (95% CI)			**1579**			**2164**	**100.0%**	**189.79 [173.29, 206.28]**

Heterogeneity: Chi² = 51.66, df = 4 (P < 0.00001); I² = 92%
Test for overall effect: Z = 22.55 (P < 0.00001)



(1) 3 studies were not considered for extraction as the data mentioned regarding measured blood loss was in median(IQR) format.

G) Clinical Impact of NASG and PPH in India:

According to National Rural Health Mission Hospital Management Information System data 2010-12,

The maternal mortality rate = 178 per 1,00,000 live births (HMIS 2010-12)

The annual live births in India as per UNICEF (in thousands) = 27098 (UNICEF 2011) Thus, annual maternal deaths (d) could be calculated as,

d = (27100000 x 178) / 100000 = 271 x 178 = 48,238 deaths per year

Percentage of total maternal deaths due to obstetric haemorrhage = 29.6%

Total number of OH associated deaths= "X" = 29.6% x 48,238 = 14,278 cases.

From the risk difference forest plot (Figure -1), RR for mortality in NASG group to Pre-NASG group is 0.41.This means there is 59% less risk of death by use of NASG additional to conventional haemorrhage management protocol.

Thus,

Total risk reduction by use of NASG additional to OH protocol based management = 59%

Thus, mortality difference with current obstetric haemorrhage associated deaths as baseline. i.e. 14,278 cases per year can be calculated as follows:

Total reduction in deaths due to NASG (RD) = 59% x 14,278 = 8424 deaths

H) Cost Effectiveness Analysis:

Cost-effectiveness analysis is a method of comparing the cost and effectiveness of two or more alternatives. Such comparisons are useful when one of the alternatives being considered is standard care, as this allows the decision maker to consider whether an alternative is better or not. The standard care, however, could also be a placebo or "Do Nothing" scenario.

The cost effectiveness analysis was conducted in 4 steps:

I) Calculation of absolute numbers of annual maternal deaths in India that can be saved using NASG

II) Estimation of total number of NASGs required per year with consideration of NASG life time.

III) Calculation of cost per life saved

IV) Estimation of the cost at which the NASG technology would be cost effective in national health programs.

❖ **Step -1: Calculation of difference in mortality by application of NASG:**

Total deaths can be averted by applying NASG = R_D = 8424 deaths/annum, which is 59% of annual burden of obstetric haemorrhage of 14,278 cases per year.

However, this assumes that all women use referral transport to reach an institutional delivery, and thus all women have access to NASG. This may not be true. Hence, the actual number of maternal deaths prevented will vary from 2856 to 8567, assuming that 20% to 60% women utilize referral transport and thus have access to NASG during pregnancy.

❖ **Step-2: Requirement of total numbers of NASGs on basis of total PPH in India if placed in publicly provided ambulances in India**

Considering at least one NASG required in each ambulance, total no. of NASG annually required would be 17,000.

Given the increase in number planned in some ares a total of 20, 000 could be considered as a demand.

Although each NASG could be used for minimum of 40 cases, the average life span of NASG can be considered to be 3 to 5 years at a maximum.

Total cost/annum = 20,000 units X Rs 3000 (cost/unit)

5 years

=Rs. 20,00 X 600/annum

Effect Of application= 8424 deaths averted

$$= \frac{\text{Rs. 20,000 X 600}}{8424}$$

= Rs 1424.5

Assuming, more realistic rates of utilization of referral transport and thus access to NASG, the cost per death averted ranges from Rs 1400 to Rs 19520, assuming that 60% and 20% of the total pregnant women access the NASG service. Thus, NASG is an extremely cost effective health intervention form Indian perspective. Our analysis is limited in the context of measurement of costs of intervention. The true costs of the service would include the cost of the delivery system, i.e. the operating costs of the ambulance. The study results should be viewed within this limitation.

I) NASG strengths:

- ❖ Simple design and light weight
- ❖ Handy and made up of environmentally safe material
- ❖ Adoption of NASG requires minimum degree of training
- ❖ Non-pharmacological intervention, thus no side effects
- ❖ Scope of large scale manufacturing by considering vast textile sector in India.

J) NASG limitations/challenges:

- ❖ It cannot be generalized to patients with other trauma (no sufficient evidence available)
- ❖ Not recommended to be removed by lay health worker except clinician.
- ❖ For deployment in India, cultural constraints and several stigmas. For example, with use of sari, application of NASG may be difficult. Thus cultural clothing may act as an obstacle for successful acceptance of technology among the patients.
- ❖ Biological plausibility of NASG design is yet to be justified.

- ❖ More evidences are required to assess
  - ✓ Whether NASG is better than the " feet-up " position for directing blood flow
  - ✓ Whether foam ball pressurises aorta and produce assured effects on the blood loss by influencing blood flow.
  - ✓ Whether there is physiological significance of the foam ball and its position in terms of pressure on uterus.

K) Regulatory Aspects:

3. A very small number of devices are regulated in India; the NASG is not formally regulated.
4. The current technology is not FDA or CE certified which are international medical device regulatory standards.
5. Patent status –
   - ❖ The non-pneumatic anti-shock garment is now off-patent and produced in several different locations.
   - ❖ However, there is similar device filed as US patent 3933150 which is for general trauma and uses pressurized gas for increasing venous blood flow to victim's heart. This was patented in 1974.
   - ❖ From the 1970s, NASA was involved in developing a non-pneumatic version of the anti-shock garment. This was originally used for haemophiliac children, but has since been developed into the garment known as the Non-pneumatic Anti-Shock Garment (NASG). Several modifications of these devices were patented in 1982 and 1986.
   - ❖ The use of the garment for obstetrical haemorrhage in low-resource settings began in 2002 when Dr. Carol Brees and Dr. Paul Hensleigh introduced the garment into a hospital in Pakistan and reported on a case series of its use.

L) Market status:

- ❖ NASG is listed internationally at a cost of US$ 54
- ❖ Hong Kong manufacturer Blue Fuzion Group charges a wholesale rate of $53.
- ❖ India: VISCO-a medical device manufacturing firm with PATH and WHO is providing this at $50.
- ❖ However, given the technology design, the cost should be much lower.

Results and Recommendations:

Taking the effect of NASG as potential positive outcome; cost per life saved is Rs.1424.57.This could be a cost-effective option provided the fabric based NASG could be manufactured at a cost much lesser than current MRP .Since it is off-patent ,more domestic manufacturers could be encouraged to supply. This could be made possible by formulating generic technical specifications of the product and procuring it through an identified nodal agency such as Directorate General of Supplies and Disposals (DGS&D), Ministry of Commerce and Industry- Govt. of India.

Hence, the technology - NASG could be suggested to be included in Emergency Response Systems ambulances.

Bibliography:

1. Sutherland T et al. Use of the Non-Pneumatic Anti-Shock Garment (NASG) for Life-Threatening Obstetric Hemorrhage: A Cost-Effectiveness Analysis in Egypt and Nigeria. PLoS ONE 2013;Vol. 8(4): e62282.
2. UNICEF (n.d.)http://www.unicef.org/infobycountry/india_statistics.html
3. Kausar F, Morris JL, Fathalla M, Ojengbede O, Fabamwo A, Mourad-Youssif M, Morhason-Bello IO, Galadanci H, Nsima D, Butrick E, Miller S.. Nurses in low resource settings save mothers' lives with non-pneumatic anti-shock garment.. MCN Am J Matern Child Nurs. 2012;37(5):308-316.
4. Miller S, Hamza S, Bray EH, Lester F, Nada K, Gibson R, Fathalla M, Mourad M, Fathy A, Turan JM, Dau KQ, Nasshar I, Elshair I, Hensleigh P.. First aid for obstetric haemorrhage: the pilot study of the non-pneumatic anti-shock garment in Egypt.. BJOG 2006 Apr;113(4):424-9. [PubMed: 16553654]
5. Miller S, Ojengbede O, Turan JM, Morhason-Bello IO, Martin HB, Nsima D.. A comparative study of the non-pneumatic anti-shock garment for the treatment ofobstetric hemorrhage in Nigeria. Int J Gynaecol Obstet 2009 Nov;107(2):121-5.
6. Miller S, Fathalla MM, Youssif MM, Turan J, Camlin C, Al-Hussaini TK, Butrick E, Meyer C.. A comparative study of the non-pneumatic anti-shock garment for the treatment of obstetric hemorrhage in Egypt.. Int J Gynaecol Obstet 2010 Apr;109(1):20-4..
7. Miller S, Fathalla MM, Ojengbede OA, Camlin C, Mourad-Youssif M, Morhason-Bello IO, Galadanci H, Nsima D, Butrick E, Al Hussaini T, Turan J, Meyer C,Martin H, Mohammed AI.. Obstetric hemorrhage and shock management: using the low technology Non-pneumatic Anti-Shock Garment inNigerian and Egyptian tertiary care facilities.. BMC Pregnancy Childbirth. 2010 Oct 18;10(64):1-8.
8. Miller S, Bergel EF, El Ayadi AM, Gibbons L, Butrick EA, Magwali T, Mkumba G, Kaseba C, Huong NT, Geissler JD, Merialdi M.. Non-Pneumatic Anti-Shock Garment (NASG), a First-Aid Device to Decrease Maternal Mortality from Obstetric Hemorrhage: A Cluster Randomized Trial.. PLoS One 2013 Oct 23;8(10):e76477.
9. Mourad-Youssif M, Ojengbede OA, Meyer CD, Fathalla M, Morhason-Bello IO, Galadanci H, Camlin C, Nsima D, Al Hussaini T, Butrick E, Miller S.. Can the Non-pneumatic Anti-Shock Garment (NASG) reduce adverse maternal outcomes from postpartum hemorrhage? Evidence from Egypt and Nigeria.. Reprod Health. 2010 Sep 1;7(24):1-8. [DOI: 10.1186/1742-4755-7-24.]
10. Ojengbede OA, Morhason-Bello IO, Galadanci H, Meyer C, Nsima D, Camlin C, Butrick E, Miller S.. Assessing the role of the non-pneumatic anti-shock garment in reducing mortality from postpartum hemorrhage in Nigeria.. Gynecol Obstet Invest. 2011;71(1):66-72. [PubMed: 21160197]

CHAPTER 2

Handheld Ultrasonography (HHUS)

Introduction

What Is an Ultrasound?

An ultrasound scan is a medical test that uses high-frequency sound waves to capture live images from the inside of your body.

Ultrasound is an oscillating sound pressure wave with a frequency greater than the upper limit of the human hearing range. Ultrasound devices operate with frequencies from 20 kHz up to several gigahertz.

Ultrasound is used in many different fields. Ultrasonic devices are used to detect objects and measure distances. Ultrasonic imaging (sonography) is used in both veterinary medicine and human medicine. Animals such as bats and porpoises use ultrasound for locating prey and obstacles.

Ultrasound image of a fetus in the womb, viewed at 12 weeks of pregnancy (bidimensional-scan)

Ultrasonics is the application of ultrasound. Ultrasound can be used for medical imaging, detection, measurement and cleaning. At higher power levels, ultrasonics is useful for changing the chemical properties of substances.

Medical sonography (ultrasonography) is an ultrasound-based diagnostic medical imaging technique used to visualize muscles, tendons, and many internal organs, to capture their size, structure and any pathological lesions with real time tomographic images. Ultrasound has been used by radiologists and sonographers to image the human body for at least 50 years and has become a widely used diagnostic tool. The technology is relatively inexpensive and portable, especially

when compared with other techniques, such as magnetic resonance imaging (MRI) and computed tomography (CT). Ultrasound is also used to visualize fetuses during routine and emergency prenatal care. Such diagnostic applications used during pregnancy are referred to as obstetric sonography. As currently applied in the medical field, properly performed ultrasound poses no known risks to the patient. Sonography does not use ionizing radiation, and the power levels used for imaging are too low to cause adverse heating or pressure effects in tissue. Although the long term effects due to ultrasound exposure at diagnostic intensity are still unknown, currently most doctors feel that the benefits to patients outweigh the risks. The ALARA (As Low As Reasonably Achievable) principle has been advocated for an ultrasound examination — that is, keeping the scanning time and power settings as low as possible but consistent with diagnostic imaging. Ultrasound is also increasingly being used in trauma and first aid cases, with emergency ultrasound becoming a staple of most EMT response teams. Furthermore, ultrasound is used in remote diagnosis cases where tele consultation is required, such as scientific experiments in space or mobile sports team diagnosis.

Most people associate ultrasound scans with pregnancy. These scans can provide an expectant mother with the first view of her unborn child. However, the test has many other uses.

According to the Radiological Society of North America, doctor orders an ultrasound if patients are experiencing pain, swelling, or other symptoms that require an internal view of your organs (RSNA, 2012).

An ultrasound can provide a view of the:

1. bladder
2. brain (in infants)
3. eyes
4. gallbladder
5. kidneys
6. liver
7. ovaries
8. pancreas
9. spleen
10. thyroid
11. testicles
12. uterus
13. blood vessels
14. An ultrasound is also a helpful way to guide surgeons' movements during certain medical procedures, such as biopsies.

B) Handheld Ultrasound Device as an intervention:-

Handheld Ultrasound Device displays real time movement and color Doppler, which produces color coded images of blood flow that are overlaid on the black and white anatomical images produced by the device. The ultrasound images can quickly and noninvasively display organ anatomy and functions as well as check for normal blood flow or blockages, monitor pregnancies than that of traditional large mainframe ultrasound machines. Being pocket-sized ultrasound machines look similar to smart phones, and can diagnose heart, lung and other problems, it can also be used in place of stethoscope. The ability to get a better look inside the body could prevent misdiagnoses, and help doctors detect abnormalities that need to be followed up with other tests.

A handheld ultrasound device in India can offer significant potential health benefits to millions who suffer from painful or potentially life threatening diseases. Handheld Ultrasound Device also has the potential to increase efficacy and early detection in diverse medical fields such as anesthesia delivery, cardiac surgery, sports medicine, and emergency medicine. Handheld Ultrasound Device is also uniquely powerful in that it is the imaging technology that can be transported to a patient or used where a patient might most urgently need it- if on the side of a road after a serious motor accident or in remote communities where a patient may have to travel for several hours just to reach a basic primary health center.

Handheld Ultrasound Device

Clinical Effectiveness of Handheld Ultrasound Device

Objectives

1. To understand role of HHUD in maternal and infants health.
2. To assess the clinical effectiveness of Handheld Ultrasound Device (HHUD).
3. To assess the cost effectiveness of Handheld Ultrasound Device (HHUD).

Materials and Methods

The review of this technology's effectiveness is given in terms of its diagnostic accuracy as it is an imaging technology.

Search Methods

We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, MEDLINE, PUBMED Science Direct, SCOPUS and Society of Radiologist in Ultrasound for relevant studies. We also conducted secondary referencing by manually reviewing reference lists of key articles and searching citations by using Web of Science. We also conducted specific searches for primary studies published more recently than the included systematic reviews and meta-analyses. Types of studies included during search were: Randomized controlled trials, observational analytical studies, Case control and cohort studies.

Keywords:

The key words used were “Handheld Ultrasound”, “Intermittent auscultation”, “Handheld Ultrasound systematic review”, “Handheld Ultrasound sensitivity specificity” and “Handheld Doppler Ultrasound”.

Study Outcomes:

A) Outcomes for three studies -

1. Diagnostic Test accuracy (sensitivity and specificity)

a) **Sensitivity -** The sensitivity of a test is defined as the proportion of people with disease who will have a positive result. If we apply Test A to our hypothetical population, and 8 of the 10 people with Disease A test positive, then the sensitivity of the test is 8/10 or 80%.

b) **Specificity -** The specificity of a test is the proportion of people without the disease who will have a negative result. We can see from our hypothetical population that 90 people do not have Disease A. If we apply Test A to these 90 people and 85 of them test negative, then the specificity of the test is 85/90 = 94%

2. Likelihood Ratio-

Likelihood ratio is used for assessing the value of performing a diagnostic test. They use the sensitivity and specificity of the test to determine whether a test result usefully changes the probability that a condition (such as a disease state) exists.

Two versions of the likelihood ratio exist, one for positive and one for negative test results. Respectively, they are known as the likelihood ratio positive (LR+) and likelihood ratio negative (LR–).

The likelihood ratio positive is calculated as

$$LR+ = \frac{\text{sensitivity}}{1 - \text{specificity}}$$

which is equivalent to =

$$LR+ = \frac{\Pr(T+|D+)}{\Pr(T+|D-)}$$

or "the probability of a person who has the disease testing positive divided by the probability of a person who does not have the disease testing positive." Here "T+" or "T−" denote that the result of the test is positive or negative, respectively. Likewise, "D+" or "D−" denote that the disease is present or absent, respectively. So "true positives" are those that test positive (T+) and have the disease (D+), and "false positives" are those that test positive (T+) but do not have the disease (D−).

The likelihood ratio negative is calculated as-

$$LR- = \frac{1 - \text{sensitivity}}{\text{specificity}}$$

which is equivalent to-

$$LR- = \frac{\Pr(T-|D+)}{\Pr(T-|D-)}$$

or "the probability of a person who has the disease testing negative divided by the probability of a person who does not have the disease testing negative."

The pretest odds of a particular diagnosis, multiplied by the likelihood ratio, determine the post-test odds. This calculation is based on Bayes' theorem. (Note that odds can be calculated from, and then converted to, probability.)

If likelihood ratio is greater than 1 indicates the test result is associated with the disease. Likelihood ratio less than 1 indicates that the result is associated with absence of the disease. Tests where the likelihood ratios lie close to 1 have little practical significance as the post-test probability (odds) is little different from the pre-test probability.

In summary, the pre-test probability refers to the chance that an individual has a disorder or condition prior to the use of a diagnostic test. It allows the clinician to better interpret the results of the diagnostic test and helps to predict the likelihood of a true positive (T+) result.

B) Outcomes for two studies –

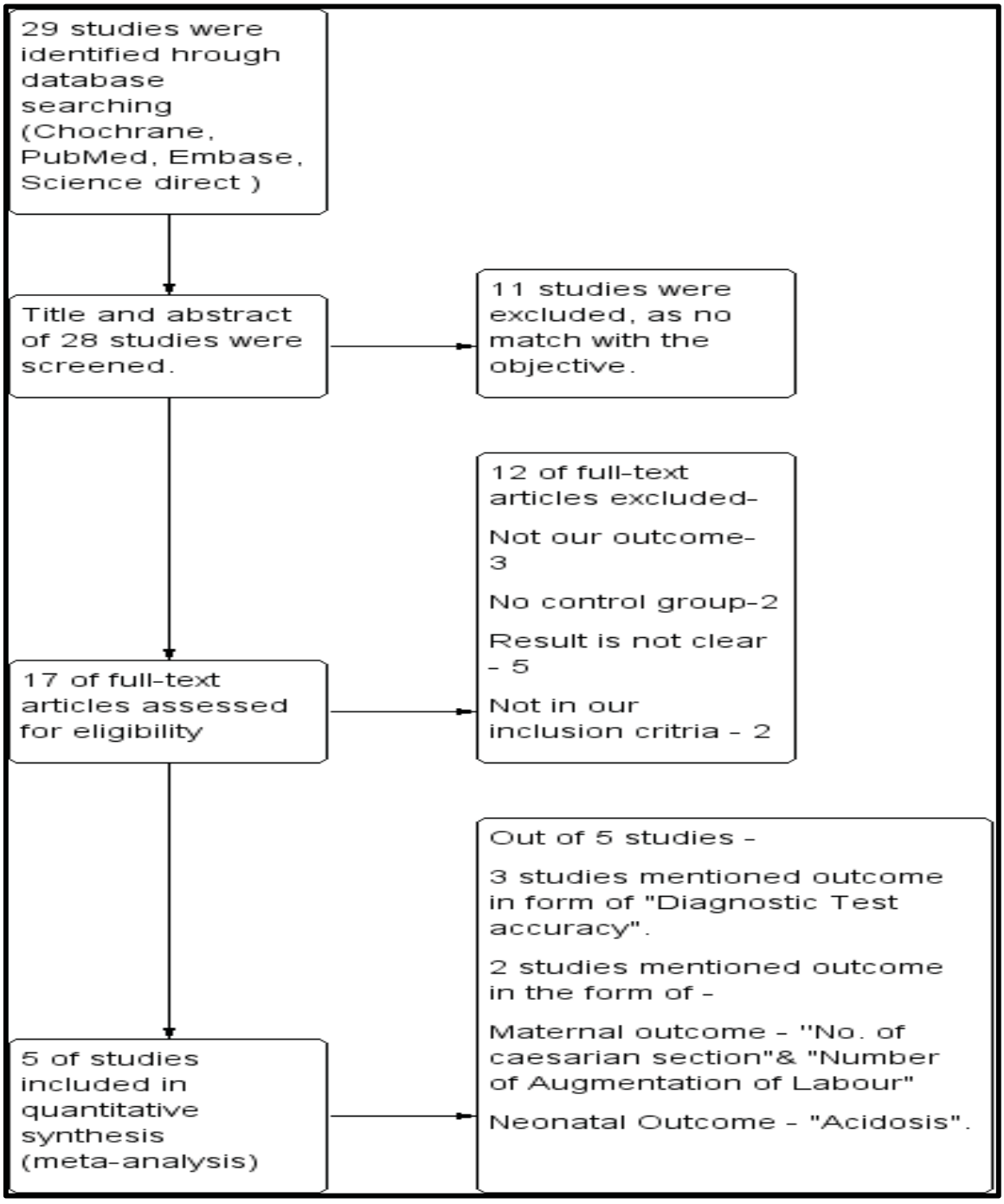
a) Maternal

- Caesarean section
- Augmentation of labour

Data extraction:

- The sensitivity and specificity data was extracted from 3 studies; TP (True Positive), TN (True Negative), FP (False positive) & FN (False Negative) were calculated. Later likelihood ratio was calculated from this data.
- Comparative observational analysis was conducted and the criteria for choice of optimal test was set according to published recommended threshold values
- i.e. +LR>= 10, -LR<=0.1(Stengel 2003)
- Two studies compared the handheld ultrasound device (HHUD) and cardiocotography (CTG) and extraction of number of cases of caesarean section and augmentation of labour was done.
- The extracted data was entered in Cochrane Review Manager 5.2 in “Data and Analysis” section and three forest plots were generated.

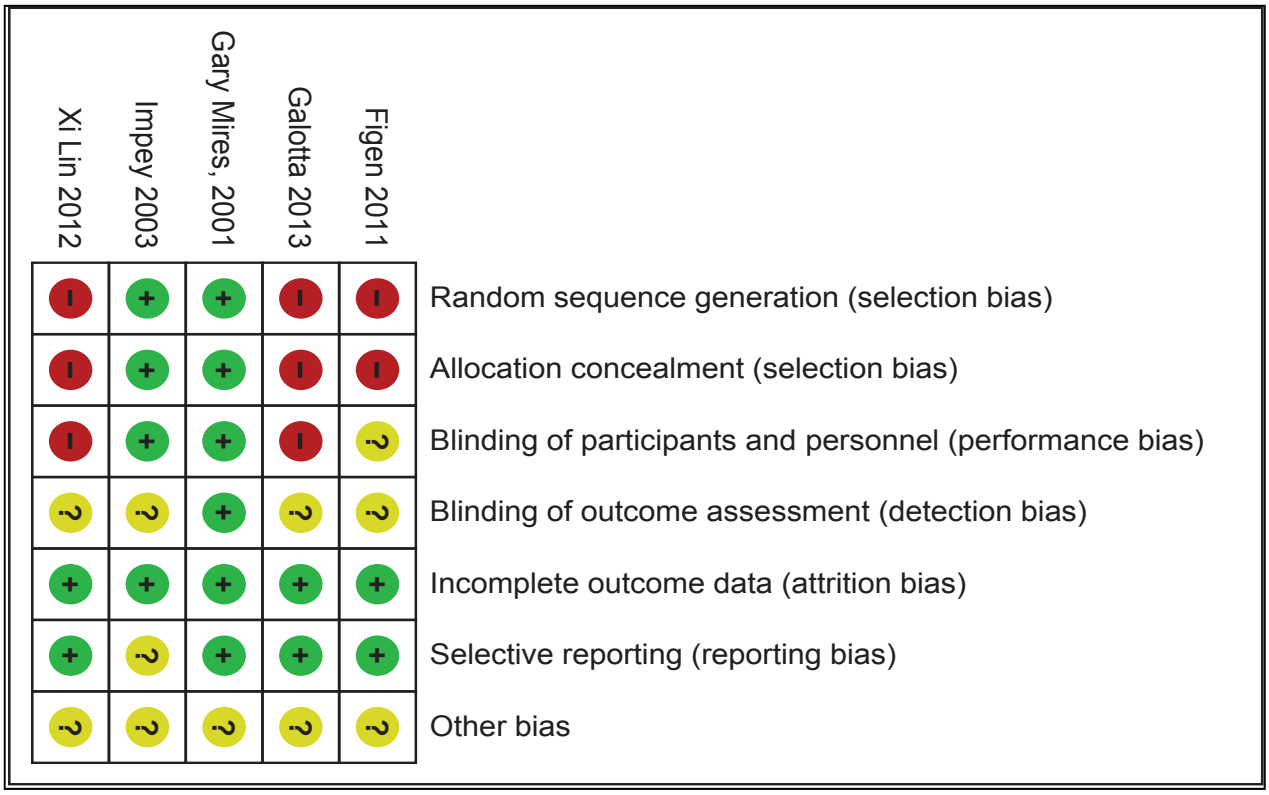
D) The study flow diagram is shown below:



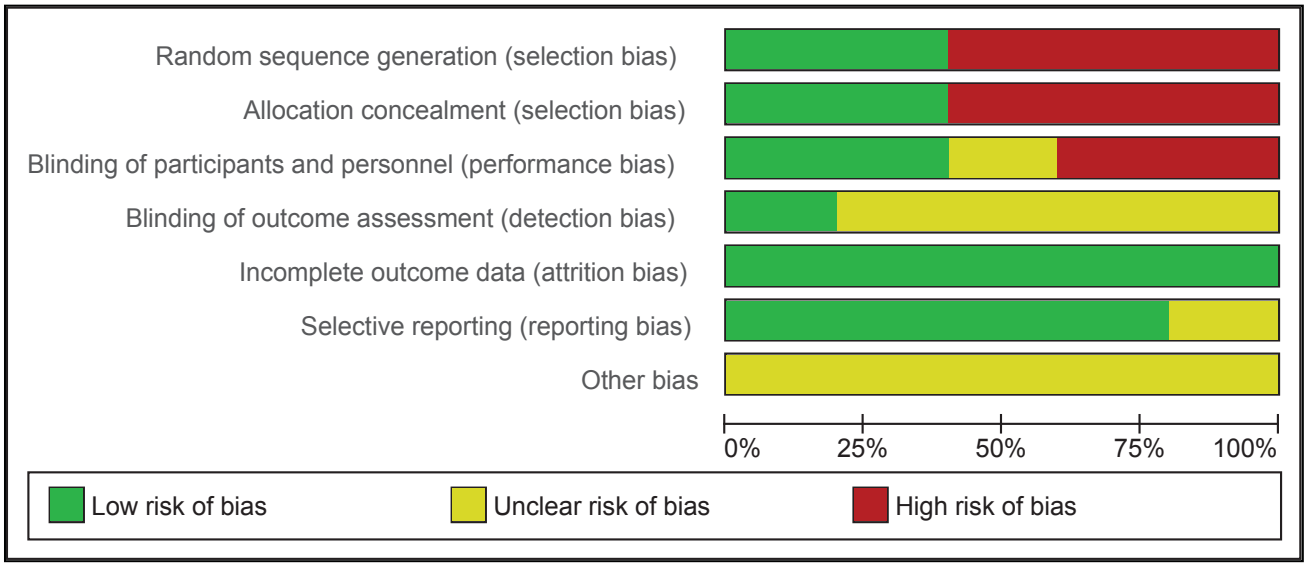
Risk of Bias of the included studies:

Methodological quality of included studies was reviewed using Cochrane review bias table. Findings of which are as follows:-

Risk of Bias Assessment



Risk of Bias Summary



Random sequence generation (Selection Bias): 3 study showed selection bias **(Figen 2011, Golatta 2013 & Xi Lin 2011),** as they have not included randomisation in the study. **Rest 2 studies showed low selection bias (Mires 2001 & Impey 2003).**

Blinding of participants and personnel (Performance bias): 2 study **(Figen 2011, Golatta 2013 & Xi Lin 2011),** having high performance bias, as blinding was not included. **Remaining 2 studies showed low risk of performance bias.**

Blinding of outcome assessment (detection bias): 1 studies (Figen 2011) showed unclear detection bias, as no such information was found.

Incomplete outcome data (attrition bias): **All studies showed low attrition bias.**

Selective reporting (reporting bias): 1 study showed unclear reporting bias **(Impey 2003)**. Rest other studies showed low risk bias.

Results –

A. Diagnostic test [Hand Held Ultrasound Device (HHUD)]–

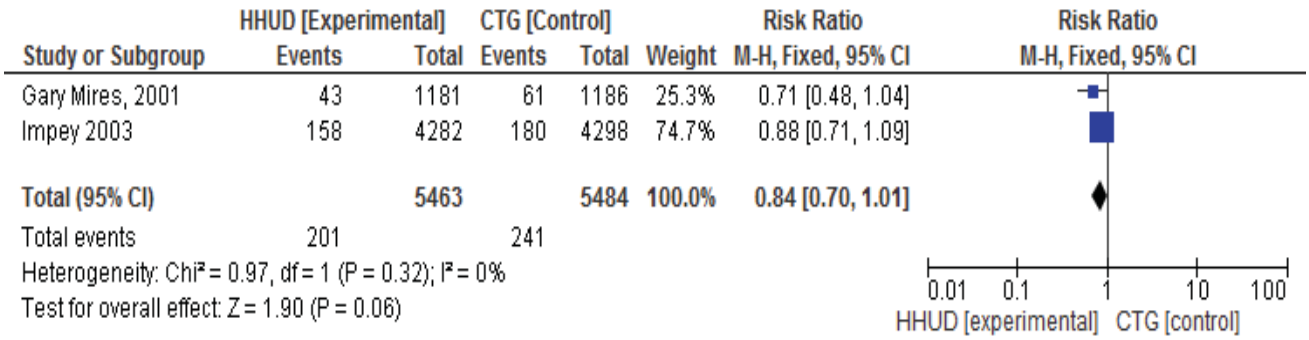
Data Extraction Diagnostic Test Accuracy : Hand Held Ultrasound Device (HHUD)										
S. No	Study ID (First Author_ Year)	Sensitivity	Specificity	True +ve	True –ve	False +ve	False -ve	Total	Likelihood ratio +ve	Likelihood ratio -ve
1	Golatta 2013	1.00	0.25	32	1	3	0	36	1.333	0
2	Xi Lin 2011	1.00	0.85	15	17	3	0	35	6.666	0
3	Figen 2011	0.889	0.976	89	98	2	11	200	37.04	0.1137
				136	116	8	11	271	17	0.095

B. Interventional test [Hand Held Ultrasound Device (HHUD) versus Cardiocotography (CTG)]

a. Maternal Outcome – Caesarean section

LR +ve for two out of three studies is higher than or closer to 10 and LR-ve is less than or close to 0.1 for all three studies. Since LH +ve > 10 and LR –ve <0.1 indicate god outcomes, the studies largely highlights diagnostic accuracy of HHUD.

Forest Plot showing Caesarean section data



As per Forest plot, findings:

RR =0.84, <1

Risk Ratio (RR) less than 1 means experimental intervention (HHUD) is more effective than control (CTG)

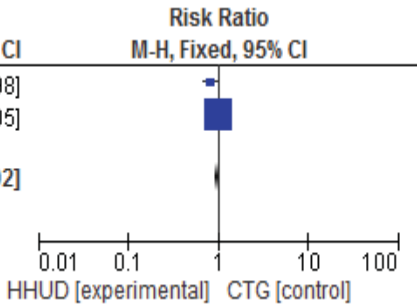
RR of 0.84 means 16% reduction in Caesarian due to HHUD as compared to CTG.

Forest Plot showing Augmentation of Labour data

Study or Subgroup	HHUD [Experimental] Events	Total	CTG [Control] Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gary Mires, 2001	202	1175	246	1183	13.0%	0.83 [0.70, 0.98]
Impey 2003	1629	4282	1647	4298	87.0%	0.99 [0.94, 1.05]
Total (95% CI)		**5457**		**5481**	**100.0%**	**0.97 [0.92, 1.02]**
Total events	1831		1893			

Heterogeneity: Chi² = 4.18, df = 1 (P = 0.04); I² = 76%

Test for overall effect: Z = 1.11 (P = 0.27)



As per Forest plot, findings:

Risk Ratio = 0.97, <1

Risk Ratio (RR) less than 1 means experimental intervention (HHUD) is more effective than control (CTG)

RR of 0.97 means 3% reduction in oxytocin use for the augmentation of labor due to HHUD as compared to CTG.

C. Cost effectiveness Analysis–

Cost analysis are done in following steps –

i. Cost of single unit of conventional Ultrasound and Handheld Ultrasound machine.

Ultrasound machine = Rs. 26 Lakh

Handheld Ultrasound Device = $7,900 [*]

= Rs 4.74 Lakh

= Rs. 5 Lakh (Approximately)

Cost per test for Ultrasound –

S. No.	Ultrasound Investigations	Rate
Public Sector		
1	Routine Ultrasound[8]	200.00
CGHS rate for Private hospitals –		
1	Image Intensifiers	680.00
2	Obstetric First Scan	255.00
3	Obstetric Follow up (2nd visit)	255.00
4	Quick look check-up for IUCD & Infants	340.00
5	Special procedures & Aspiration etc.	765.00
6	Stress test (treadmill)	935.00
7	Total Abdominal survey or Multiple study	635.00
8	Upper abdomen First scan	385.00
9	Upper abdomen Follow up (2nd visit)	385.00

[*]- http://www.themebuilders.com/GEvScanPricing.html

[*]- http://www.themebuilders.com

ii. Cost per test of conventional Ultrasound and Handheld Ultrasound machine.

Time taken by ultrasound machine for a single test [#] = 15 min – 40 min

= 25min (Approx)

Total test/machine/year =

$$\frac{\text{No. of Hours/day X Total minutes/hour X Total number of days/ week X Total no. of weeks per month x Total No. months in a year}}{\text{Total Time taken for 1 ultrasound test}}$$

$$= \frac{8 \times 60 \times 6 \times 12 \times 4}{25 \text{ min}}$$

= 5,529.6 test /machine /year.

= 5,530 test /machine /year (Approx)

Apparent life time for a single ultrasound machine = 7 years

Total number of tests during the life span of an ultrasound machine

= Total test/ machine/year x Life time of ultrasound machine

= 5,530 x 7

= 38,710 tests/machine/life span

a. Cost per test for conventional ultrasound machine

$$= \frac{\text{Cost of ultrasound machine}}{\text{Total number of tests}}$$

$$= \frac{26,\ 00000}{38,710} = \textbf{67.16 Rs/test}$$

b. Cost per test for Handheld ultrasound machine

$$= \frac{\text{Cost of Handheld ultrasound machine}}{\text{Total number of tests}}$$

$$= \frac{5,\ 00000}{38,710} = 12.91\ \textbf{Rs/test}$$

[#] - http://www.nhs.uk/conditions/ultrasound-scan/pages/introduction.aspx

To summarize –

Types	Conventional Ultrasound	Handheld Ultrasound
Cost per test (Rs/test)	67.16	12.91

Note: This does not include HR costs which may be the same in either case.

The above analysis is a cost-outcome description which compared the costs and outputs associated with use of alternative modes of technology for ultrasound. A full economic evaluation calls for much greater data inputs and analysis. This is recommended as a future priority area of research in this area.

For a full economic evaluation, we recommend that there should be assessment of the costs of a wrong diagnosis (as a result of less than 100% sensitivity and specificity). Each case which is wrongly diagnosed false positive or false negative using a given diagnostic test has costs associated with the same, both for the provider as well as the individual. Such costs are most often poorly defined, and often underestimated.

Secondly, there is a need to estimate the cost of a caesarean section (CS) versus a normal delivery, as the hand-held ultrasounds have been shown to be somewhat efficiacious in reducing the extent of caesarean sections. A reduction in CS rate implies reduction in costs.

Finally, the outcomes in terms of reduced complications of caesarean sections also need to be evaluated. These outcomes, in turn, will have both costs associated with the complications besides the impact on quality of life.

H) Trend of sex selective abortion in India –

According to the Census of India, 2001, the sex ratio stands at 933 for the country as a whole. This is a welcome improvement from the 1991 Census, which had recorded 927 females for every 1000 males. The sex ratio in the country had always remained unfavorable to females. Moreover, barring some hiccups, it has shown a long term declining trend. The sex ratio at the beginning of the twentieth century was 972 and thereafter showed continuous decline until 1941. In 1951 there was a marginal increase of one point, but thereafter it again dropped for two consecutive decades to reach 930 in 1971. In fact between 1961- 71 the country saw the sharpest decline of 11 points in the sex ratio. Thereafter, it has fluctuated marginally around 930 in successive censuses.

S. No	Year	Sex Selective Abortion	Male/Female ratio	Sex Ratio in Age group 0-6 years
1.	1984-1990(1991 census)	1.0 million	927	945
2.	1994 –2000(2001census)	2·6 million	933	927
3.	2004-2010 (2011 census)	4.5 million	930	919

Trend of market sales of Ultrasound machine in India[$] –

S. No	Year	No. of Ultrasound machine
1	2009	3970 Units
2	2011	4431 Units
3	2012	6821 Units

Market trend is also showing a significant increase number of machines.

[$]-http://censusindia.gov.in/Data_Products/Library/Provisional_Population_Total_link/PDF_Links/chapter6.pdf

Discussion –

Handheld ultra sound device is a well accepted technology in the market as well as cost effective as compared to the conventional ultrasound machine.

As per the trends and current scenario in India, Ultrasound technology could be misused for female feticide. The Indian government implemented Pre Natal Diagnostic Techniques Act (PNDT Act) in 1996 to prevent and misuse of techniques for the purpose of prenatal sex determination leading to selective abortion of girls.

Despite of these laws selective abortion of girls, has increased substantially in India along with increase number of sales of ultrasound machine.

The compact, portable and relatively low cost nature of Handheld Ultrasound device will increase the complexity in the existing system for sex- selective abortions. Also, it can be used to determine sex and implant male embryos selectively in, in-vitro fertilization and pre- implantation genetic diagnosis thereby further skewing the sex ratio.

If it included as unregulated sale in the market, then manufacturer should introduce a GPRS tracking device inside the Handheld Ultrasound Device, so that location of use could be tracked.

Also, the ultrasound machine purchased by the healthcare professional should be registered with PNDT (Pre Natal Diagnostic technique) cell just like diagnostic centers.

Bibliography

1. Gary Mires, Fiona Williams, Peter Howie. Randomised controlled trial of cardiotocography versus Doppler auscultation of fetal heart at admission in labour in low risk obstetric population. BMJ 2001; 322:1457-1462.
2. Lawrence Impey, Margret Reynolds et al. Admission cardiotocography: a randomised controlled trial. Lancet 2003; 361:465-70.
3. FigenCoskun, EmineAkinci et al. Our new stethoscope in the Emergency Department: Handheld ultrasound. Turkish general of trauma & Emergency Surgery 2011; 17(6): 488-492.
4. Michael Golatta, Dorothea Franz, Aba Harcos et al. Interobserverreliabilityof automated breast volume scanner (ABVS) interpretation and agreement of ABVS findings with hand held breast ultrasound (HHUS), mammograpghy and pathology results. European Journal of Radiology 2013;82:e332-e336.
5. Xi Lin, Jianweiwang, Feng Han et al. Analysis of eighty one cases with breast lesions using automated breast volume scanner and comparison with handheld ultrasound. European Journal of radiology 2012; 81:873-878.
6. D Stengel, K Bauwens, J Sehouli, AEkkernkamp, F Przsolt. A likelihood ratio approach to meta-analysis of diagnostic studies. J Med Screen 2003;10:47-51.
7. GE Vscan Pricing detail. Available at - http://www.themebuilders.com/GEvScanPricing.html (Accessed on 15th April 2014)
8. Revised rates of Hospital charges. All India Institute of Medical Sciences New Delhi, India. Available at - http://www.aiims.edu/aiims/hosp-serv/revised-rate-list.htm#_Toc471767124 (Accessed on 16th April 2014).
9. NHS. Available at- http://www.nhs.uk/conditions/ultrasound-scan/pages/introduction.aspx (Accessed on 20th April 2014).
10. Government of India. Ministry of Health Affairs. Office of the registrar General & Census Commissioner, India. Available at http://censusindia.gov.in/2011census/censusinfodashboard/index.html (Accessed on 16th April 2014).
11. PrabhatJha, Maya AKesler, Rajesh Kumar, Faujdar Ram, et al. Trends in selective abortions of girls in India: analysis of nationally representative birth histories from 1990 to 2005 and census data from 1991 to 2011. The Lancet 4 June 2011;377:1921-1928.
12. Census of India. Avalable at - http://censusindia.gov.in/Data_Products/Library/Provisional_Population_Total_link/PDF_Links/chapter6.pdf (Accessed on 16th April 2014)
13. Medical Buyer. Ultrasound Equipment: Gleaning New Market. Avaialable at - http://www.medicalbuyer.co.in/index.php?option=com_content&task=view&id=
14. Gardner, M.; Altman, Douglas G. (2000). Statistics with confidence: confidence intervals and statistical guidelines

CHAPTER 3

Oxygen Therapy in COPD Patients and use of Oxygen Concentrators

A) Background

Chronic obstructive pulmonary disease (COPD), also known as chronic obstructive lung disease (COLD), and chronic obstructive airway disease (COAD), is a type of obstructive lung disease characterized by chronically poor airflow.

COPD is a type of obstructive lung disease in which chronic incompletely reversible poor airflow (airflow limitation) and inability to breathe out fully (air trapping) exist. The poor airflow is the result of breakdown of lung tissue (known as emphysema) and small airways disease known as obstructive bronchiolitis. The relative contributions of these two factors vary between people. Some also have a degree of airway hyper responsiveness to irritants similar to those found in asthma. COPD develops as a significant and chronic inflammatory response to inhaled irritants. Chronic bacterial infections may also add to this inflammatory state.

The inflammatory cells involved include neutrophils, granulocytes and macrophages, two types of white blood cell. Those who smoke additionally have Tc1 lymphocyte involvement and some people with COPD have eosinophil involvement similar to that in asthma. Part of this cell response is brought on by inflammatory mediators such as chemotactic factors.

Other processes involved with lung damage include oxidative stress produced by high concentrations of free radicals in tobacco smoke and released by inflammatory cells, and breakdown of the connective tissue of the lungs by proteases that are insufficiently inhibited by protease inhibitors. The destruction of the connective tissue of the lungs is what leads to emphysema, which then contributes to the poor airflow and, finally, poor absorption and release of respiratory gases. General muscle wasting that often occurs in COPD may be partly due to inflammatory mediators released by the lungs into the blood.

Narrowing of the airways occurs due to inflammation and scarring within them. This contributes to the inability to breathe out fully. The greatest reduction in air flow occurs when breathing out, as the pressure in the chest is compressing the airways at this time. This can result in more air from the previous breath remaining within the lungs when the next breath is started, resulting in an increase in the total volume of air in the lungs at any given time, a process called hyperinflation or air trapping. Hyperinflation from exercise is linked to shortness of breath in COPD, as it is less comfortable to breathe in when the lungs are already partly full. (*)

C) Risk Factors for COPD:

Exposure to particles:-

1. Tobacco smoke (10 pack Years; 50% smokers develop COPD)

'Bidi' is a "Poor Man's Cigarette" popular smoking product of Indian cottage industry in which crude tobacco (0.15 - 0.25 g) is loosely packed unfiltered, hand wrapped in brown leaves, tied with thread, dried leaf of Tendu tree (Diisopyros melanoxylon) and is smoked as a cigarette. More addictive than cigarettes (x 7 times more Nicotine content) has 2 times tar content. Frequently actively inhalant varies from 4 - 7.5 cm in length and is available in bundles of 8-24 bidis. 'Chutta' is a product similar to a bidi but smoked in a reverse fashion with the burning end kept inside the mouth. Other popular method is to put tobacco in a clay container or a 'chilum' similar to a pipe and smoke either directly or drawing the smoke with the help of a long tube passing through a water container (i.e., hubble-bubble or 'hukkah') – a habit especially common among the elderly. COPD is reported among smokers of almost all those different forms of tobacco products. Bidi smoking, in particular, is a more common habit than cigarette smoking in India. The COPD prevalence's among bidi and hukkah smokers were 8.2 and 9.5 per cent with odds ratio of more than 2.6 in each case and both the prevalence rates as well as the odds ratio were significantly more than those for cigarette. Bidi smoking of more than 2.5 pack years was more commonly associated with chest symptoms and airways obstruction than cigarette smoking.

2. Indoor air pollution from heating and cooking with Biomass fuel in poorly ventilated homes (at least 25 years of exposures) by using dried dung, wood and crop residue is reported as an important cause of chronic bronchitis and COPD in women in India. Respiratory symptoms in India were reported in 13 per cent of 3608 nonsmoking women involved in domestic cooking. Exposure to solid fuel combustion is also shown to be an additive risk factor along with Environmental Tobacco Smoke exposure in causing COPD. Chronic "Cor Pulmonale" frequently resulting from COPD progression is reported to be common in women who are otherwise nonsmokers but have got prolonged household exposure from early life to domestic cooking in the kitchens especially in the poorly ventilated houses.

3. **Occupational dusts, organic and inorganic substances:-**

    a. Automobile-drivers, vehicular mechanics , fertilizer manufacturing, chlorinated organic compounds dyes, explosives, rubber products, metal etching, plastics, ammonia exposure in refrigeration and petroleum refining, grain dust and funguses in farmers, textile mill manufacturing, leather manufacturing, food products manufacturing and sales, beauty care workers and welders in automotive industries.

    b. Exposures to crystalline silica: cement industry, brick manufacturing, pottery and ceramic work, silica sand, granite and diatomaceous earth industries, gold mining, and iron and steel founding.

4. Outdoor air pollution due to causes-Ambient air pollution in metropolitan cities has been frequently blamed for chronic respiratory morbidity causing:-

    a. Reduced Lung volumes

    b. Lung growth and development

    c. Aggravating Previous Tuberculosis (28-68% cases of post-treated TB; 2.9-6.6 folds increase risk)

    d. Increasing Early childhood Recurrent Lower Respiratory infections (2-3 fold risk).

Genes:-

Many genes have been associated with COPD. Till date the only well-established genetic risk factor identified for COPD is SERPINA1 gene which codes for serine protease inhibitor, alfa-1 antitrypsin (AAT).2,8 Perturbation in SERPINA1 gene leads to deficiency of AAT-1, causing uninhibited action of proteases and culminating

in development of emphysema. The M allele is associated with normal AAT while Z alleles constitute AAT deficiency. However, only 1-2% of the population exhibits anomaly in SERPINA1, suggesting that many other genetic variations would be responsible for development of COPD. Current understanding is that COPD is a polygenic disease involving complex interactions between various gene polymorphisms. (#)

{Reference-

(*) Risk Factors and Pathophysiology of Chronic Obstructive Pulmonary Disease (COPD) Bill B Brashier1, Rahul Kodgule

(#) Chronic obstructive pulmonary disease- V.K. Vijayan Vallabhbhai Patel Chest Institute, University of Delhi, Delhi, India Management of COPD Jaising Phadtare,)}*

D) Management of COPD:

(I) Pharmacological agents

The drugs for treatment of COPD are inhaled bronchodilators, inhaled corticosteroids, oral theophylline and oral phosphodiesterase-4 inhibitor. Oxygen therapy is indicated in COPD patients with chronic respiratory

(a) **Bronchodilators**: Inhaled bronchodilators are the main pharmacological agents that improve symptoms, decrease exacerbations and improve quality of life in COPD. Bronchodilators can cause only a small (<10%) increase in FEV1 in patients with COPD.

(b) **Corticosteroids**: The fact that COPD is associated with chronic inflammation is the rational for the use of inhaled corticosteroids in COPD.

(c) **Phosphodiesterase inhibitors**: Theophylline, a weak oral bronchodilator is a non-selective phosphodiesterase inhibitor and has some anti-inflammatory properties. However, its narrow therapeutic index is a concern requiring frequent monitoring of blood levels, adverse drug reactions and drug interactions. COPD patients, if continued to be symptomatic despite combined inhaled bronchodilator treatment, can be prescribed theophylline and it provides additional improvement in lung function with a few exacerbations.

Roflumilast is a phosphodiesterase-4 (PDE-4) inhibitor and it reduces inflammation by inhibiting the breaking down of intracellular cyclic AMP. It is administered orally with a once a day schedule (500 mg) and it reduces acute exacerbations in patients with COPD

(d) **Vaccines**: Influenza and Pneumococcal vaccines are available. Influenza vaccines reduce serious illness and death in COPD patients by 50%.Given once a year in winter. However, pneumococcal vaccine is recommended once in five years.

(e) **Mucolytic Agents**: (mucokinetic, mucoregulator): Patients having thick, tenacious sputum could be benefited; otherwise its regular use in stable patients is not recommended.

(f) **Anti-tussives**: Regular use contraindicated in stable COPD.

(g) **Antibiotics**: Only to be used in infectious exacerbations and other bacterial infections.

(h) **Respiratory Stimulants**: Irrespective of type, regular use is not recommended. (@)

(Reference – (@) Emergence of chronic obstructive pulmonary disease as an epidemic in India Surinder K. Jindal)

(II) Non-pharmacotherapy

1. Smoking cessation: Smoking cessation is the most important step in the treatment of COPD.

Long-Term Oxygen Therapy (LTOT):-

Long-term oxygen therapy (LTOT) is the treatment proven to improve survival in chronic obstructive pulmonary disease (COPD) patients with chronic respiratory failure. Oxygen therapy decreases pulmonary hypertension and red cell mass while simultaneously increasing exercise capacity.

2. Pulmonary Rehabilitation:-

Pulmonary rehabilitation is an important component of therapy of COPD. The components of a comprehensive pulmonary rehabilitation programme include exercise training, smoking cessation, nutrition counselling and education. The benefits of pulmonary rehabilitation include improvement in exercise capacity, reduction in the perceived intensity of breathlessness, improvement in health-related quality of life, reduction in the number of hospitalizations and days in the hospital and reduction in anxiety and depression associated with COPD.

3. Surgical Intervention

Lung volume reduction surgery: The National Emphysema Treatment Trial is a randomized, multicenter clinical trial that compared lung-volume-reduction surgery (LVRS) with medical treatment. Patients with emphysema who have a low FEV1 and either homogeneous emphysema or a very low carbon monoxide diffusing capacity are at high risk for death after surgery and also are unlikely to benefit from the surgery.($)

In this Heath Technology Assessment Report we will discuss Long Term Oxygen Therapy by using Oxygen Concentrators.

(Reference - ($) Management of COPD a Clinical Scenario- Jaising Phadtare)

E) Long Term Oxygen Therapy

Long-term oxygen therapy is extended use of oxygen. Oxygen therapy needs vary depending on activity levels. Patients with daytime resting hypoxemia may need LTOT during sedentary periods, when they are typically resting at home or performing non stressful domiciliary activities of daily living. Increased activity levels, such as casual walking, may require ambulatory or supplemental oxygen to meet higher systemic demands. Patients with COPD have decreased sensitivity to the normal neuro - chemical control of breathing during sleep, which results in nocturnal oxygen desaturation. As a result, nocturnal oxygen therapy may be needed. Some guidelines recommend increasing the oxygen dose during periods of extended exercise and during sleep.

F) As per WHO key facts on COPD,

1. Chronic obstructive pulmonary disease (COPD) is a life-threatening lung disease that interferes with normal breathing – it is more than a “smoker’s cough”.
2. An estimated 64 million people have COPD worldwide in 2004. (*)
3. More than 3 million people died of COPD in 2005, which is equal to 5% of all deaths globally that year.
4. Almost 90% of COPD deaths occur in low- and middle-income countries.
5. COPD is not curable, but treatment can slow the progress of the disease.
6. Total deaths from COPD are projected to increase by more than 30% in the next 10 years without interventions to cut risks, particularly exposure to tobacco smoke.

Scenario in India,

- 160 million smokers in India.
- More than 3 million people died of COPD in 2005, which is equal to 5% of all deaths globally that year in India.
- COPD predicted to be third leading cause of death in 2030.
- India will have 5 to 6times the population of New Zealand with COPD next 6yrs.(#)

(References – (*) http://www.who.int/mediacentre/factsheets/fs315/en/
(#) - Management of COPD a Clinical Scenario- Jaising Phadtare, (http://apiindia.org/pdf/medicine_update_2007/134.pdf) (http://www.who.int/choice/documents/economic_evaluation/en/) (http://www.jthoracdis.com/article/view/403/html), Clinical use of Oxygen in hospitals with limited resources by WHO

G) Oxygen Concentrator as an intervention for COPD patients:

A concentrator draws in air from the room/environment (which contains 21% oxygen) and passes the air through a special filter collecting only the oxygen into a reservoir. When the machine is turned on, this process of collection takes place. The reservoir and the concentrator have limited storage, so virtually all the oxygen saved is released into the oxygen tubing for delivery to the patient. The concentration of oxygen delivered by a concentrator is 90-95%. The concentrator is run by electricity. The concentrator weighs about 50 pounds (23 kg) and is usually on wheels so that it can be easily moved in the home from room to room. The machine should be located where there is good circulation and away from furniture and walls. Given the lack of oxygen pipelining systems in hospital and complete absence of any kind of oxygen therapy at home, oxygen concentrators are a good substitute to traditional Oxygen cylinder and pipeline based oxygen therapy. ($)

Reference – ($) (http://apiindia.org/pdf/medicine_update_2007/134.pdf)
(http://www.who.int/choice/documents/economic_evaluation/en/) (http://www.jthoracdis.com/article/view/403/html),Clinical use of Oxygen in hospitals with limited resources by WHO

H) Clinical Effectiveness of Oxygen Concentrators for COPD Patients:

Objective:

- Effectiveness of oxygen concentrators in reducing mortality in comparison to conventional oxygen therapy

Search Methods:

We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, MEDLINE, PUBMED Science Direct, SCOPUS, EMBASE, LANCET, and Google Scholar for relevant studies. We also conducted secondary referencing by manually reviewing reference lists of key articles and searching citations by using Web of Science. We also conducted specific searches for primary studies published more recently than the included systematic reviews and meta-analyses. All the studies selected or rejected were based on our inclusion and exclusion criteria.

Key Words:

- The key words used were "Use of oxygen Concentrator in COPD patients "OR" Oxygen concentrators and COPD" OR "COPD Management".

Selection Criteria:

Below mentioned selection criteria was used:-

- Population: - People above 20 years of age.
- Intervention :- Oxygen Concentrator
- Comparator :- Conventional Oxygen Therapy
- Primary Outcome :- Mortality

Criteria for considering studies for this review:

Types of studies

- Randomized clinical trials, Non-Randomized clinical trials, Case control and cohort studies which were available on this subject are included in this review.

Types of interventions:

- Experimental :- Oxygen Concentrator
- Control :- Conventional Oxygen Therapy

Outcome:

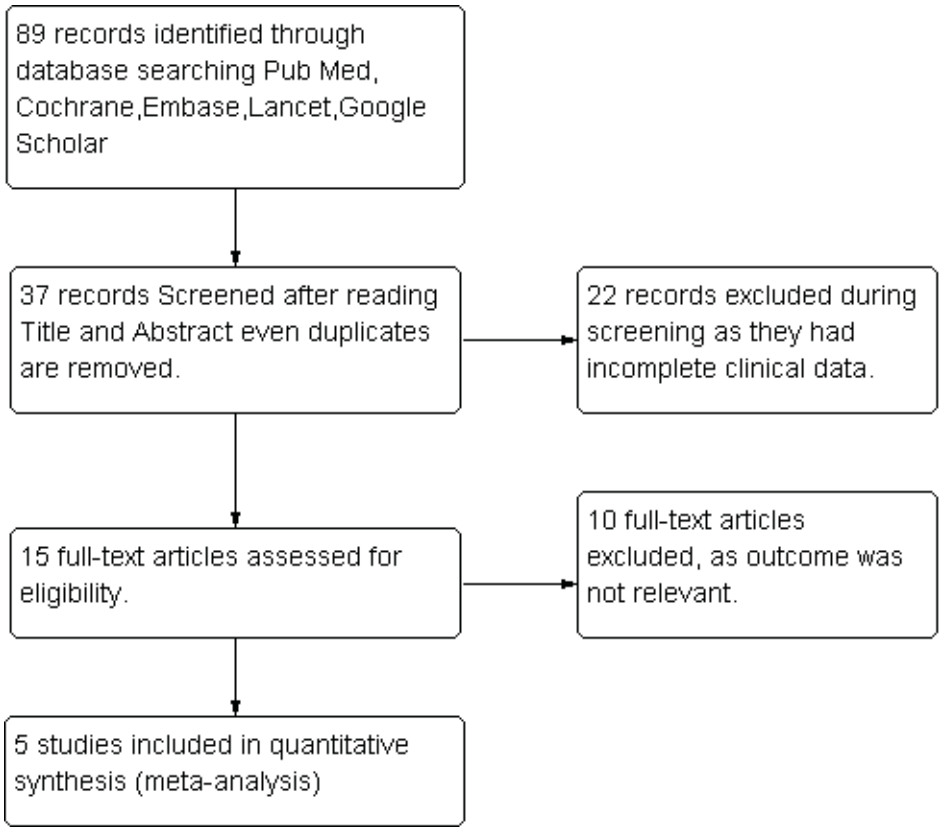
- Mortality from COPD was assessed in both experiment and control group.

I) Data Collection and Analysis:

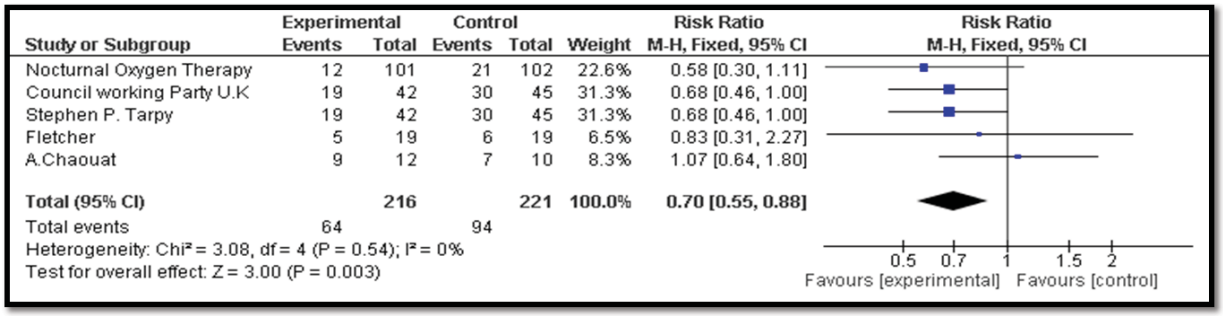
89 studies were selected, after reading the abstract 22 were rejected and 37 were selected. Among these 15 articles were assessed for eligibility and 10 articles were rejected as outcome was not relevant, finally only 5 studies were included for quantitative synthesis.

As shown in the figure below:-

I) Study Flow diagram:



J) Forest Plot



As, per Forest Plot,

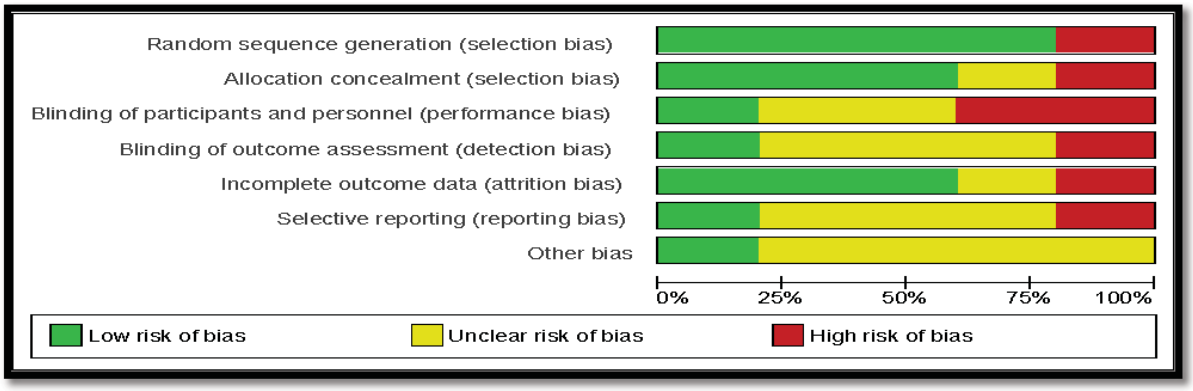
RR= 0.70% < 1

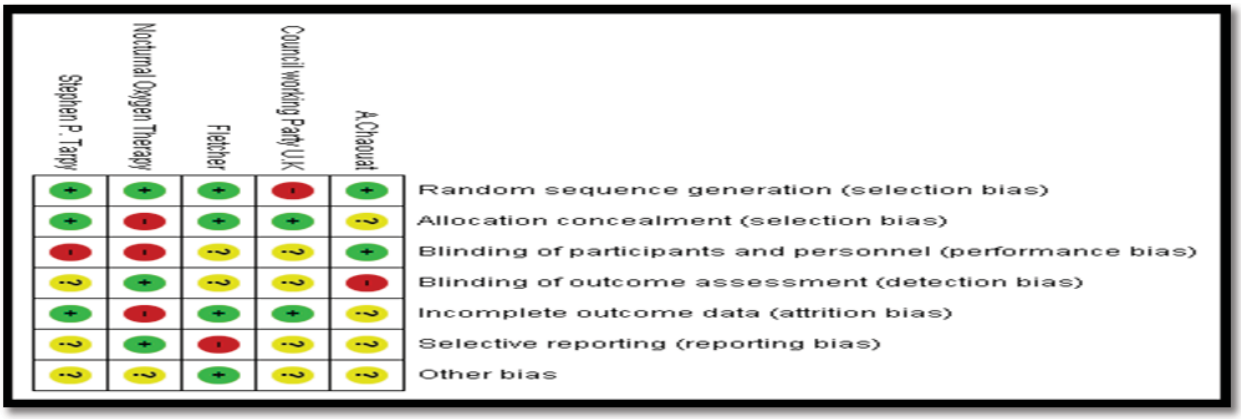
This means reduction in mortality due to by using Oxygen Concentrator as compared to Conventional Oxygen Therapy is 30 %.

Moreover it is also observed that Risk Ratio (RR) is less than1, means that experimental intervention (Oxygen Concentrator) is more effective than control (Conventional Oxygen Therapy).

This Systematic Review shows 30% reduction in mortality by using Oxygen Concentrators in COPD Patients. However the studies have not assessed outcomes at the same time. Number of studies considered here are too small to make any confident conclusions and the current conclusion is with limited evidence.

K) Risk of Bias Table





Explanation of the above mentioned Table:-

Overall the studies show a low risk of any form of bias meaning that the findings of respective studies are of high scientific validity and credibility.

L) Cost effectiveness Analysis

Cost-effectiveness analysis is a method of comparing the cost and effectiveness of two or more alternatives. Such comparisons are useful when one of the alternatives being considered is standard care, as this allows the decision maker to consider whether an alternative is better or not.

In this review,

Table showing Comparison of Costs	
Oxygen Concentrator	
Initial cost of Investment	Rs. 8,00,000
Estimated Cost of Maintenance for ten years	Rs.2, 00, 00
Estimated Cost of Electricity for 10 yrs at 0.9kva	Rs.2, 50, 000
Total Cost of Ownership for 10 yrs	(5000 units /year @Rs.5/unit for 10 years at0.9kav)
Average Cost of ownership /year	Rs.12, 50, 000
Total Cost of Production of O2 per year	Rs.125000
(20lpmX60mtsX24daysX12Months)	6912000 liters oxygen
6912000 liters oxygen is equal to	987 Jumbo Cylinders
Oxygen Cylinder	
Average Cost of one Jumbo Cylinder/day	Rs.350
Total cost of 987 Jumbo cylinders	Rs.350 x987=Rs.345450
Hence, net savings	Rs.345450-Rs.125000=Rs.220450

Reference - (#) – Helix Corporation –Oxygen concentrator manufacturing company

Breakeven analysis		
1.	Production of oxygen	20LPM
2.	Oxygen production for 20 hours a day	24000L
3.	Equivalent Cylinders	3
4.	Cost per cylinder including transportation etc	Rs.300
5.	Daily expenses on oxygen procurement	Rs.900
6.	Monthly cost of oxygen incurred	Rs.27000
7.	Cost of Oxygen for 30 months	Rs.8,10,000
8.	Initial Cost of Oxygen Concentrator is	Rs.8,00,000
9.	The investment is recovered in a period of 2.5 yrs. (Warranty of Oxygen System is 24 Months) (Reference – Helix Corporation –Oxygen concentrator manufacturing company)	

Social and Economic Impact of COPD in India:-

Disability-adjusted life year is a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death. It extends the concept of potential years of life lost due to premature death to include equivalent years of healthy life lost by virtue of being in states of poor health or disability - mortality and morbidity are combined into a single, common metric. Calculated by the below mentioned formula:-

DALYs = Disability-Adjusted Life Years lost = Years of life lost due to premature mortality (YLLs) plus years lived with disability (YLDs).

One DALY, therefore, is equal to one year of healthy life lost.
In India, COPD contributes to = 6,740,000 DALYs lost/year (*)

- Cost of Oxygen concentrator /patient/day = Rs.342
- Cost of Oxygen Cylinder /patient/day = Rs.350
- Cost of Oxygen Cylinder - Cost of Oxygen concentrator = Rs.350– Rs.342
- Difference in cost = Rs.8
- Total number COPD cases in India in 2012= 22 million (*)

As Cost Effective Analysis (CEA) has been conducted and cost effectiveness has been calculated, ratios combining the expected results are calculated and reported.

There are three types of cost effectiveness ratios (CERs):

- Average cost-effectiveness ratio (ACER),
- Marginal cost-effectiveness ratio (MCER), and
- Incremental cost-effectiveness ratio (ICER).

Among the above mentioned three types the one applicable to this report is ICER-

- compares the differences between the costs and health outcomes of two alternative interventions that compete for the same resources, and
- Is generally described as the additional cost per additional health outcome.
- When comparing two competing programs incrementally, one program should be compared with the next-less-effective alternative.
- The ICER numerator includes the differences in program costs, averted disease costs, and averted productivity losses if applicable.
- Similarly, the ICER denominator is the difference in health outcomes.

Hence, calculations which are below mentioned are based on above mentioned concept.

$$\frac{\text{Difference in cost}}{\text{Difference in effect}} = \frac{22\text{X } 10 \text{ Lakhs X } 8}{6740{,}000}$$

$$= \frac{1760\text{X}100{,}000}{6740{,}000}$$

$$= \text{Rs. } 26.11/\text{ DALY averted}$$

{Reference – (*) COPD in India: Iceberg or volcano?Arvind B. Bhome Professor Pulmonary Critical Care Sleep Medicine, B.V. Medical College, Pune 411043, India}

M) Regulatory Aspect

As per the World Health Organization's "The clinical use of oxygen in hospitals with limited resources – Guidelines for health-care workers, hospital engineers and managers" key technical points and specifications for oxygen concentrators suited for district hospital are as mentioned below:

a. The concentrator should achieve >85% oxygen concentration at a flow rate of up to 10 liters / minute.

b. The concentrator should operate at power and frequency that is suitable for the local power supply; this differs between countries.

c. For energy efficiency the power requirements should not exceed 350 W for units providing 5litres/ minute, 410 W for 8 liters/minute units, and 600 W for 10 liters /minute units.

d. The concentrator should have a minimum efficiency of 850 liters/kilowatt hour for units providing 5 liters /minute, 1150 liters /kilowatt hour for 8 liters /minute units and 1000 liters /kilowatt hour for 10 liters /minute units.

e. The concentrator should have one or two outlets with individual flow controls and flow indicators.

f. Outlet pressure should be no less than 55 kPa for units providing 5 liters / minute and 138 kPa for 8 and 10 liters /minute units.

g. Weight should not exceed 25 kg.

h. An hour meter should record total hours of unit operation.

i. Maximum operating altitude should be not less than 2000 m, with not less than 85% oxygen concentration at maximum flow.

j. Maximum operating temperature should be not less than 40 °C.

k. Maximum operating humidity should be not less than 95% relative humidity.

l. A list of all spare or replacement parts and their costs for 40 000 hours of operation (e.g. compressor, sieve beds and valve spares kits) should be provided.

m. The concentrator should comply with ISO 8359:1996 and carry a 75 and IEC 60601- and carry a CE marking.

n. A user manual intended for guide should be provided.

o. There should be a 60-months part warranty.

The unit should include a 4-way flow splitter plugs, which can deliver flows of 0.5, 1.0 and 2.0 liters /minute; OR a flow meter stand. Each flow meter should be continuously adjustable from 0.5 to 2 liters /minute. (#)

N) Ethical and Social Aspect

There is a continuous improvement in the design and manufacture of oxygen concentrators, resulting in smaller, lighter, quieter, more power-efficient, and less expensive models. New models of oxygen concentrators appear every year. However, within a hospital or health service, standardizing on one model helps ensure continuity of spare parts, maintenance and training. As liquid oxygen and cylinders are expensive and difficult to transport, there is now an increasing move toward the use of oxygen concentrators. Concentrators can produce an unlimited quantity of oxygen. This makes them suitable for any application, from a small clinic to a 1000-bed teaching hospital. Oxygen concentrators have proven to be the most economical way to provide oxygen therapy throughout the world. A challenge for oxygen concentrators is in the use of alternative, renewable or hybrid sources of power, to solve the problem of running concentrators and other electricity-dependent medical equipment in health facilities with unreliable or no mains power. (#)

{Reference – (#) - The clinical use of oxygen in hospitals with limited resources WHO Guidelines for health-care workers, hospital engineers and managers}

O) Recommendations and Suggestions

This report explains the clinical effectiveness and cost-benefit analysis of oxygen concentrator over conventional oxygen therapy. The following key points of consideration are summarized below:-

- Mortality in patients using oxygen concentrators is 30% lesser than in patients using conventional oxygen therapy. The absolute number of deaths averted would depend upon the number of patients actually accessing any form of oxygen therapy.
- Infrastructure for oxygen pipe line is not adequate in Indian hospitals that are mainly located in urban and sub – urban areas. Creating oxygen supply systems in rural areas is a demanding task in terms of installation, maintenance and risk management. This is applicable to cylinder based, pipeline base medical gasses supply as well as liquid oxygen systems. Oxygen Concentrators thus is a technology of choice in providing access to oxygen therapy in all forms of health care settings irrespective of geographical and infrastructural limitations.
- Oxygen concentrators is a cost effective intervention compared to traditional oxygen Therapy in long term use as break even can be achieved within a period of 2.5 yrs, and also leads to a saving of Rs.8 /Patient /Day which is enormous when factored with the large number of patients requiring and using oxygen therapy in India.

Hence, use of oxygen concentrators over conventional oxygen therapy (cylinder/pipeline based) is suggested to improve access to oxygen therapy, better management of COPD and other Oxygen therapy requiring respiratory conditions.

P) References

1. Risk Factors and Pathophysiology of Chronic Obstructive Pulmonary Disease (COPD) Bill B Brashier1, Rahul Kodgule
2. Chronic obstructive pulmonary disease- V.K. Vijayan* Vallabhbhai Patel Chest Institute, University of Delhi, Delhi, India Management of COPD Jaising Phadtare,)
3. Emergence of chronic obstructive pulmonary disease as an epidemic in India Surinder K. Jindal
4. Management of COPD a Clinical Scenario- Jaising Phadtare
5. (http://apiindia.org/pdf/medicine_update_2007/134.pdf)

   (http://www.who.int/choice/documents/economic_evaluation/en/) (http://www.jthoracdis.com/article/view/403/html),Clinical use of Oxygen in hospitals with limited resources by WHO
6. Helix Corporation booklet.
7. COPD in India: Iceberg or volcano?Arvind B. Bhome Professor Pulmonary Critical Care Sleep Medicine, B.V. Medical College, Pune 411043, India
8. The clinical use of oxygen in hospitals with limited resources WHO Guidelines for health-care workers, hospital engineers and managers)
9. A. Chaouat (A.Chaouat. A randomized trial of nocturnal oxygen therapy in chronic obstructive pulmonary disease patients.)
10. Council working Party U.K
11. Fletcher (A double blind trial of nocturnal supplemental oxygen.)
12. Nocturnal Oxygen Therapy (Nocturnal Oxygen Therapy Trial Group- Continuous or Nocturnal Oxygen Therapy in Hypoxemic Chronic Obstructive Lung Disease.)

13. Stephen P. Tarpy (Stephen P. Tarpy Long term oxygen therapy.)John TJ, Dandona L, Sharma VP, Kakkar M. Continuing challenge of infectious diseases in India. Lancet 2011; published online Jan 12. DOI:10.1016/S0140-6736(10)61265-2.

14. Paul VK, Sachdev HS, Mavalankar D, et al. Reproductive health, and child health and nutrition in India: meeting the challenge. Lancet 2011; published online Jan 12. DOI:10.1016/S0140-6736(10)61492-4.

15. The global burden of disease: 2004 updatehttp://www.whoInt/healthinfo/global_burden_disease/GBD_report_2004update_ full.pdf (accessed Oct 12, 2010).Gaziano TA, Galea G, Reddy KS. Scaling up interventions for chronic disease prevention: the evidence. Lancet 2007; 370: 1939–46.

16. Abegunde DO, Mathers CD, Adam T, Ortegon M, Strong K.The burden and costs of chronic diseases in low-income and middle-income countries. Lancet 2007; 370: 1929–38.

17. Report of the National Commission on Macroeconomics and Health.

18. http://www.atsjournals.org/doi/abs/10.1164/rccm.200703-456so#.U1AXtlWSyGQ

19. GOLD Standards.

20. The Economic Burden of COPD*Sean D. Sullivan, PhD; Scott D. Ramsey, MD, PhD; and Todd A. Lee, PharmD

21. Domiciliary liquid oxygen versus concentrator treatment in chronic hypoxaemia: a cost-utility analysis.

22. World Health Organization. Burden of COPD [Last accessed on 2013 Jun 5]. Available from: http://www.who.int.

23. http://ispub.com/IJHCA/7/1/8093# Original Article -Application of Modern Management Techniques in Healthcare.

24. Article by:-Dr Sundeep Salvi, Director, Chest Research Foundation, Pune expounds on the threat that COPD poses to India and the need for a National COPD Prevention and Control Programme to tackle the menace.

25. Original Article -Prevalence of chronic obstructive pulmonary disease in rural women of Tamil Nadu: implications for refining disease burden assessments attributable to household biomass combustion.

26. India: Towards Universal Health Coverage 3 Chronic diseases and injuries in India

27. India Needs a National COPD Prevention and Control Programme Sundeep Salvi, Anurag Agrawal.

28. Emergence of chronic obstructive pulmonary disease as an epidemic in India Surinder K. Jindal

29. Economic Implications of Chronic Diseases in India Sukumar Vellakkal - South Asia Network for Chronic Disease.

30. The clinical use of oxygen in hospitals with limited resources Guidelines for health-care workers, hospital engineers and managers The World Health Organization Editor: Trevor Duke November 2011

CHAPTER 4

Home Hemodialysis Systems

Introduction

The function of kidneys is to purify body by removing waste and excess fluid. Dialysis is a treatment used for people whose kidneys don't work properly. It's a common treatment that has been used for people with kidney problems since the 1940s.

In medicine, **dialysis** comes from a Greek word **dialusis**, "διάλυσις", meaning **dissolution, dia,** meaning **through**, and **lysis**, meaning **loosening or splitting**, hence it is a process for removing waste and excess water from the blood, and is used primarily as an artificial replacement for lost kidney function in people with renal failure. Dialysis may be used for those with an acute disturbance in kidney function (acute kidney injury, previously acute renal failure), or progressive but chronically worsening kidney function–a state known as chronic kidney disease stage 5 (previously chronic renal failure or end-stage renal disease). The latter form may develop over months or years, but in contrast to acute kidney injury is not usually reversible, and dialysis is regarded as a "holding measure" until a renal transplant can be performed, or sometimes as the only supportive measure in those for whom a transplant would be inappropriate.

The kidneys have important roles in maintaining health. When healthy, the kidneys maintain the body's internal equilibrium of water and minerals (sodium, potassium, chloride, calcium, phosphorus, magnesium, sulfate). The acidic metabolism end-products that the body cannot get rid of via respiration are also excreted through the kidneys. The kidneys also function as a part of the endocrine system, producing erythropoietin and calcitriol. Erythropoietin is involved in the production of red blood cells and calcitriol plays a role in bone formation. Dialysis is an imperfect treatment to replace kidney function because it does not correct the compromised endocrine functions of the kidney. Dialysis treatments replace some of these functions through diffusion (waste removal) and ultrafiltration (fluid removal).

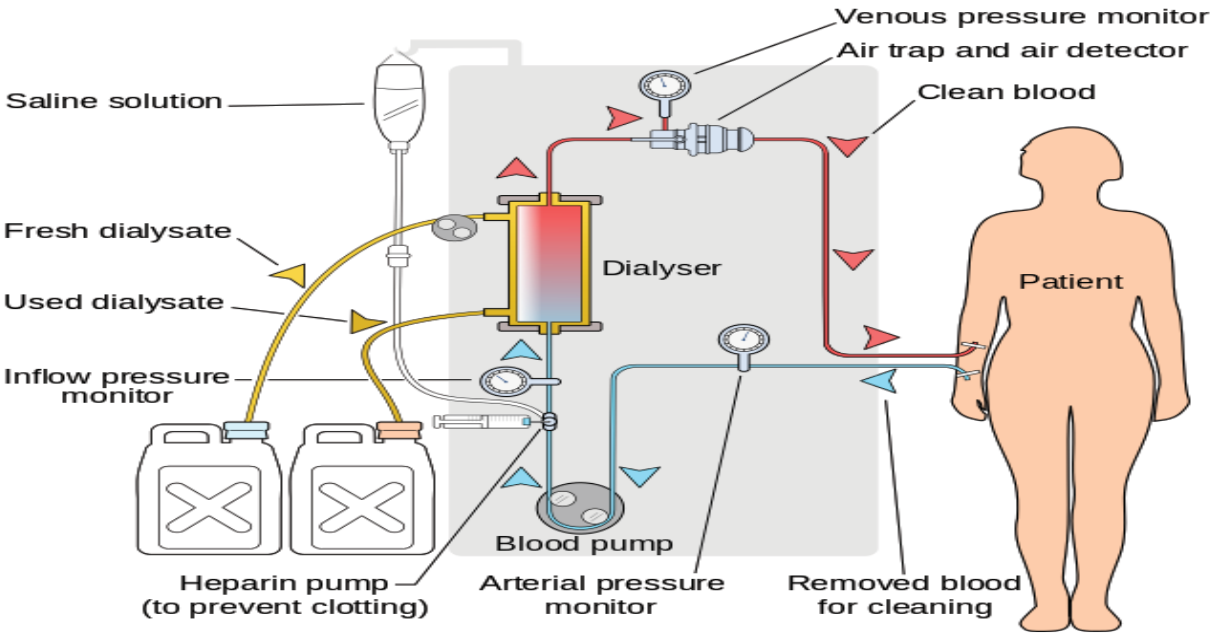
B) Types of Dialysis:

There are three primary and two secondary types of dialysis:

1. Hemodialysis (Primary),
2. Peritonealdialysis (Primary),
3. Hemofiltration (Primary),
4. Hemodiafiltration (Secondary), and
5. Intestinal dialysis (Secondary)

Hemodialysis:

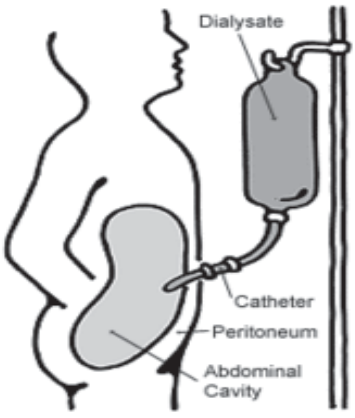
In hemodialysis, the patient's blood is pumped through the blood compartment of a dialyzer, exposing it to a partially permeable membrane. The dialyzer is composed of thousands of tiny hollow synthetic fibers. The fiber wall acts as the semipermeable membrane. Blood flows through the fibers, dialysis solution flows around the outside of the fibers, and water and wastes move between these two solutions. The cleansed blood is then returned via the circuit back to the body. Ultrafiltration occurs by increasing the hydrostatic pressure across the dialyzer membrane. This usually is done by applying a negative pressure to the dialysate compartment of the dialyzer. This pressure gradient causes water and dissolved solutes to move from blood to dialysate, and allows the removal of several litres of excess fluid during a typical 4-hour treatment. As shown below-



Hemodialysis schematic

Peritoneal dialysis:

In peritoneal dialysis, a sterile solution containing glucose (called dialysate) is run through a tube into the peritoneal cavity, the abdominalbody cavity around the intestine, where the peritoneal membrane acts as a partially permeable membrane. The peritoneal membrane or peritoneum is a layer of tissue containing blood vessels that lines and surrounds the peritoneal, or abdominal, cavity and the internal abdominal organs (stomach, spleen, liver, and intestines). Diffusion and osmosis drive waste products and excess fluid through the peritoneum into the dialysate until the dialysate approaches equilibrium with the body's fluids. Then the dialysate is drained, discarded, and replaced with fresh dialysate.



This exchange is repeated 4-5 times per day; automatic systems can run more frequent exchange cycles overnight. Peritoneal dialysis is less efficient than hemodialysis, but because it is carried out for a longer period of time the net effect in terms of removal of waste products and of salt and water are similar to hemodialysis. Peritoneal dialysis is carried out at home by the patient, often without help. This frees patients from the routine of having to go to a dialysis clinic on a fixed schedule multiple times per week.

Peritoneal dialysis can be performed with little to no specialized equipment (other than bags of fresh dialysate). Explained in below mentioned figure:-

Hemofiltration

Hemofiltration is a similar treatment to hemodialysis, but it makes use of a different principle. The blood is pumped through a dialyzer or "hemofilter" as in dialysis, but no dialysate is used. A pressure gradient is applied; as a result, water moves across the very permeable membrane rapidly, "dragging" along with it many dissolved substances, including ones with large molecular weights, which are not cleared as well by hemodialysis. Salts and water lost from the blood during this process are replaced with a "substitution fluid" that is infused into the extracorporeal circuit during the treatment.

Hemodiafiltration

Hemodiafiltration is a combination of hemodialysis and hemofiltration.

Intestinal dialysis

In intestinal dialysis, the diet is supplemented with soluble fibres such as acacia fibre, which is digested by bacteria in the colon. This bacterial growth increases the amount of nitrogen that is eliminated in fecal waste. An alternative approach utilizes the ingestion of 1 to 1.5 liters of non-absorbable solutions of polyethylene glycol or mannitol every fourth hour.

Starting Indications:

The decision to initiate dialysis or hemofiltration in patients with renal failure depends on several factors. These can be divided into acute or chronic indications.

- Indications for dialysis in the patient with acute kidney injury are summarized with the vowel acronym of "AEIOU"
    1. Acidemia from metabolic acidosis in situations in which correction with sodium bicarbonate is impractical or may result in fluid overload.
    2. Electrolyte abnormality, such as severe hyperkalemia, especially when combined with AKI.
    3. Intoxication, that is, acute poisoning with a dialyzable substance. These substances can be represented by the mnemonic SLIME: salicylic acid, lithium, isopropanol, magnesium-containing laxatives, and ethylene glycol.
    4. Overload of fluid not expected to respond to treatment with diuretics
    5. Uremia complications, such as pericarditis, encephalopathy, or gastrointestinal bleeding.
- Chronic indications for dialysis:
    1. Symptomatic renal failure.
    2. Low glomerular filtration rate (GFR) (renal replacement therapy (RRT) often recommended to commence at a GFR of less than 10-15 mls/min/1.73m2). In diabetics, dialysis is started earlier.
    3. Difficulty in medically controlling fluid overload, serum potassium, and/or serum phosphorus when the GFR is very low.

Home Haemodialysis (HD):

It is the provision of hemodialysis in the home of people with kidney disease.

It is initiated after a period of training of the patient and their care takers. Home HD offers the opportunity to tailor the dialysis regime more closely to individual requirements by changing the timing, the length and/or the frequency of dialysis sessions.

Hospital Haemodialysis (HD):

It is provided in a specialized unit in a usually where nephrology care is available. In the current scenario where nephrology beds, dialysis beds and nephrologist are well short of the numbers required to tackle burden of disease, hospital HD seems to inadequately cover the current need.

This HTA evaluates:

1. The clinical benefits of home HD over hospital based HD.
2. Explains cost effectiveness analysis of home based HD.
3. Elaborates on demand and supply assessment.

F) Clinical Effectiveness of Home Hemodialysis versus Hospital Hemodialysis

Objectives:

1. To assess the clinical effectiveness of HomeHemodialysis(HD) versus Hospital Hemodialysis (HD) for patient with Renal Failure.
2. To assess the cost-effectiveness of Home HD and Hospital HD.
3. To understand practicality of home HD in an Indian house hold setting and device market context.

Methodology:

We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, MEDLINE, PUBMED Science Direct, SCOPUS and Journal of the American Society of nephrology for relevant studies. We also conducted secondary referencing by manually reviewing reference lists of key articles and searching citations by using Web of Science. We selected studies on the basis of inclusion and exclusion criteria. We also conducted specific searches for primary studies published more recently than the included systematic reviews and meta-analyses. We included studies showing comparison of cost effectiveness of Home HD and Hospital HD. Types of studies included during search were: Randomized controlled trial, observational analytical studies, Case control and cohort studies.

Types of interventions taken are Home HD &Hospital HD.

Overall outcome measure was survival (overall mortality)

Keywords:

The key words used were “Home dialysis”, “Portable Dialysis”, “Effectiveness of Home dialysis”, “Clinical effect of Home dialysis”.

Data collection and analysis:

Hard copies of studies whose title or abstract were assessed as potentially relevant were obtained, and were assessed for subject relevance and methodological quality. Extraction of data from each study describing the characteristics of participants, interventions and outcome were measured. Only published data in the identified trials was used.

Selection of studies:

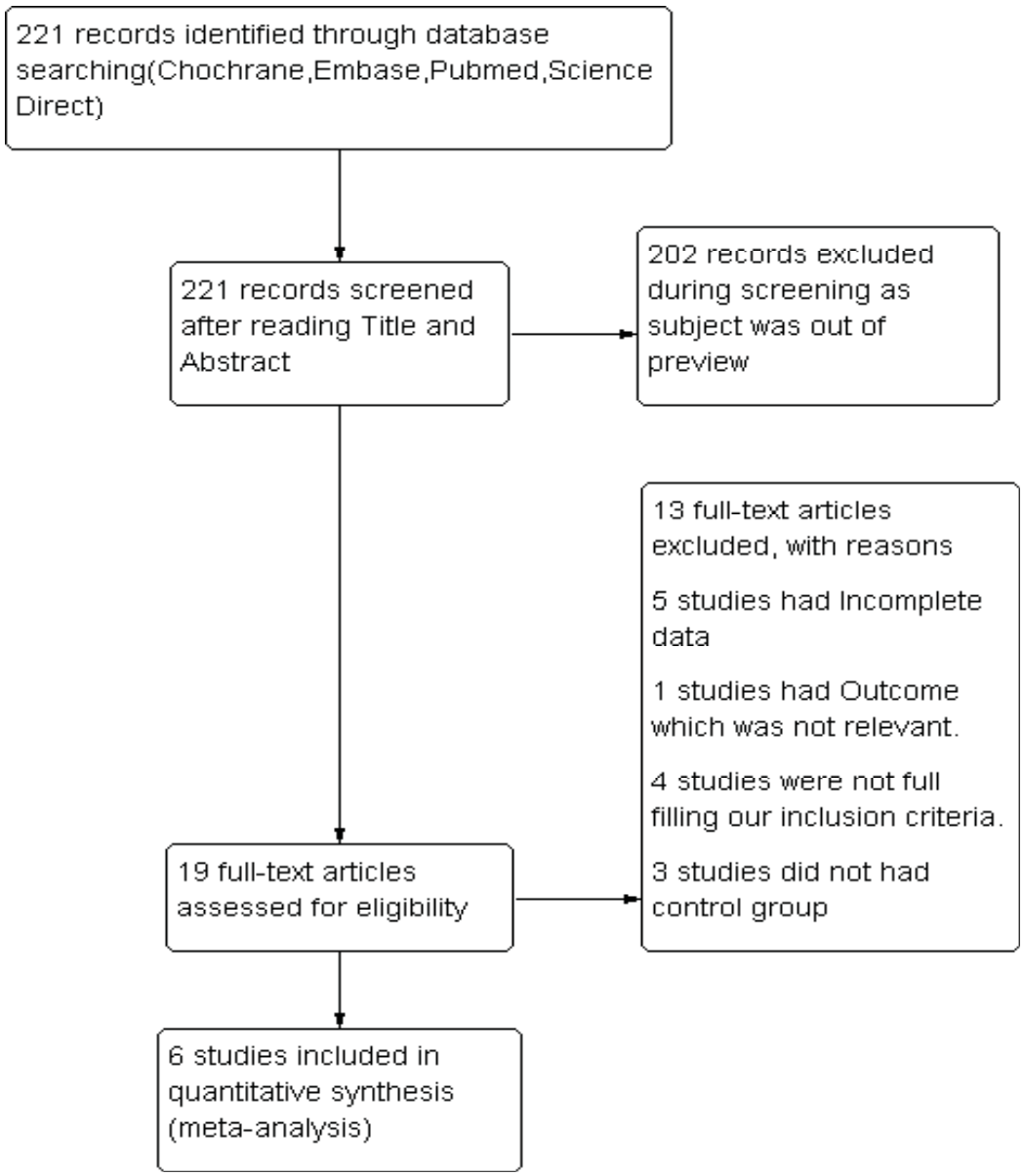
The search strategy described was used to obtain titles and abstracts of studies that were relevant to the review. The titles and abstracts were screened all those studies that were not relevant were excluded. Those satisfying the inclusion criteria were finally included and full text of these were considered for review. Studies and reviews including relevant data or information were retained.

Data management:

Survival rate of two modalities (Home HD and Hospital HD), were extracted from the studies included.221 studies were identified through database searching. 202 were excluded during screening. 19 full articles were assessed for eligibility to include in systematic analysis. Finally, 6 studies were included in systematic review on the basis of selection criteria.

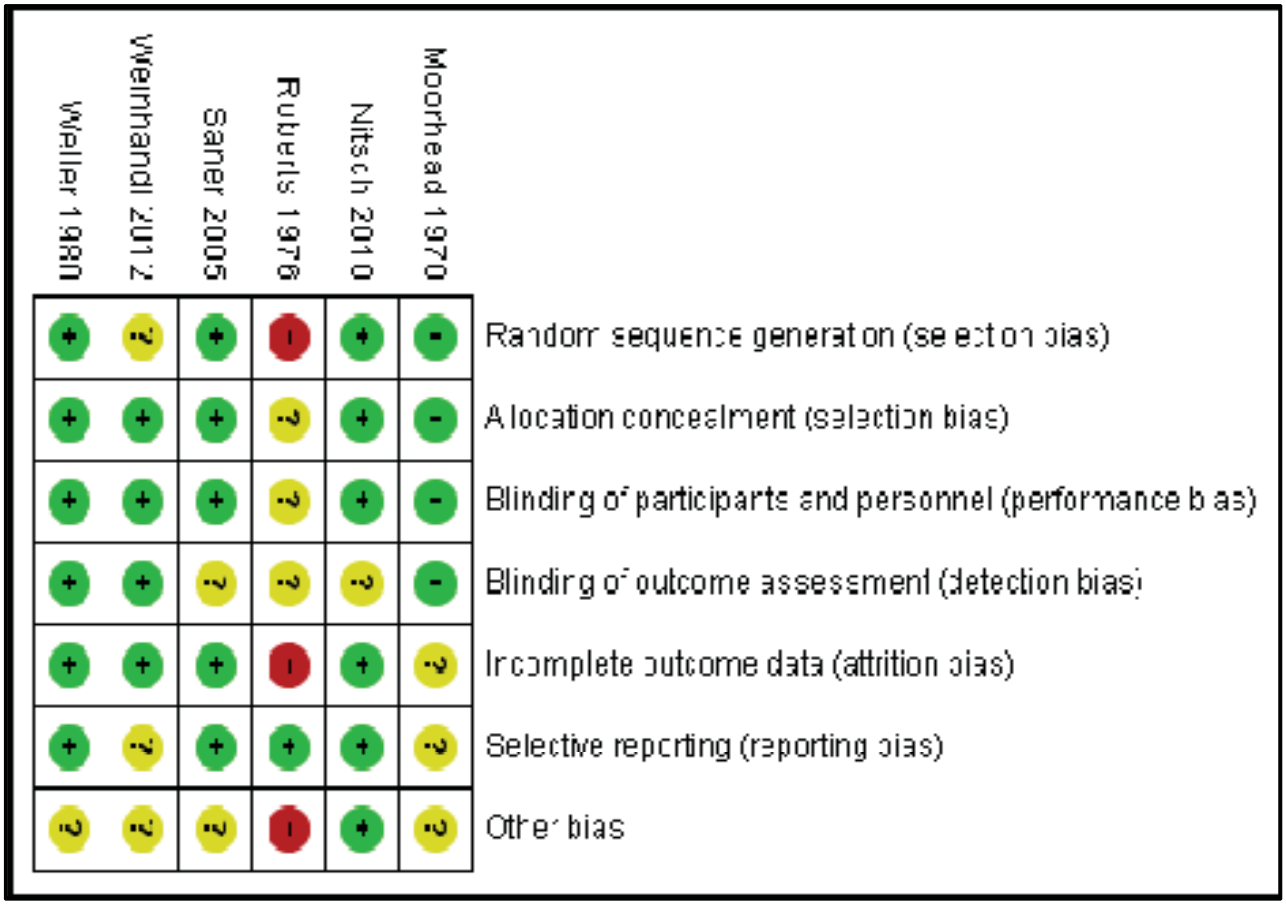
G) Study Flow Diagram

Risk of Bias:

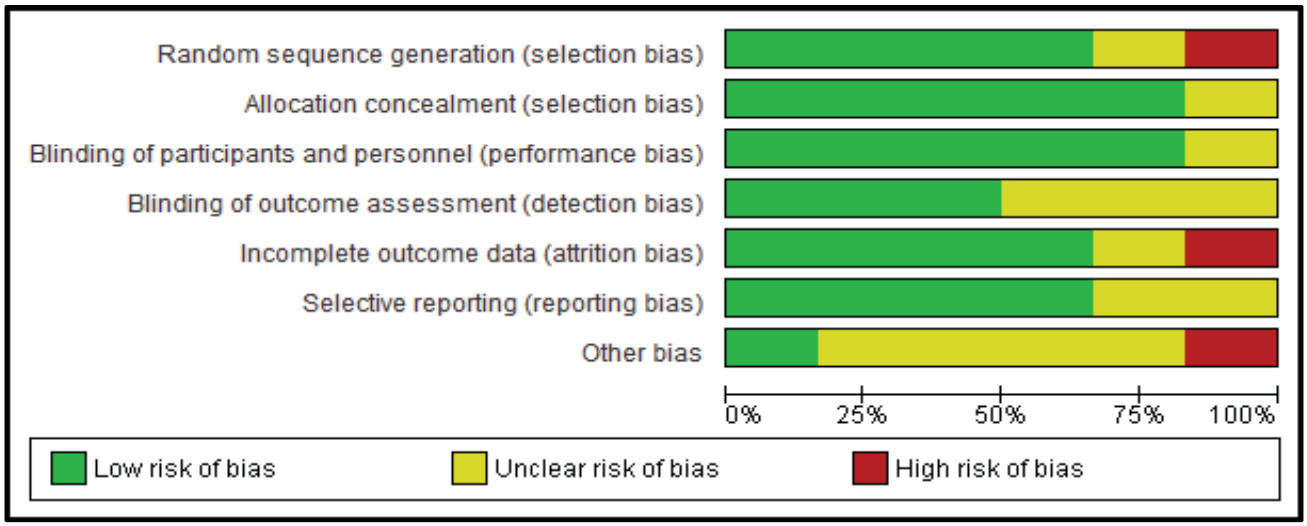


Methodological quality of included studies was reviewed using Cochrane review bias table. Findings of which are as follows:-

Risk of Bias Table



Risk of Bias Summary



Random sequence generation (Selection Bias):1 study showed selection bias *(Roberts 1976)*, as the criteria used by centers in making diagnoses cannot be documented and 1 study having unclear selection bias *(Weinhandl 2012). Rest 4 studies showed low selection bias (Moorhead 1970, Nitsch 2010, Saner 2005, Weller 1980).*

Blinding of participants and personnel (Performance bias): 1 study *(Roberts 1976)* having unclear performance bias, as blinding not possible due to criticality of the intervention.***Remaining 5 studies showed low risk of performance bias.***

Blinding of outcome assessment (detection bias): 3 studies *(Nitsch 2010, Roberts 1976 and Saner 2005)* showed unclear detection bias, as no such information was found.

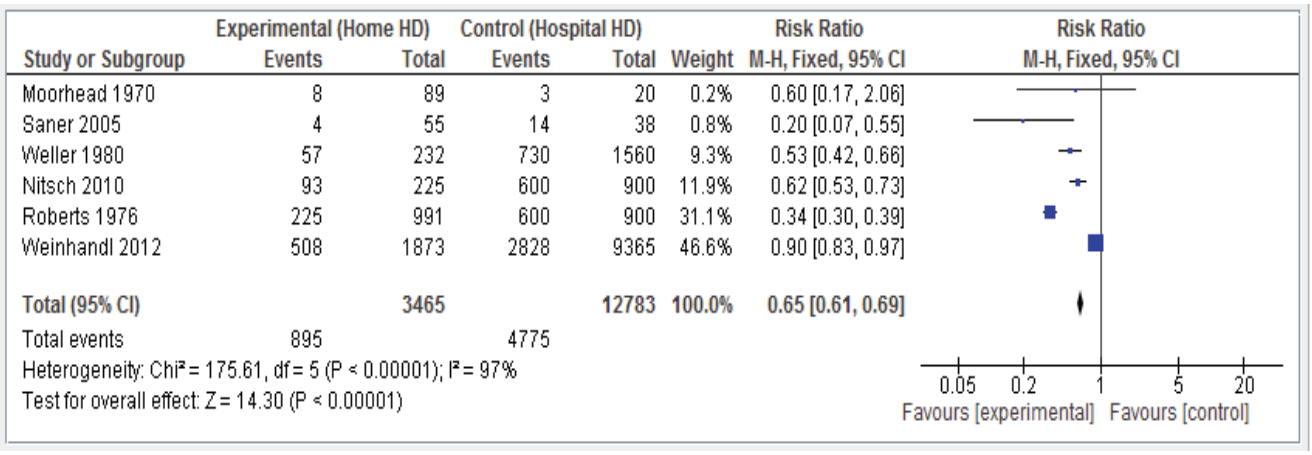
Incomplete outcome data (attrition bias) :Only 1 study *(Roberts 1976)*showed attrition bias, as outcomes are biased for the entire patient.***Rest (Moorhead 1970, Nitsch 2010, Saner 2005, Weller 1980) studies showed low bias.***

Selective reporting (reporting bias) : In *Moorhead 1970,* no information was given and *Weinhandl 2012,* the study did not have data regarding dialysis adequacy, dose, or frequency during follow-up, hence both showed unclear reporting bias.

Overall the risk of bias in all studies was low indicating high quality of results.

Results:

A). Forest Plot showing Impact on mortality by different modalities of Hemodialysis



As per Forest plot, findings:

RR = 0.65, which is less than 1.

Risk Ratio (RR) less than 1 means experimental intervention (Home HD) is more effective than control (Hospital HD)

RR of 0.65 means 35% reduction in mortality (Primary outcome) due to Home HD as compared to Hospital HD.

However the studies have not assessed outcomes at the same time .Home dialysis could have immense role in enhanced patient satisfaction and reduction in hospital acquired infections. This may be contributing towards reduction in mortality.

J) Impact of Home HD (Hemodialysis) –

1. Current burden of disease:

- ❖ It is reported that annual number of new cases for the ESRD is 2, 20, 000 andannual death due to ESRD (end stage renal failure disease) in India, is 2,00,000(Sudarshan B 2007).
- ❖ Also, the total annual number of patients currently on HD is estimated to be 55,000. (Vivekanand A 2013).

2. Effect of Home HD on the population which are on HD

a. Hospital HD –

- ❖ According to the forest plot , death rate in Hospital HD –

= Events (Deaths) /Total Number of participants

= 4775/12783

= 37.4%

- ❖ Total number of patients on Hospital HD in India = 55,000/annum
- ❖ Expected deaths due to Hospital HD will be -

=37.4% X Total number of patient on HD

= 37.4% X 55,000

= 20,570 deaths/ year

b. Home HD –

- ❖ Total deaths in Home HD = 35% less than that in Hospital HD

= 65% X deaths in Hospital HD

= 65% X 20,570 deaths/year

= 13,370 deaths/ year

Decline in deaths (ΔD) = Deaths due to Hospital HD – Deaths due to Home HD

= (20,570 – 13,370)

= 7,200 decline in deaths per year

7,200 per year are the additional lives saved, if Home HD be used in place of Hospital HD, even for the target population of 55,000 patients that are having access to dialysis in India, currently.

3. Effect of Home HD on the total target population of ESRD

Fresh estimates on total number of patient of ESRD in India–

Total number of patient per year suffering from ESRD = 2, 20,000

Number of patient on HD in India per year = 55,000

Therefore, Number of patient don't receive the treatment

= No. of patient suffering from ESRD – No. of patient on HD

= 1, 65,000

Therefore, 1, 65,000 are the patients who do not have excess to any kind of HD.

Hospital HD –

- ❖ According to the forest plot, death rate in Hospital HD –

  = Events (Deaths) /Total Number of participant

  = 4775/12783

  = 37.4%

- ❖ Expected deaths due to Hospital HD, on population will be -

  =37.4% X Total number of patient not having access to HD.

  = 37.4% X 1, 65,000 deaths/ year

  = 61,710 deaths / year

- ❖ Expected death in population currently on hospital HD (55,000)

  = 20,570 deaths

- ❖ Therefore, total deaths per year in total population (2, 20,000)

  = Expected death in population not having access to HD (1,65,000) + Expected death in population on HD (55,000)

  = 61,710+20,570

=82,280 deaths, even if we able to generate sufficient infrastructure to provide "Universal Access" to ESRD by Hospital based HD, which is not feasible currently, due to infrastructural constraints, financial limitations and lack of skill sets to provide dialysis are in all geographic areas of the country.

In absence of plan to provide dialysis facility to 1,65,000, their fate is known.

Home HD –

a. **For patients currently not having any access to HD –**

- ❖ Population = 1,65,000
- ❖ Number of deaths by Hospital HD = 61,710
- ❖ Total deaths in home HD = 65% of deaths by Hospital HD

  =65% X 61,710

  = 40, 112 deaths/year

Therefore, Total lives saved in total target population:

= Lives saved per year in population of 1, 65,000 (not undergoing any form of dialysis) + Lives saved per year in population of 55,000 (undergoing hospital based HD)

= (2, 2000 -40. 112) + 7200 = 187080

=Which is 85% of ESRD patients (target population i.e. 2, 20,000).

In current scenario, what happens to the fate of 1.65000 patients who fail to receive any type of dialysis care is unknown; although a small % of them undergo peritoneal dialysis which requires hospital based prolonged care.

20,570 patients loose life despite having access to hospital based HD.

4. Demand and Supply of HD in India

a. Supply of HD in India -

Now, total number of HD center presently, in India = 5,500. 90% are private and rest is Government (*Vivekanand A 2013*) based institutions.

S. No.	Private	Government	Total
Number of centers	4,950	550	5,500
Number of beds	24,750	2,750	27,500

Total number of beds available in India = 27,500, at an average of 5 dialysis needs per center.

Now,

Number of patient per day who could be provided/dialysis bed/machine

(HD) = 2

Number of days per year for HD = 300

(Approximate number of working days)

Present supply of HD cycles per year = No. of total beds X No. of patient per day X No. of days available per Year

= 27,500 X 2 X 300

= 1.65 crore HD/year

b. Demand of HD in India –

Total number of target population of ESRD = 2,20,000

Average no. of HD sessions required per week = 3

Total number of weeks per year= 52

Demand of HD per year = No. of total target population X HD required per Week X Total number of weeks per year.

= 2,20,000 X 3 X 52

= 3.432crore HD/year

Hence, Shortage of HD in India = 51.92%

Thus, current infrastructure is sufficient to provide dialysis support to less than half of the target population.

5. Cost effectiveness analysis:

Cost-effectiveness analysis is a method of comparing the cost and effectiveness of two or more alternatives. Such comparisons are useful when one of the alternatives being considered is standard care, as this allows the decision maker to consider whether an alternative is better or not.

A quality-adjusted life-year (QALY) takes into account both the quantity and quality of life generated by healthcare interventions. It is the arithmetic product of life expectancy and a measure of the quality of the remaining life years.

In other words, the QALY is a measure of the value of health outcomes. Since health is a function of length of life and quality of life. The basic idea underlying the QALY is simple: it assumes that a year of life lived in perfect health is worth 1 QALY (1 Year of Life × 1 Utility value = 1 QALY) and that a year of life lived in a state of less than this perfect health is worth less than 1. In order to determine the exact QALY value, it is sufficient to multiply the utility value associated with a given state of health by the years lived in that state. QALYs are therefore expressed in terms of "years lived in perfect health": half a year lived in perfect health is equivalent to 0.5 QALYs (0.5 years × 1 Utility), the same as 1 year of life lived in a situation with utility 0.5 (e.g. bedridden) (1 year × 0.5 Utility). QALYs can then be incorporated with medical costs to arrive at a final common denominator of cost/QALY. This parameter can be used to develop a cost-effectiveness analysis of any treatment.

- QALY gained by Home HD per patient = 2.73 (Graham Mowatt, 2002).
- QALY gained on total target population:

  = QALY per patient on Home HD X Total target population needs Home HD

  = 2.73 X 2, 20,000

  = 6, 00,600 QALY
- QALY gained by Hospital HD per patient = 2.02 (*Graham Mowatt, 2002*).
- QALY gained on total population on Hospital HD:

  = QALY per patient on Hospital HD X Total population on Hospital HD

  = 2.02 X 55,000

  = 1, 11,100 QALY
- Difference in QALY (ΔQ):

  = QALY gained for Home HD – QALY gained for hospital HD

  =6, 00,600 – 1, 11,100

  = 4, 89,500 QALY

  $$\text{ICER} = \frac{\text{7878 cr-4752 cr}}{\text{489500 QALY}}$$

  $$= \frac{\text{32400 lakhs}}{\text{489500 QALY}}$$

  =0.638 lakhs /QALY gained= Rs. 63,800 per QALY gained

This value is less than the per capita GDP of India, and hence the home dialysis is a very cost effective option as compared to hospital dialysis. However, the financial sustainability of the ESRD treatment versus other competing health priorities would need consideration before any recommendation for wide public health commissioning of home-dialysis is undertaken.

6. Home HD machine–

a. Models of Home HD:

Home HD machine is not manufactured in India.However, models available for Home HD are:

i. Nx Stage-System One [#].

The NxStage System One acts like any other piece of home electronics . NxStage innovations are expanding and improving treatment options – and giving patients and caregivers the ease and flexibility to perform treatment when they want,where they want, and how they want. The

NxStage System One allows users more free range as to when they perform treatments and for how long (such as frequent short daily treatments).

ii. **Fresenius K at Home [#]:**

Offering a broad range of therapies, including traditional or short-daily home hemodialysis therapy, the Fresenius-K allows patients to tailor treatments to their needs. Physicians have a choice of a wide variety of dialysate and dialyzer options, thereby creating a customized prescription for each patient. Step-by-step instructions keep regular home hemodialysis treatments easy to perform. The Fresenius-K at Home offers users the flexibility to schedule the frequency and duration of their treatments on their terms.

Models, Suppliers in India

Cost of Home HD machine = $ 10,000 (*Christopher R Blagg,*)

= Rs. 6,20,000

=Rs. 6.20 lakh

References-{#}

Fresenius. http://www.fresenius.com/84.htm

Nx Stage. http://www.nxstage.com/homehemodialysis/products/the-system-one-cycle

Conclusion

Home HD offers a reliable and safe modality of dialysis with better survival results in full care Hospital HD. In addition, Home HD ensures a striking financial benefit as compared with higher costs if the patients were treated with Hospital HD. These modalities should be encouraged for all HD patients who could be treated by Home HD.

In one of the studies it was reported that outcome of 13 patients, "long survivors", who have been maintained on home hemodialysis for 20 or more years (*Delano BG, 1996*).

In another study the 5 year and median survival estimates were significantly better for the home HD patients versus other dialysis modalities, and home HD patients had less co - morbidity (*Mailloux LU, 1996*).

The current dependence on the private sector for the treatment of kidney patients with severe renal disease needs to be reduced with infrastructure up gradation in government run hospitals to facilitate accessibility of treatment for the majority of our population who cannot afford treatment in private hospitals. However infrastructure capable of providing 3.432 cr dialysis sessions cannot be achieved immediately. Home dialysis may be considered as a safe and cost effective method coupled with periodic consultation with physician / nephrologists.

Bibliography:

1. VivekanandJha. Current status of end stage renal disease care in India and Pakistan. Kidney International Supplements 2013(3), 157-160
2. John F. Moorhead, R.A. Baillod, J.P.Hopewell, A.H Knight, R.E Crockett, O.N. Fernando, Z. Varghese. Survival rates of Patients Treated by Home and Hospital Dialysis and Cadaveric Renal Transplantation. British Medical Journal, 1970 1970;4:83-85.

3. Eric D. Weinhandl, Jiannong Liu, David T. Gilbertson,Thomas J. Arneson, and Allan J. Collins. Survival in Daily Home Hemodialysis and MatchedThrice-Weekly In-Center Hemodialysis Patients.. [Other:]
4. Jimmy L Roberts. Analysis and outcome of 1063 patients trained for home hemodialysis.. Kidney International 1976;9:363-374.
5. Esther Saner, Dorothea Nitsch, Claude Descoeudres, Felix J. Frey and Dominik E. Uehlinger. Outcome of home haemodialysis patients: a case cohort study. Nephrol Dial Transplant 2005; 20:604-610.
6. Eric D. Weinhandl, Jiannong Liu, David T. Gilbertson, Thomas J. Arneson,and Allan J. Collins. Survival in Daily Home Hemodialysis and MatchedThrice-Weekly In-Center Hemodialysis Patients.. Journal of the American Society of Nephrology 2012;23(5):895-904.
7. John M. Weller, Friedrich K. Port, Richard D. Swartz, C. William Fergusan, George W. Williams and John F. Jacobs, JR..Analysis of survival of end stage renal disease patients. Kidney International 1982; 21:78-83.
8. Dialysis in India.
   http://www.dialysis.org.in/2010/06/cost-comparison.html
9. Delano BG.. Home hemodialysis offers excellent survival..AdvRen Replace Ther 1996;3:106-111
10. Mailloux LU, Kapikian N, Napolitano B et al..Homehemodialysis: patient outcomes during a 24-year period oftime from 1970 through 1993..AdvRen Replace Ther 1996;3:112-119.
11. Christopher R Blagg. Advance safety in medical Technology. http://www.aami.org/publications/hh/home.blagg.pdf.
12. Graham Mowatt, Luke Vale, Juan Perez, Laura Wyness et al, Systemetic review of the effectiveness and cost effectiveness of home versus hospital or satellite unit hemodialysis for people with end stage renal failure.
    http://en.wikipedia.org/wiki/Dialysis

CHAPTER 5 Diagnostic Tests for Thalassemia

A) Introduction

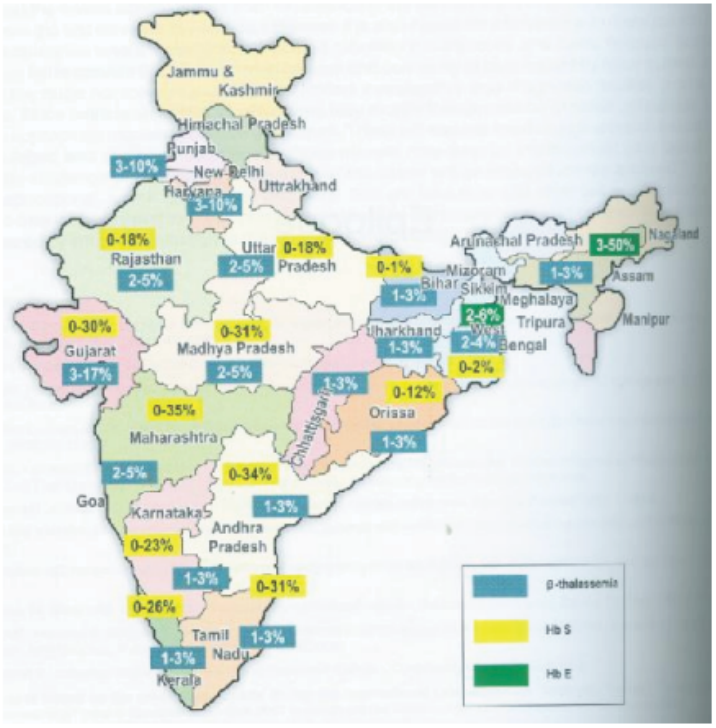
Thalassemias are grouped as recessive autosomal inherited anaemic conditions caused by mutations in the β- and β-globin genes, eventually resulting in the decreased production of either of the globin chains of haemoglobin (Hb). Thalassemias are also the most common of monogenic disorders in the world.

World Health Organization - estimates that 5% of the world population is carriers for Hb disorders. The frequency of β-thalassemia in India ranges from 3.5 to 15% in general population. Ethnic groups like Sindhis, Kutchi Bhanushalis, Punjabis, Jains and Muslims are more prone. Every year 10,000 children with thalassemia major are born in India, accounting for 10% of the total numbers in the world. India spends nearly Rs. 1,000 crore per annum in the treatment of thalassemia patients. Majority of the centers in India use conventional methods for diagnosis of hemoglobinopathies, which includes clinical and family history, red cell indices, complete blood counts (CBC), HbA2, HbF estimation, sickling test, and Hb electrophoresis.

Around 200 mutations are known to cause β-thalassemia worldwide of which, 65 mutations have been characterized in India. Predominantly, 7β-thalassemia mutations are accounting for around 90% of the molecular defects.

B)

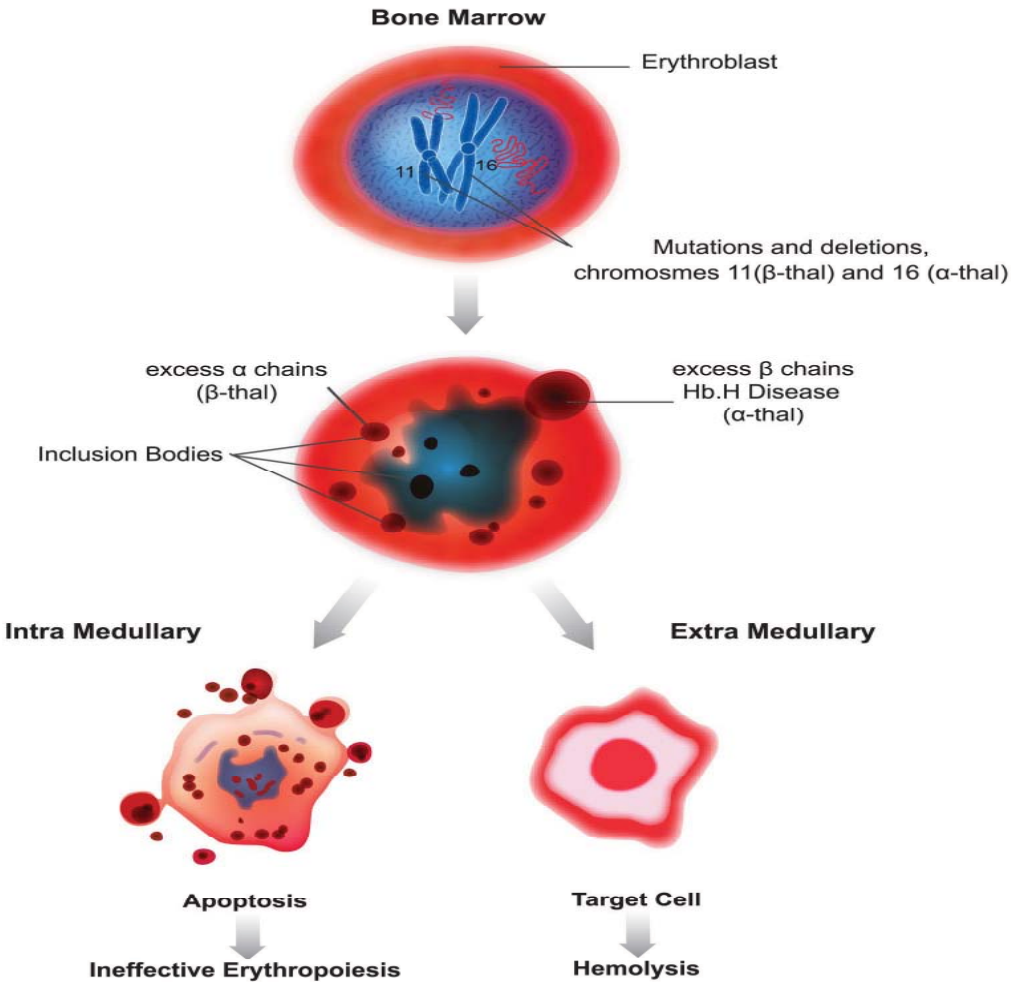
Map showing Distribution of Hemoglobinopathies in India



(Ref: Press Information Bureau of India)

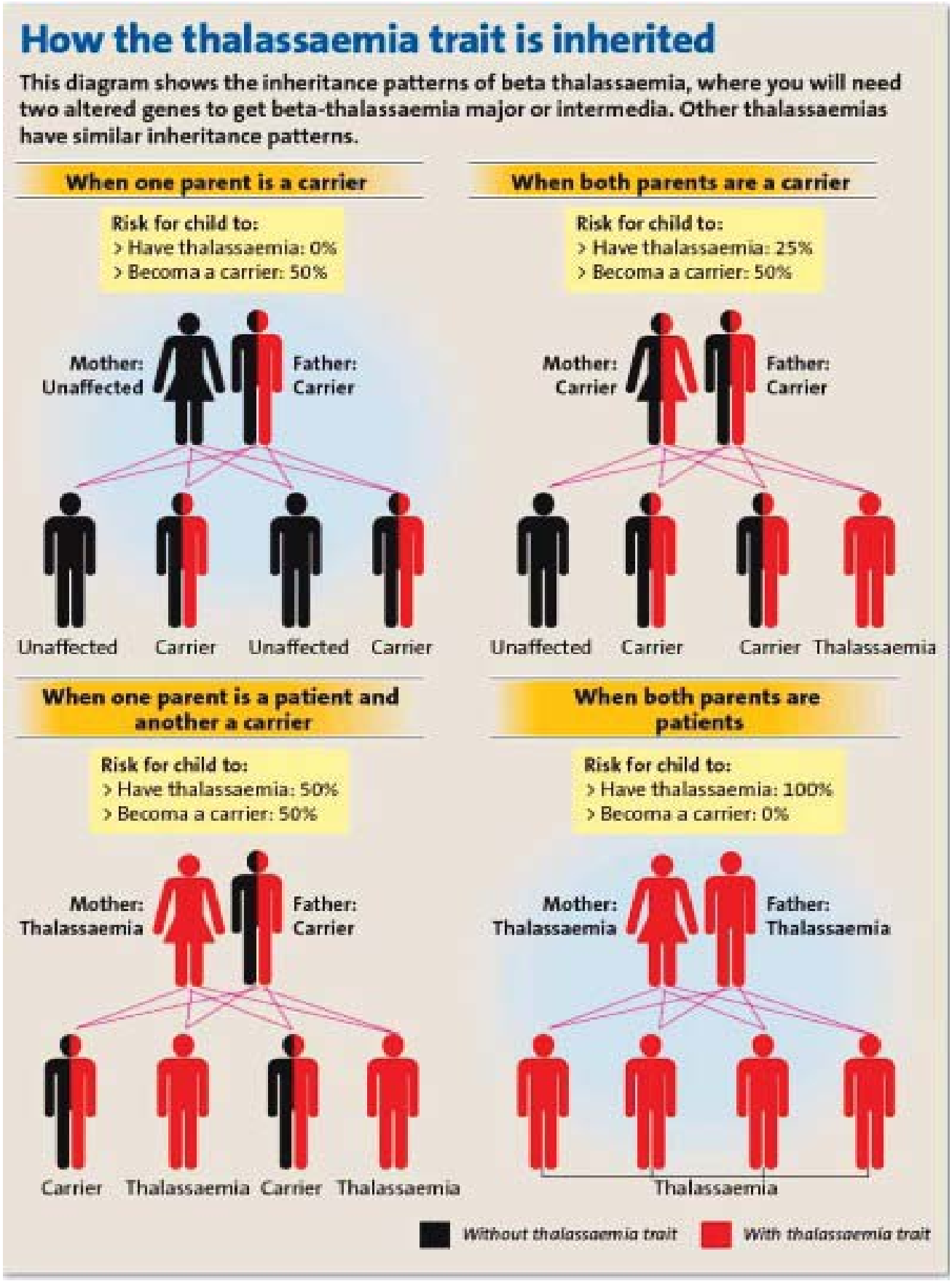
- In the above mentioned figure:-
- Highest distribution of Thalassemia is at Gujarat with 3.17%
- Lowest distribution of Thalassemia is at Bihar, Tamil Nadu and Kerala, Orissa, Andhra Pradesh, Jharkhand and Chhattisgarh with 1.3%
- Highest distribution of Hb S is at Maharashtra with 0.35%
- Lowest distribution of Hb S is at Bihar with 0.1%
- Highest distribution of Hb E is at Nagaland with 3.50%
- Lowest distribution of Hb E is at Meghalaya with 2.6%

C) Pathophysiology of Thalassaemia –



1. This pathology is characterized by decreased Hb production and red blood cell (RBC) survival, resulting from the excess of unaffected globin chain, which form unstable homotetramers that precipitate as inclusion bodies lead to premature cell destruction.
2. In patients with alpha-thalassemia, the defect in alpha chain synthesis results in an accumulation of gamma chains in the fetal and neonatal periods and of beta chains thereafter.
3. The excess of beta chains oxidize and precipitate with cell aging
4. In homozygous beta-thalassemia, a deficiency of beta chain synthesis results in an accumulation of alpha chains
5. The free alpha chains aggregate to form insoluble inclusions in bone marrow erythroid precursors.
6. In thalassemia syndromes there is often ineffective erythropoiesis and hemolysis, which leads to anemia.

D) Genetics of Thalassaemia



E) Diagnostic test available –

The key to controlling and minimizing the disease prevalence begins with appropriate and feasible screening procedures. There are various methods available for carrier screening. These are –

1. Mean Corpuscular Volume (MCV) [*] –

The mean corpuscular volume, or "mean cell volume"(MCV), is a measure of the average volume of a red blood corpuscle (or red blood cell). The measure is attained by multiplying a volume of blood by the proportion of blood that is cellular (the hematocrit (or haematocrit)), and dividing that product by the number of erythrocytes (red blood cells) in that volume. The mean corpuscular volume is a part of a standard complete blood count. In a laboratory test that computes MCV, erythrocytes are compacted during centrifugation.

2. Naked Eye Single Tube Red Cell Osmotic Fragility Test (NESTROFT) –

The principle of NESTROFT is based on the limit of hypo tonicity which the red cell can withstand. In this procedure 2 ml of 0.36% buffered saline is taken in a test tube, 20ml of whole blood is added to it, and is allowed to stand at room temperature. After 20 minutes reading is taken on a NESTROFT stand on which a thin black line is marked. If the line is visible through the solution, the test is considered as negative and if line is not visible it is considered as positive. Positive test is due to the reduced osmotic fragility of red cells.

3. Osmotic Fragility Test –

Blood is drawn from a vein, usually from the inside of the elbow or the back of the hand. The site is cleaned with germ-killing medicine (antiseptic). The health care provider wraps an elastic band around the upper arm to apply pressure to the area and make the vein swell with blood.

Next, the health care provider gently inserts a needle into the vein. The blood collects into an airtight vial or tube attached to the needle. The elastic band is removed from the arm. Once the blood has been collected, the needle is removed, and the puncture site is covered to stop any bleeding.

In infants or young children, a sharp tool called a lancet may be used to puncture the skin and make it bleed. The blood collects onto a slide or test strip. A bandage may be placed over the area if there is any bleeding.

4. Reverse Dot Blot Hybridisation (RDBH)–

This test is used for the identification of seven common beta-thalassaemia mutations and two common abnormal hemoglobins (Hb S and Hb E) which will cover most of mutations in hemoglobinopathies.

In RDBH DNA is obtained from a 12-week-old foetus by chorionic villus sampling and was amplified using specific primers by the polymerase chain reaction and analysed by the reverse dot blot test in following steps *(Muralitharan S, 1996)*–

i. The amplified DNA is labelled using 5′ modified primers with biotine.

ii. Oligonucleotide probes are 5' amino-modified. A NH2 group is added during the last step of the synthesis.

iii. Membrane (Biodyne-C, PALL-Biosupport) is activated by EDC and the oligonucleotide probe is spotted on the surface of the membrane using a 2 μL pipette. On the left and on the right of the same lane are spotted the normal and the mutant oligonucleotides.

iv. After inactivation of membrane, it is pre-hybridized for 15 min at 45oC.

v. Amplified DNA is diluted in hybridization solution and de naturated at 95oC for 10 minutes. Then it is added to the pre-hybridized membrane.

vi. Membranes are incubated for 60 min at 45oC and then washed for 20 min at 45oC.

vii. Conjugation step with streptavidin-AP is performed for 30 min at room temperature.

viii. The membranes are washed for 15 min at room temperature.

ix. Finally, the filters are incubated in a solution containing NBT/BCIP and the color is developed in 30-45 min.

Results were available within 36 hours after sampling.

[*]-MCV

From a critical perspective and aiming at future mutant free populations, the most feasible option could be to test the mothers antenatally in early pregnancy preferably in the first trimester.{Reference - ($)-Manjula Maheshwari, Sadhna Arora, Madhulika Kabra and P.S.N. Menon , Carrier Screening and Prenatal Diagnosis of b-Thalassemia Indian Pediatrics 1999;36: 1119-1125].}

F) Management & Treatment –

a. Long term treatment –

Blood Transfusions

Transfusions of red blood cells are the main treatment for people who have moderate or severe thalassemias. This treatment gives you healthy red blood cells with normal hemoglobin.

During a blood transfusion, a needle is used to insert an intravenous (IV) line into one of your blood vessels. Through this line, you receive healthy blood. The procedure usually takes 1 to 4 hours.

Red blood cells live only for about 120 days. So, you may need repeated transfusions to maintain a supply of healthy red blood cells.

If you have thalassemia, you may need blood transfusions on frequent occasions. For example, you may need this treatment when you have an infection or other illness, or when your anemia is severe enough to cause tiredness.

If you have beta thalassemia major, or Cooley's anemia, you need regular blood transfusions (often every 2 to 4 weeks). These transfusions will help you maintain normal hemoglobin and red blood cell levels.

Blood transfusions allow you to feel better, enjoy normal activities, and live into adulthood. This treatment is lifesaving, but it's expensive and carries a risk of transmitting infections and viruses (for example, hepatitis).

Leucodepletion filter –

Leucodepletion refers to reduction in leucocyte count to $< 5X\ 10^6$ cells / unit of blood component. Leucocyte reduced , leuco-poor and leuco-free are the various terms used but “leucocyte depleted” is the universally accepted one.

Most of the complications associated with blood transfusion are due to the presence of leucocytes in blood and blood products. Blood components like packed red cells and platelets are rich in allogenic leucocytes which are responsible for complications like febrile non-hemolytic transfusion reactions (FNHTRs) and platelet refractoriness.

Iron Chelation Therapy

Because the hemoglobin in red blood cells is an iron-rich protein, regular blood transfusions can lead to a buildup of iron in the blood. This condition is called iron overload. It damages the liver, heart, and other parts of the body.

To prevent this damage, iron chelation therapy is needed to remove excess iron from the body. There are two types of iron Chelation therapy are present –

i. Parenteral
ii. Oral

Folic Acid Supplements

Folic acid is a B vitamin that helps build healthy red blood cells. You may need to take folic acid supplements in addition to treatment with blood transfusions and/or iron chelation therapy.

a. Permanent Treatment –

Blood and Marrow Stem Cell Transplant

A blood and marrow stem cell transplant replaces faulty stem cells with healthy ones from another person (a donor). Stem cells are the cells inside bone marrow that make red blood cells and other types of blood cells.

A stem cell transplant is the only treatment that can cure thalassemia. But only a small number of people who have severe thalassemias are able to find a good donor match and have the risky procedure.

G) Materials and Methods:

Strategic literature search was conducted using the biomedical literature databases: Cochrane databases of systematic review, PUBMED and Science Direct. The keywords used were "sensitivity and specificity detection thalassemia", "Screening Thalassemia diagnostic accuracy", "Mean Corpuscular Volume test sensitivity and specificity thalassemia", "MCV sensitivity and specificity thalassemia," "MCV diagnostic accuracy", "Osmotic Fragility test thalassemia", " NESTROFT sensitivity and specificity", " NESTROFT thalassemia sensitivity specificity"."PCR diagnosis Thalassemia", "PCR sensitivity specificity thalassemia" and Red Dot Blot Thalessimia sensitivity and specificity", "Red Dot Blot Thalessimia thalassemia sensitivity specificity" "Red Dot Blot Thalessimia diagnosis Thalassemia", "Red Dot Blot Thalessimia sensitivity specificity thalassemia". 25 diagnostic test studies were retrieved.10 articles were excluded as they had no representation of quantitative outcome in terms of diagnostic accuracy. 15 studies were found to have relevance with the review objective including abstracts. 6 studies had data – of number of patients with true positive (TP), true negative (TN), false negative (FN), false positive (FP) - and were considered for the data extraction.

The extracted data was entered in Cochrane Review Manager 5.2 Diagnostic Test Accuracy Review in "Data and Analyses" section after entering the study name and year. The multiple test based analysis was selected to have simultaneous graphical representation of forest plots of 3 different diagnostic tests. Positive and negative likelihood ratios were calculated and comparative observational analysis was conducted and relevant inference was concluded. The formula for positive and negative likelihood ratios are as follows:

+ve LR = Sensitivity/ (1-specificity) = TP/FP

-ve LR = (1-sensitivity)/specificity = FN/TN

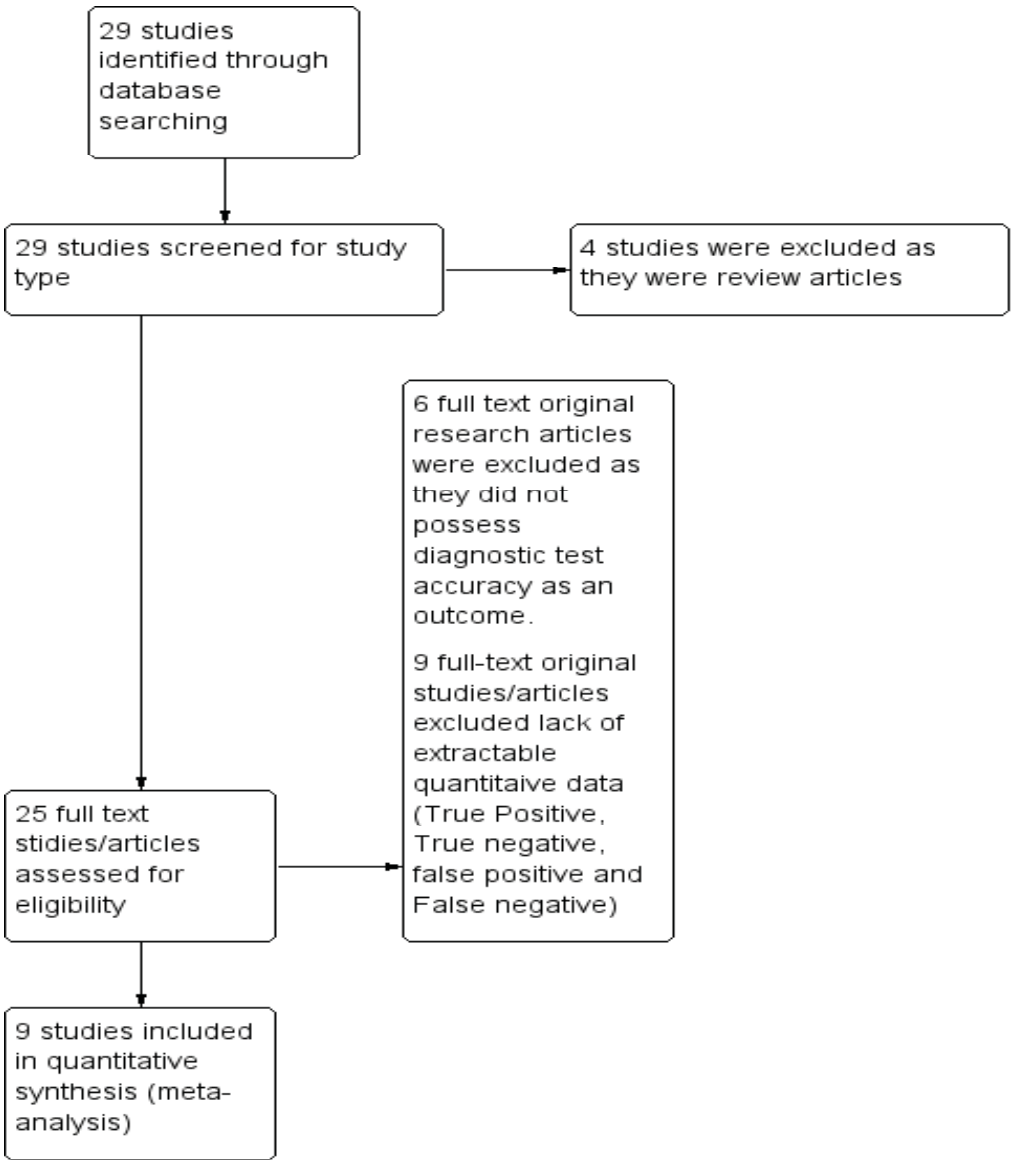
The criteria for choice of optimal test was set according to published recommended threshold values i.e. +LR >= 10, -LR <= 0.1(Stengel D 2003). The findings for LR values for each tests were matched to this criteria and if required adjustment were made.

For economic evaluation, market costs of all screening technologies were considered in form of cost of diagnostic test kit, cost of test or cost of both kit and test. Cost per true positives per test was calculated so as to identify the recommendable diagnostic test technology with most optimum diagnostic accuracy.

For foreseeable impact estimation, epidemiological data on thalassemia was extracted.

From public health point of view, target states and tribal areas with increased prevalence of thalassemia were identified. Current status of thalassemia prevention programme and current technology used for the same under Govt. of India was also determined. For coverage considerations, target population was identified especially in terms of gender and age.

H) The study flow diagram is shown below:



I) Results:

Diagnostic Test –

Data extraction Diagnostic test accuracy: MCV										
S/no.	Study ID (First author _year)	Sensitivity	Specificity	True Positive	True negative	False positive	False negative	Total (N)	Likelihood Ratio Positive	Likelihood Ratio Negative
1	Amna A 2010	0.79	0.30	42	14	33	11	100	1.1286449	0.6967655
2	Sirichotiyakul S 2009	0.93	0.93	39	267	19	3	328	13.977444	0.0765115
3	Sanchaisuriya 2005	0.81	0.76	209	126	39	49	423	3.427251	0.248708
				290	407	91	63	851	3.18	0.15
Data extraction Diagnostic test accuracy: NESTROFT Osmotic fragility test										
S/no.	Study ID (First author _year)	Sensitivity	Specificity	True Positive	True negative	False positive	False negative	Total (N)	Likelihood Ratio Positive	Likelihood Ratio Negative
1	Manglani 1997 (NESTROFT)	0.94	0.64	134	442	246	8	830	2.6391847	0.0876936
2	Piplani 2013(NESTROFT)	1.00	0.85	33	100	17	0	150	6.8823529	0
				167	542	263	8	980	0.63	0.014
Data extraction Diagnostic test accuracy: Osmotic fragility test										
S/no.	Study ID (First author _year)	Sensitivity	Specificity	True Positive	True negative	False positive	False negative	Total (N)	Likelihood Ratio Positive	Likelihood Ratio Negative
1	Sirichotiyakul 2004	0.98	0.75	42	302	101	1	446	3.897306	0.0310334
Data extraction Diagnostic test accuracy: Reverse Dot Blot Hybridisation										
S/no.	Study ID (First author _year)	Sensitivity	Specificity	True Positive	True Negative	False positive	False negative	Total (N)	Likelihood Ratio Positive	Likelihood Ratio Negative
1	Min Lin_2011	1	1	387	40	0	0	427	∞	0
2	George_2012	1	1	258	16	0	0	274	∞	0
2	Winichagoon_1999	1	1	90	16	0	0	106	∞	0
				735	72	0	0	701	∞	0

To neutralize effect of varying sample size in the included studies, the study sample sizes were added together for each category of Test. As per the choice of optimal test, + LR should be greater than 10 and –LR should be less 0.1, for the test to be considered as "robust".

Therefore, Reverse Dot Blot Hybridisation (RDBH) diagnostic test for thalassemia is fulfilling the criteria and gives best outcome as compared to all other tests

J) Cost Effectiveness Analysis:

Cost-effectiveness analysis is a method of comparing the cost and effectiveness of two or more alternatives. Such comparisons are useful when one of the alternatives being considered is standard care, as this allows the decision maker to consider whether an alternative is better or not. The standard care, however, could also be a placebo or "Do Nothing" scenario.

Total number of babies born per year with Thalassaemia major (Tm) = Rs.10, 000/- (Mohanty, 2012).

Total number of individual of age group 20-44 yrs (Tt) = 44.77 crore (CBHI).

A. Cost of Screening per person –

S. No	Type of screening (Revised AIIMS Rate)	Cost per person(Rs.)	Cost of total population (Cost per patient X Tt) (Crore)
1	MCV	50/-	2,239/-
2	NESTROFT	300/-	13,431/-
3	PCR	3,500/-	1,56,695/-
4	RDBH	400/-	17,908/-

b. Cost of the Treatment/Management –

S. No	Particulars	Cost (Rs)	Cost per Year Per Patient(Rs)
A. Life Long Recurrent /Periodic Treatment –			
1	Blood & Blood transfusion (According to Calcutta Mercy Hospital for Thallasaemia)	1000/- per blood transfusion	12000/-
2	Leucodepletion filters (per transfusion) (According to TSCS, Hyderabad)	1,000/-	12000/-
3	Iron Chelation (According to TSCS, Hyderabad)		
	a Desferal (Parental Chelation) (According to TSCS, Hyderabad)		
	i. Infusion pump (once in life time)	27,500/-	27,500/-
	ii. Drugs (life long)	8,000 / month	96,000/-
	b) Oral Chelation (According to TSCS, Hyderabad)		
	i. Kelfer (life long)	3,000 / month	36,000/-
	ii. Asunra (life long)	6,000 / month	72,000/-
4	Other drugs and disposables (life long) (According to TSCS, Hyderabad)	7,500 / month	9,000/-
5	Periodic medical check-up (life long) (According to TSCS, Hyderabad)	2,500 / year	2,500
	Total Treatment cost per patient per Year	1,43,500/- (with oral chelation)	1,59,000/- (with parentral chelation)
B. Permanent Treatment -			
1	Bone marrow transplantation (permanent cure) (According to TSCS, Hyderabad)	12,00,000 to 15,00,000/-	

Cost of treatment for Total number of patient suffering from Thalassaemia major (Tm) –

A. Life Long Treatment –

Cost of treatment per patient per year (Oral Chelation) = Rs. 1,43,500/-

Cost of treatment per patient per year (Parentral Chelation) = Rs. 1,59,000/-

Average Cost of treatment per patient per year = Rs. 1, 51, 250/-

= Rs. 1.51 Lakh/year/parient

Total cost of treatment for total number of Tm per year

= Tm X Total cost of treatment per patient per year

= 10,000 X 1.51

= Rs. 151 Crore/year

B. Permanent Treatment –

Cost of Bone marrow transplantation (permanent cure) = Rs. (12 -15) Lakh

Total cost of Bone marrow transplantation for total number of Tm per year

= Tm X Cost of Bone marrow Transplantation

= (10,000 X 12) – (10,000X15)

= Rs. 1,200- 1, 500 crores / year

People can prevent of having thalassaemic major child, with the help of screening by keeping following points in mind –

i. Thalassaemia is a genetic disorder. If both the parents are carriers of Thalassemia gene, there is 25% chance that their offspring may get thalassemia major, 50% of having a Thalassemia carrier/ Minor child and 25% Normal i.e. not even a carrier.

ii. However, if only one of the couple is a carrier, none of the child will be a Thalassemia Major.

This could be against right to life.

Bone marrow transplantation can cure the disease but is possible only for those whose Histocompatibility Linked Antigen (HLA) matched donor (sibling) is available. However HLA matched donor is not always available and the procedure is very risky, which restricts its viability. Therefore, lifelong treatment is preferable.

Our analysis has certain limitations. One of the challenges in such situations is computing the cost of a wrong diagnosis as a result of less than 100% sensitivity and specificity. Each case which is wrongly diagnosed false positive or false negative using a given diagnostic test has costs associated with the same, both for the provider as well as the individual. Such costs are most often poorly defined, and often underestimated. Secondly, the health benefits of early detection is not captured in our analysis. Inclusion of value of these benefits will result in the intervention to be more cost effective.

Any conclusion on cost effectiveness of screening for thalassemia should thus be viewed in light of these limitations.

K) Thalassiamia and Indian Scenario:-

Every year approximately 100,000 children with Thalassemia Major are born world over, of which 10,000 are born in India.

It is estimated that there are about 65,000-67,000 b - thalassemia patients in our country with around 9,000-10,000 cases being added every year.

A concerted effort is needed to have a National Thalassemia Prevention Program in place. This needs involvement of all government health agencies, scientific research bodies, institutions caring for thalassemia, parents' societies, dedicated and committed social workers along with the medical fraternity to be able

to successfully eradicate thalassemia from the country. With this in mind Indian Academy of Pediatrics has envisaged Thalassemia Prevention Program under IAP Vision 2007. Moreover, care of thalassaemia has been included in the 12th 5-year Plan of the Government of India. Many States now provide blood transfusions and chelation free of cost.

L) Benefits of Thalassiamia Screening:

Screening would not only be a good public health practice, as envisioned in Alma Ata declaration, but it would also be cost-effective, as the ratio of the cost of treatment to prevention is 4:1, as shown in a study from Israe. It would help tremendously in reducing the burden of the disease for patients, families and the health services. The strongest argument for prevention is that it would ensure the best possible care for the affected, by curbing the increase in their number.

M) Ethical, legal and social issues in genetic screening

a. Ethical issues

Ethical aspects of management of β-thalassaemia, falls back to the traditional sources of ethical guidelines in medicine. These ethical principles include beneficence: giving highest priority to the welfare of persons and maximizing benefits to their health; non-malfeasance: avoiding and preventing harm to persons or, at least, minimizing harm; respect for the autonomy of persons: respecting the self-determination of individuals and protecting those with diminished autonomy and distributive justice: treating persons with fairness and equity, and distributing the benefits and burdens of health care as fairly as possible in society .

In medical genetics the main concerns, are that genetic information may affect an entire family, rather than only the individual; genetic discoveries may be predictive of future adverse events in an individual's or family member's health, and that the choices of the present may affect future generations.

There are concerns about the need for informed consent and about the availability of genetic counseling and support prior to and after screening.

It is the moral dilemma about termination of pregnancy that often causes controversy in prenatal diagnosis. Prenatal diagnosis may be considered controversial because the results may be used to justify termination of pregnancy, which could be against right to life. Those who oppose it consider it to be contrary to the goal of medicine, which is to save lives. Those who support medical termination of pregnancy do so because they wish to prevent unsafe abortions, reduce suffering and poor quality of life for children whom are severely affected by their respective genetic condition. It has been suggested that physicians opposed to abortion on moral grounds and therefore under difficulties in counseling their patients about screening, have an ethical obligation to refer their pregnant patients to a colleague an authorized counseling centre.

b. Legal issues

All genetic testing must be performed by accredited medical laboratories and staffed by scientists and technologists experienced in genetic technology.

C. Social issues

There are human risks involved in all genetic screening programs and these include labeling, discrimination, and loss of self-esteem, prevention or damage to parent-child bonding, stigmatization, unnecessary anxieties and invasion of privacy. Hence, a proper centrally planned genetic screening programme with its various institutional ethical safeguards is crucial and desirable. The undesirable would be an unregulated genetic screening tests being offered by commercial concerns to anxious families and couples without appropriate

supervision. A study in India of 200 families with Thalassaemia found that ignorance and prejudice in the community led to social isolation for families (Sangani et al., 1990). Social concern should play a central role via planning of screening programs.

N) Suggestions and Recommendations

There is a need to increase the number of centers in India able to perform thalassaemia screening, and provide this facility at a subsidized cost, or free for the poor, and introduce quality control programmes. Reverse Dot Blot Hybridisation (RDBH) diagnostic test for thalassemia gives optimal outcomes. Techniques as Reverse Dot Blot Hybridisation (RDBH) diagnostic test for prenatal diagnosis would be worthwhile, as this would help to provide prenatal diagnosis in peripheral areas also. The need of the hour is to introduce screening programmes in the high risk States.

O) Bibliography:

1. *WHO-EXECUTIVE BOARD EB118/5, 118th Session Report by the Secretariat on Thalassaemia and other aemoglobinopathies: Prevalence of Haemoglobinopathies. 11 May 2006. p. 1-8.*
2. *Balgir RS. The genetic burden of hemoglobinopathies with special reference to community health in India and the challenges ahead. Indian J Hematol Blood Trans 2002;20:2-7.*
3. *Varawalla NY, Old JM, Sarkar R, Venkatesan R, Weatherall DJ.The spectrum of beta thalassaemia mutations on the Indian subcontinent; the basis of prenatal diagnosis. Br J Haematol 1991;78:242-7.*
4. *Atul Shrivastav, Umang Patel1, Jayesh R Joshi, Amarjeet Kaur1, Ashok S Agnihotri. Study of hemoglobinopathies and Hb variants in population of Western India using HPLC:A report of 7,000 cases.Journal of Applied Hematology 2013;4:3.*
5. *http://pib.nic.in/newsite/PrintRelease.aspx?relid=101924, 2013.*
6. *Manjula Maheshwari, Sadhna Arora, Madhulika Kabra and P.S.N. Menon , Carrier Screening and Prenatal Diagnosis of b-Thalassemia Indian Pediatrics 1999;36: 1119-1125].*
7. *Amna A, Zehra N, Haider G, Anjum F, Rani S, Munir AA. Role of mean corpuscular volume as screening test for thalassaemia in pregnant women at Isra University Hospital Hyderabad. Pak J Med Sci 2010; 26(2):390-393.*
8. *Supatra Sirichotiyakul, Chanane Wanapirak, Kasemsri Srisupundit, Suchaya Luew an, Theera Tongsong. A comparison of the accuracy of the corpuscular fragility and mean corpuscular volume tests for the alpha-thalassemia 1 and beta-thalassemia traits. International Journal of Gynecology & Obstetrics October 2009; 107 (1):26-29.*
9. *Kanokwan Sanchaisuriya, MSc, Supan Fucharoen, DSc,Goonnapa Fucharoen, MSc,Thawalwong Ratanasiri, MD,Pattara Sanchaisuriya, PhD, Yossombat Changtrakul, MSc,Uthai Ukosanakarn, MD,Wichai Ussawaphark, MD and Frank P. Schelp, MD. A Reliable Screening Protocol for Thalassemia and Hemoglobinopathies in Pregnancy An Alternative Approach to Electronic Blood Cell Counting. Am J Clin Pathol 2005;123:113-118.*
10. *Mamta Manglani, M.R. Lokeshwar, Vani V.G., Nishi Bhatia and Vijay Mhaskar.'NESTROFT'-An Effective screening test for beta thalessemia trait. Indian Pediatrics August 1997; 34: 702-707.*
11. *Sanjay Piplani, Rahul Manan, Monika Lalit, Mridu Manjari, TajinderBhasin, Jasmine Bawa. NESTROFT - A Valuable, Cost Effective Screening Test for Beta Thalassemia Traitin North Indian Punjabi Population. Journal of Clinical and Diagnostic Research. 2013 Dec, Vol-7(12): 2784-2787.*
12. *S. Sirichotiyakula,, C. Tantipalakorna, T. Sanguansermsrib, C. Wanapiraka, T. Tongsong. Erythrocyte osmotic fragility test for screening of alphathalassemia- 1 and beta-thalassemia trait in pregnancy. International Journal of Gynecology and Obstetrics 86 (2004) 347–350.*
13. *Pranee Winichagoon1, Vannarat Saechan, Roongrat Sripanich, Chamnong Nopparatana, Sujin Kanokpongsakdi, Aurelio Maggio and Suthat Fucharoen Prenatal Diagnosis of â-thalassaemia by Reverse*

Dot-blot Hybridization. PRENATAL DIAGNOSIS. Prenat. Diagn 1999;19: 428–435.

14. *E George, LK Teh, R Rosli, MI Lai & JAMA Tan. Beta Thalassaemia Mutations in Malays: A Simplified Cost-effective Strategy To Identify the Mutations. Malaysian Journal of Medicine and Health Sciences January 2012;Vol. 8 (1).*
15. *Min Lin , Juan-Juan Zhu, Qian Wang, Long-Xu Xie et al. Development and evaluation of a reverse dot blot assay for the simultaneous detection of common alpha and beta thalassemia in Chinese. Blood Cells, Molecules, and Diseases 2012;48: 86–90.*
16. *D. Mohanty & R. B. Colah & A. C. Gorakshakar & R. Z. Patel & D. C. Master & J. Mahanta & S. K. Sharma & U. Chaudhari &M. Ghosh & S. Das& R. P. Britt & S. Singh & C. Ross& L. Jagannathan & R. Kaul & D. K. Shukla & V. Muthuswamy. Prevalence of β-thalassemia and other haemoglobinopathies in six cities in India: a multicentre studyJ Community Genet (2013) 4:33–42.*
17. *Muralitharan S, Srivastava A, Shaji RV, Mathai M, Srivastava VM, Dennison D, Lu CY, Krishnamoorthy R. Prenatal diagnosis of beta-thalassaemia mutations using the reverse dot blot technique. Natl Med J India. 1996 Mar-Apr;9(2):70-1.*
18. *MCV*
19. *Indian Pediatrics. Available at - http://www.indianpediatrics.net/99nov6.htm (Assessed on 5th May 2014).*
20. *MedlinePlus. Available at – http://www.nlm.nih.gov/medlineplus/ency/article/003641.htm (Assessed on 5th May 2014).*
21. *Sangani B, Sukumaran PK, Mahadik C, Yagnik H, Telang S, Vas F, Oberroi RA, Modell B, Merchant SM. (1990) Thalassemia in Bombay: the role of medical genetics in developing countries. Bull World Health Organ, 68(1), pp 75-81*
22. *http://icmr.nic.in/ijmr/2011/october/1016.pdf Review Article*
23. *Past, present & future scenario of thalassaemic care & control in India Ishwar C.*
24. *Verma, Renu Saxena & Sudha Kohli Center of Medical Genetics, Sir Ganga Ram Hospital, New Delhi, India*

    http://medind.nic.in/ibv/t07/i9/ibvt07i9p647.pdf

CHAPTER 6 Smart Cane for Visually Challenged:

A) Background

What do we understand by Blindness?

Blindness is the condition of poor visual perception.

B) Description of the condition

Various scales have been developed to describe the extent of vision loss and define blindness. Total blindness is the complete lack of form and visual light perception and is clinically recorded as NLP, an abbreviation for "no light perception." Blindness is frequently used to describe severe visual impairment with some remaining vision. Those described as having only light perception have no more sight than the ability to tell light from dark and the general direction of a light source. The World Health Organization defines low vision as visual acuity of less than 20/60 (6/18), but equal to or better than 20/200 (6/60), or visual field loss to less than 20 degrees, in the better eye with best possible correction. *Blindness* is defined as visual acuity of less than 20/400 (6/120), or a visual field loss to less than 10 degrees, in the better eye with best possible correction.

C) Causes of Blindness

According to WHO - the causes of blindness are:-

1) Cataract- 51%

A cataract is a clouding of the lens inside the eye which leads to a decrease in vision. It is the most common cause of blindness and is conventionally treated with surgery. Visual loss occurs because opacification of the lens obstructs light from passing and being focused on to the retina at the back of the eye.

2) Glaucoma - 8%

It is a term describing a group of ocular disorders with multi-factorial etiology united by a clinically characteristic intraocular pressure-associated optic neuropathy. This can permanently damage vision in the affected eye(s) and lead to blindness if left untreated. It is normally associated with increased fluid pressure in the eye

(aqueous humour). The term "ocular hypertension" is used for people with consistently raised intraocular pressure (IOP) without any associated optic nerve damage. Conversely, the term 'normal tension' or 'low tension' glaucoma is used for those with optic nerve damage and associated visual field loss, but normal or low IOP.

3) Age Related Macular Degeneration - 5%

It is a medical condition that usually affects older adults and results in a loss of vision in the center of the visual field (the macula) because of damage to the retina. It occurs in "dry" and "wet" forms. It is a major

cause of blindness and visual impairment in older adults (>50 years). Macular degeneration can make it difficult or impossible to read or recognize faces, although enough peripheral vision remains to allow other activities of daily life.

Although some macular dystrophies affecting younger individuals are sometimes referred to as macular degeneration, the term generally refers to age-related macular degeneration (AMD or ARMD).

4) Childhood blindness and corneal opacities - 4%

Childhood blindness refers to a group of diseases and conditions occurring in childhood or early adolescence, which, if left untreated, result in blindness or severe visual impairment that are likely to be untreatable later in life. The major causes of blindness in children vary widely from region to region, being largely determined by socioeconomic development, and the availability of primary health care and eye care services. In high-income countries, lesions of the optic nerve and higher visual pathways predominate as the cause of blindness, while corneal scarring from measles, vitamin A deficiency, the use of harmful traditional eye remedies, ophthalmia neonatorum, and rubella cataract are the major causes in low-income countries. Retinopathy of prematurity is an important cause in middle-income countries. Other significant causes in all countries are congenital abnormalities, such as cataract, glaucoma, and hereditary retinal dystrophies.

Corneal opacities - is a disorder of the cornea, the transparent structure on the front of the eyeball, which can cause serious vision problems. Corneal opacity occurs when the cornea becomes scarred. This stops light from passing through the cornea to the retina and may cause the cornea to appear white or clouded over.

5) Uncorrected refractive errors and trachoma - 3%

A refractive error, or refraction error, is an error in the focusing of light by the eye and a frequent reason for reduced visual acuity.

Trachoma- (Greek: τράχωμα, 'roughness') also called granular conjunctivitis, Egyptian ophthalmia, and blinding trachoma is an infectious disease caused by the bacterium Chlamydia trachomatis. The infection causes a roughening of the inner surface of the eyelids. This roughening can lead to pain in the eyes, breakdown of the outer surface or cornea of the eyes, and possibly toblindness.

The bacteria that cause the disease can be spread by both direct and indirect contact with an affected person's eyes or nose. Indirect contact includes through clothing or flies that have come into contact with an affected person's eyes or nose. Many infections are usually needed over a period of years before scarring of the eyelid becomes so great that the eyelashes begin to rub against the eye. Children spread the disease more often than adults. Poor sanitation, crowded living conditions, and not enough clean water and toilets also increase spread.

6) Diabetic Retinopathy - 1%

Diabetic retinopathy is composed of a characteristic group of lesions found in the retina of individuals having had diabetes mellitus for several years. The abnormalities that characterise diabetic retinopathy occur in predictable progression with minor variations in the order of their appearance. Diabetic retinopathy is considered to be the result of vascular changes in the retinal circulation. In the early stages vascular occlusion and dilations occur. It progresses into a proliferative retinopathy with the growth of new blood vessels. Macular oedema (the thickening of the central part of the retina) can significantly decrease visual acuity.

7) Onchocerciasis:-

Onchocerciasis is an insect-borne disease caused by a parasite Onchocerca volvulus and transmitted by blackflies of the species Simulium damnosum. Onchocerciasis is often called "river blindness" because the blackfly which transmits the disease abounds in fertile riverside areas, that frequently remain uninhabited for fear of infection. O. volvulus is almost exclusively a parasite of man. Adult worms live in nodules in a human body where the female worms produce high numbers of first-stage larvae known as microfilariae. They migrate from the nodules to the sub-epidermal layer of the skin where they can be ingested by blackflies. They further develop in the body of the insect from which more people can be infected. Eye lesions in humans are caused by microfilariae. They can be found in all internal tissues of the eye -- except the lens -- where they cause eye inflammation, bleeding, and other complications that ultimately lead to blindness.

8) Genetic eye diseases

Genetic eye diseases include a large number of ocular pathologies which have in common the transmission from parents to children by their genetic inheritance. All do not cause visual impairment.

9) Undetermined causes - 21%

D) Burden of Disease Globally of Blindness for the year 2010(*)

- 285 million people are estimated to be visually impaired worldwide: 39 million are blind and 246 have low vision.
- About 90% of the worlds visually impaired live in developing countries.
- 82% of people living with blindness are aged 50 and above.
- Globally, uncorrected refractive errors are the main cause of visual impairment; cataracts remain the leading cause of blindness in middle- and low-income countries.
- The number of people visually impaired from infectious diseases has greatly reduced in the last 20 years.
- 80% of all visual impairment can be avoided or cured.

Burden of disease in India for the year 2010:-

- 8.075 million Blind population
- 54.544 million Low vision population
- 62.619 million Visually Impaired people

Hence, by looking the above mentioned facts and figures we can very well understand the seriousness of the situation and scenario in India.

So, the main clinical need identified with blind person is mobility assistance. This need renders the blind to be dependent. There are several mobility assistive devices to overcome this problem. But in this HTA report we will discuss the technological comparison, cost effectiveness analysis, regulatory and market status of Smart Cane. For determining appropriateness of this technology, this HTA report is prepared.

(*) - http://www.who.int/mediacentre/factsheets/fs282/en/

E) Use of Smart Cane as an intervention:-

The Smart Cane is designed to help users detect obstacles above knee-level and prevent accidents from occurring.

Using sensors, the device detects obstructions up to a distance of 10ft (three metres).

It attaches to the top of a standard folding white cane, currently used by millions of visually impaired people across the globe.

The Smart Cane mimics the capabilities of bats, using sonar to detect objects in the surrounding environment.

Ultrasound waves are sent out and, when they return to the cane, they vibrate on the relevant side of to warn of an obstacle ahead.

Different patterns and intensities let the user know how far away an object is.

F) Evidence Synthesis:

The evidence synthesis was presented in different way for Smart Cane as no sufficient randomised controlled trials or systematic reviews were found on Smart Cane or similar technologies in literature search. Thus, technical data was extracted and tabulated together as follows:

G) Technological comparison:

Name of Technology	Smart Cane (IIT)	Isonar
Principle used for obstacle detection / collision avoidance	Ultrasonic signal	Ultrasonic signal
Burst Frequency used and amount of bursts produced	40 kHz	40 kHz
Power source	Rechargable Li-Ion Battery without adapter	Rechargable Li-Po Battery with 5V DC switching adapter via DC plug charger
Obstacle Detection Range(Maximum)	3 meter	(130x 50) cm
What is detected?	Distance of subject to Static object, moving objects by calculating instantaneous velocity(angular width of detection cone is 45 degree)	Distance of subject to Static object with help of sound velocity, moving objects by calculating instantaneous velocity

Name of Technology	Smart Cane (IIT)	Isonar
Major Component	Dual Transducer Ultrasonic Ranger (SRF04),Asymmetric DC ranger,8051 Microcontroller	Ultrasonic ceramic transducer,3V 80 mA 12,500 rpm vibration motor,PIC 16F684 Microflash based 8 bits CMOS microcontroller
Positive Points	Reliable, Easily Detachable without sighted assistance, design and performance analysis done using Simulator and with LASER vibrometer	High degree of user satisfaction (Likert scale 4.13)
Limitation of technology	Doesn't fully replace Cane	Have to mount on chest and also may have to use with cane
Battery	900 mAh,3.0-4.2 V	1150 mAh,3.7 V
Method of detection of charging level	MAX8606 Battery charge management IC , TPS61032 Voltage Regulator is used with 8051 Microcontroller AT89C55WD	With help of Microcontroller driven ADC
Battery Life	Maximum 8 hours of continuous use	24 hours continuous use, 48 hrs standby supply
Material used	Polycarbonate ABS plastic	No information available
Gripping style	Flexible	Flexible or fixed
Results	Reduction in collision rate - (100-18.26) = 81.73%	Reduction in collision rate - (33.3-6.67)=26.66
Evaluation Method	Self-prepared Survey Questions	Likert Scale used for satisfaction survey

H) Cost –effectiveness Analysis:

Cost-effectiveness analysis is a method of comparing the cost and effectiveness of two or more alternatives. Such comparisons are useful when one of the alternatives being considered is standard care, as this allows the decision maker to consider whether an alternative is better or not.

Total blind population in India = 12 Million

Considering collision reduction by use of intentions, total number of collision would be equal to respective collision rate multiplied by total target population.

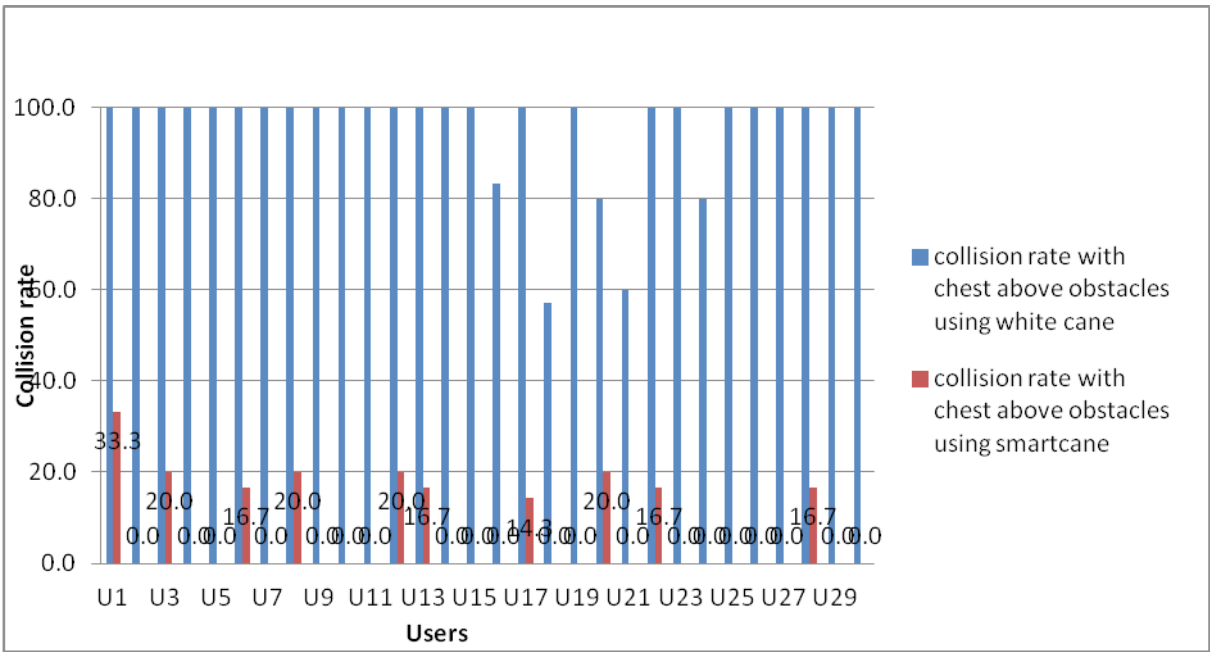
The benefit was identified in terms of reduction in collision rate.

So, the cost effectiveness ratio was obtained in terms of cost per collision averted per single use of mobility assistive device by the target population as below.

Note: Average Collision rate was obtained from IIT validation study data.

As, shown next page:-

Plot Titled "Reduction in collision rate" in Smart Cane vs. White Cane in IIT Smart Cane validation trial.



Calculation of Collision risk reduction factor:-

User No.	Collision Index with white cane(C Iw)	Collision Index with Smart Cane (C I s)
1	100	33.3
2	100	0
3	100	20
4	100	0
5	100	0
6	100	16.7
7	100	0
8	100	20
9	100	0
10	100	0
11	100	0
12	100	20
13	100	16.7
14	100	0
15	100	0
16	83.3	0
17	100	14.3
18	57.1	0
19	100	0
20	80	20
21	60	0
22	100	16.7

User No.	Collision Index with white cane(C Iw)	Collision Index with Smart Cane (C I s)
23	100	0
24	80	0
25	100	0
26	100	0
27	100	0
28	100	16.7
29	100	0
30	100	0
Average	**95.33**	**6.47**
Reduction in collision rate (%)	**88.86**	

ACER Explanation:-

Once a Cost Effective Analysis (CEA) has been conducted and cost effectiveness has been calculated, ratios combining the expected results are calculated and reported.
There are three types of cost effectiveness ratios (CERs):

- Average cost-effectiveness ratio (ACER),
- Marginal cost-effectiveness ratio (MCER), and
- Incremental cost-effectiveness ratio (ICER).

ACER

- Deals with a single intervention and evaluates that intervention against its baseline option (e.g., no program or current practice).
- Is calculated by dividing the net cost of the intervention by the total number of health outcomes prevented by the intervention.

MCER

- The marginal cost-effectiveness ratio (MCER) assesses the specific changes in cost and effect when a program is expanded or contracted.
- Because the majority of programs that are cost effective are considered good investments only at a certain level, the MCER and ACER are often considered simultaneously.

ICER

- compares the differences between the costs and health outcomes of two alternative interventions that compete for the same resources, and
- Is generally described as the additional cost per additional health outcome.
- When comparing two competing programs incrementally, one program should be compared with the next-less-effective alternative.
- The ICER numerator includes the differences in program costs, averted disease costs, and averted productivity losses if applicable.
- Similarly, the ICER denominator is the difference in health outcomes.

Hence, calculations which are below mentioned are based on above mentioned concepts.

Decline in collision index with white cane =4.66%
Cost of white cane =Rs 160
Cost /unit decline in C.I =$\frac{160}{4.66}$
=Rs.34 per unit decline in C.I

Decline in collision index with Smart Cane=95.34%
Cost of smart cane = Rs 1800
Cost/unit decline in C.I= $\frac{1800}{95.34}$
=Rs. 18 per unit decline in C.I

Smart Cane although ten times more costly seems to be twice more cost effective.

I) Regulatory Status and Market Status:

Current cost is 2500 Rs. But, it is expected to reduce up to less than 1000 after mass manufacturing. This product's patent is filled by IIT –Delhi itself with name "Multiple range obstacle detection and warning system for the visually challenged" in the Indian Patent Office, 2007 (Application: 1354/DEL/2007).

It is categorised under class I –low risk medical devices in Indian Medical Device Classification.

J) Results:

Smart Cane is an innovative orthotic aid for blind population. It reduces collision index up to 88.86%. **It is 10 times costly than White cane but was found to be 3 times cost-effective.** Its multi-centric validation is under process and current evidence shows positive results as compared. However, questionnaire response based analysis would provide robust evidence. The study design was identified to have least bias as survey was conducted by Trainers from third-party NGO-Saksham, which is non-profit organization.

K) Recommendations:

Smart Cane validation studies have used self-designed questionnaires for survey, which may have risk of introducing subjectivity. It is recommended that study design should incorporate objective assessment scores. Smart Cane could be easily mounted on white cane without the user being dependent on normal people to mount the device on cane.

In absence of RCTs, it could be said that with limited evidence, smart cane could be an innovation to support visually challenged and more studies should be conducted to establish its technical superiority over traditional white cane.

Bibliography:

1. *NPCB Orissa(http://www.orissa.gov.in/health_portal/programme/NPCB/main.html)*
2. *First Milestone Report on Smart Cane validation trial by IIT delhi and Wellcome group trust*
3. *Saksham NGO website*
4. *ASSISTECH website:*
5. *http://www.cse.iitd.ernet.in/~assistech/Smart_Cane%20Details.html.*
6. *http://icreateasia.org/2013/modules/request.php?module=oc_program&action=view.php&id=6*
7. *http://www.sightsavers.net/our_work/causes_of_blindness/childhood_blindness/16989.htm*
8. *http://www.thirdage.com/hc/c/what-is-corneal-opacity*
9. *http://www.who.int/mediacentre/factsheets/fs282/en/*

CHAPTER 7

Auto-Disposable Syringes

A) Background:

What is an Auto-disable syringe?

Auto-disable syringe is a specifically modified disposable syringe with a fixed needle, which is automatically disabled by the plunger blocking after a single use. Auto Disable (AD) syringes are designed as a single use syringe, with an internal mechanism blocking the barrel once depressed so it cannot be depressed again.

Re-use of syringes had been a major challenge in the healthcare over the past. Introduction of disposable syringes was thought to be a potent solution to the problem. Over the period it has been observed that the disposable syringes have not been able to meet the purpose of controlling the likely rates of Needle stick injuries (NSI) and thereby blood-borne virus transmission. Hepatitis-C, Hepatitis-B burden has been increasing in the countries. The burden of disease has been evaluated based on the estimates by the World health Organization(WHO).The initiative to introduce and implement auto-disable syringes in the immunization programs is the need of the hour. Introduction of auto-disable syringes in the immunization program will reduce the likely chances of developing carriers and thereby reducing the mortality related to blood-borne infections in the country. (#)

B) Why to use Auto disable syringes?

Unsafe injections have increased alarmingly not in the country but throughout the world. Two-third of the injections administered are unsafe as per the study by WHO. Unsafe injections not only harm the patients besides carry of risk to Health care-workers. The Needle stick injuries are inflicted not only by HCW but also by the cleaners, rag-pickers, laundry-men and by large the community as a whole.

It has been recognized that transmission of blood-borne pathogens is due to contaminated needles and syringes .Re-use has been attributed to be a major reason behind this. Increasing burden of disease has also resulted in huge medical expenditure.

Safe –injection practices must be mandatorily adhered to as the immunization programs are aimed to prevent disease in later stage of life.

Misconceptions regarding injection safety are prevalent among the society.

The awareness about the mode of transmission of blood-borne pathogens in the hospitals has created a fear among the general public .The coverage rate during immunization are also marred by fear. Auto-disable syringes can reduce the vaccine wastage as the dose delivered through the AD syringes is more as compared to the sterile or the disposable counterparts. Usage of AD syringes will prevent re-sale after use.Re-use of injections can cause septicemia irrespective of the fact that patient was infected or not. UNICEF recommends the use of AD Syringes for re-constitution. Safe Injection Global Network (SIGN) advocates the use of auto -disable syringes. 1999 with the goal of preventing the transfer of blood-borne diseases, World Health Organization (WHO), UNICEF and United Nations Population Fund (UNFPA) developed a policy on injection safety. UNICEF has fully endorsed and implemented the use of Auto-Disable Syringes in Immunization Services. Over the past years, WHO, UNICEF and UNFPA have launched a number of initiatives which aim to improve the safety of injections. The most recent was the precursor to this joint statement which is related to the use of auto-disable syringes and safety boxes in immunization campaigns. WHO and UNICEF have agreed to implement a strategy to ensure that special attention is paid to the safe administration of vaccines, both in routine immunization services and during mass campaigns.(*)

{References–

(#).http://www.ijcm.org.in/article.asp?issn=09700218;year=2012;volume=37;issue=2;spage=89;epage=94;aulast=Reid

(*) – http://www.who.int/injection_safety/toolbox/Bundling.pdf}

C) Clinical Effectiveness of Auto - disable Syringes

Objectives

To study the role of auto-disable syringes - the impact in controlling the likely chances of blood-borne infections and reducing financial implications of future disease.

The benefits of introducing auto-disable syringes in the Universal immunization programs (UIP)

Keywords

Extensive literature review was done using below mentioned key words -

"Auto-disable syringes", ""use of auto-disable syringes", "cross-infections", "blood borne virus"," sterile syringes", "Hepatitis-B", "Hepatitis-C","HIV".

Methodology

We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, MEDLINE, PUBMED Science Direct and SCOPUS .We also conducted secondary referencing by manually reviewing reference lists of key articles and searching citations by using Web of Science. We also conducted specific searches for primary studies published more recently than the included systematic reviews and meta-analyses from 1st January 2014 to 1st June 2014. Types of studies included during search were: Randomized controlled trial, observational analytical studies, Case control and cohort studies.

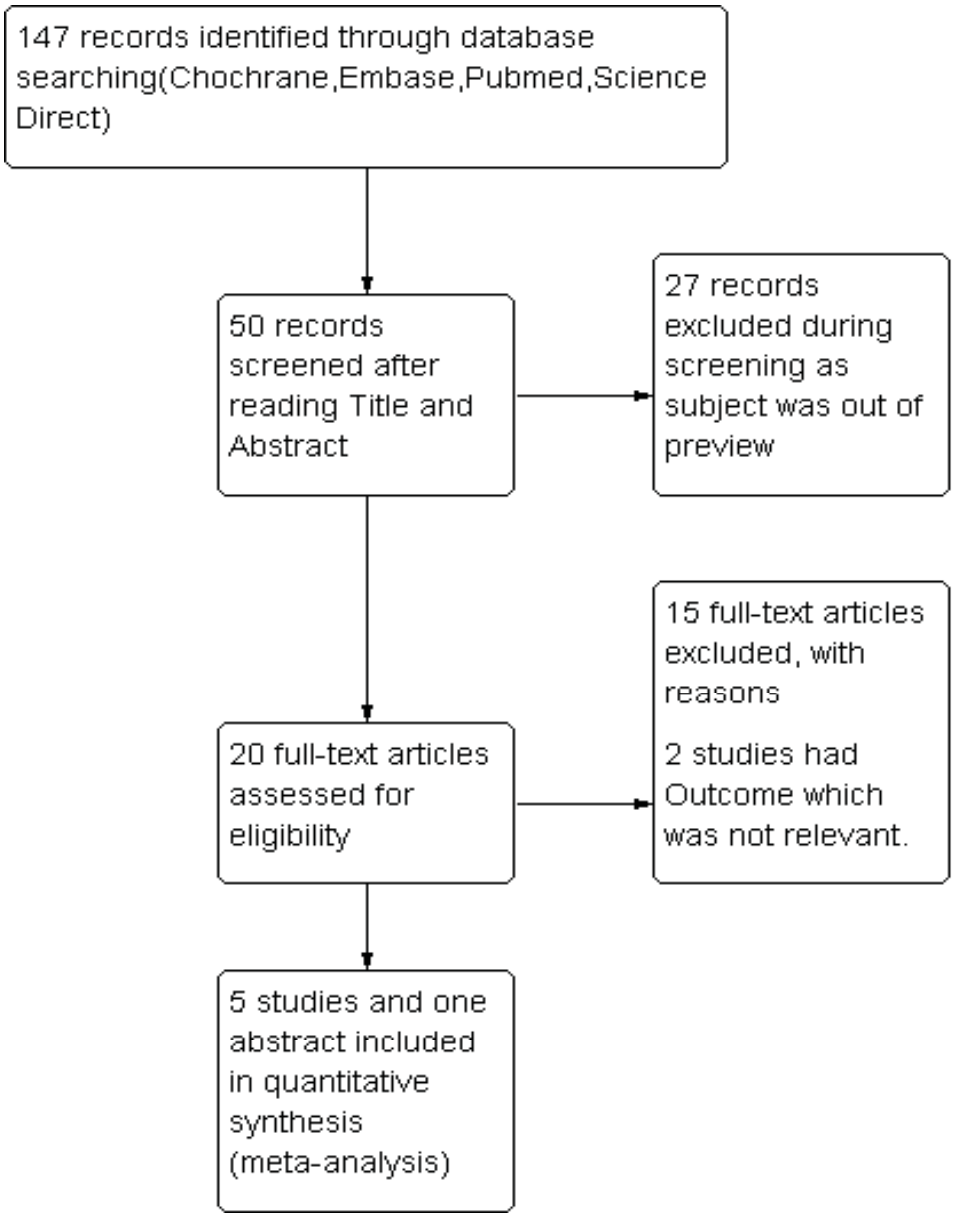
Data Collection and analysis-

Data were collected reviewing the hard copies .The information that was to be relevant and pertaining to the study was collected and analyzed through systematic review. The data related to unsafe injections and AD syringes was taken into consideration and thereby studied and analyzed. The data was summarized, tabulated and analyzed and three forest plots were made.

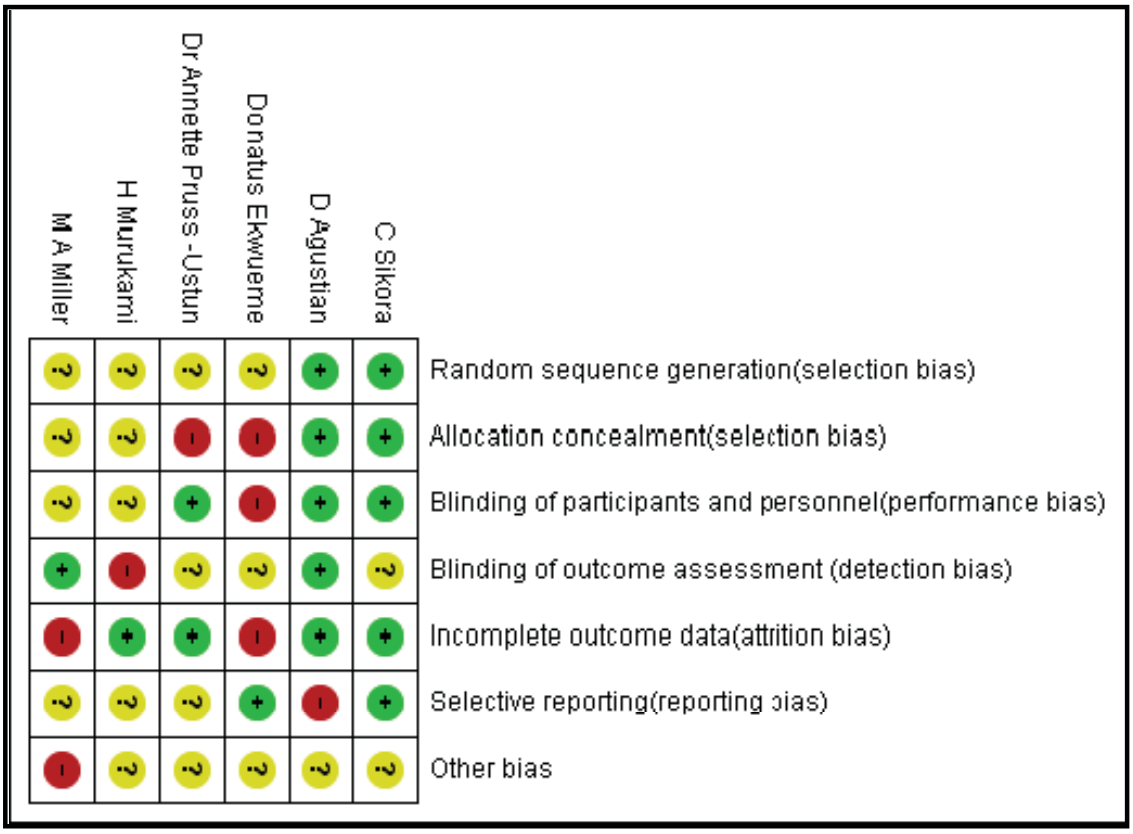
Selection of studies

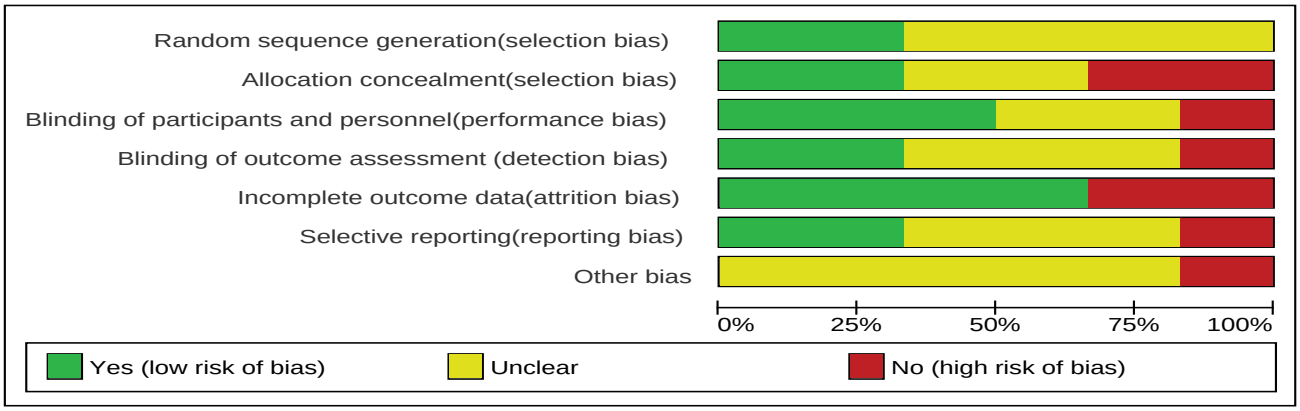
Total 147 studies were found after entering the keywords. Out of which 20 studies and 3 abstracts were found to be relevant and were selected. After extensive review it was observed that 15 studies and 2 abstract were clinically related. Out of these studies 5 studies and 1 abstract were selected for quantitative analysis as they were matching our selection criteria and had enough data to support our analysis. The selection was based on the keywords and the relevance as far as objectives and data are concerned.

D) Study flow Diagram:



E) Risk of bias summary





F) Risk involved

Transmission to patient: This is evident to occur due to re-use of syringes either intentionally or downstream reuse. In intentional re-use the constraint and paucity of resources becomes a reason behind re-use though the user is aware of hazards involved. Downstream re-use occurs when one user leaves the needle unattended after use and become negligent in discarding the needle and syringe.

Transmissions to healthcare worker: Needle stick injuries (NSI) are the biological hazard associated with injection re-use. Most of health care workers have developed a habit of recapping of needle after use. This happens due to their burden of work and a wrong perception among healthcare workers that recapping will prevent any harm or injury. Though training and awareness regarding the same is being conducted still scenario is not completely changing. Henceforth many HCW inflict injuries due to recapping. It has been

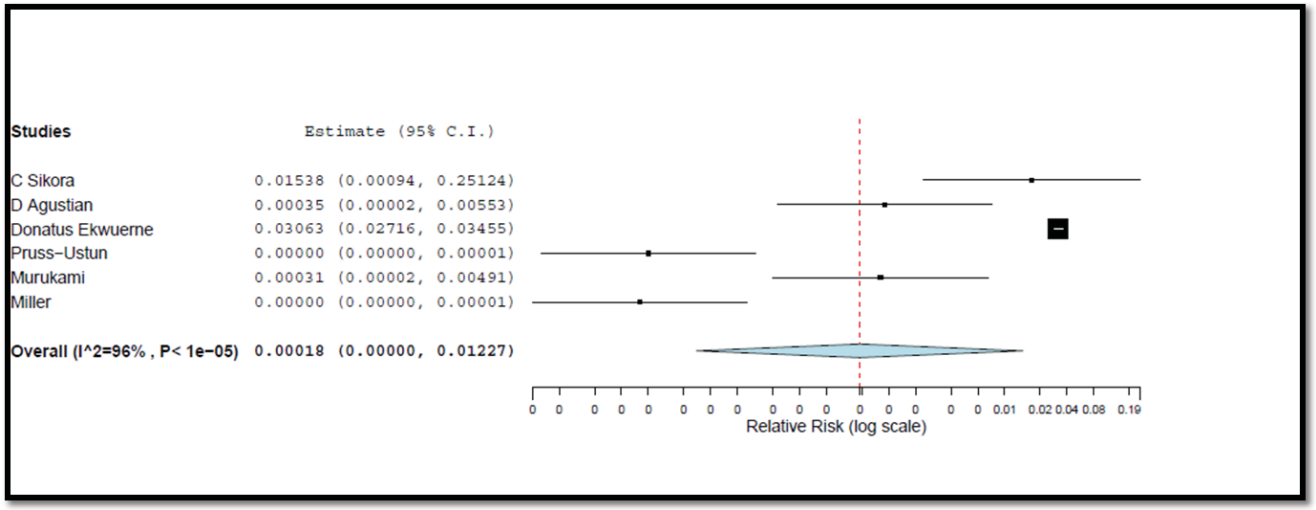
observed that the staff disposing BMW (biomedical waste) seldom wears gum boots though other personal protective equipments like masks, gloves, aprons are used.

Risk to community- The improper waste disposal leads to Needle Stick injuries

(NSI) .This occurs away from the healthcare setting when the waste is discarded or dumped away from the point of collection.

G) Results:

Forest Plot showing Incidence of Hepatitis B



Interpretation

As per Forest plot,

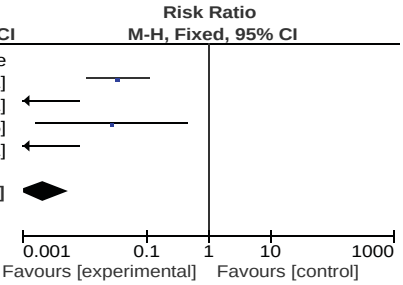
RR = 0.0, which is less than 1.

RR of 0.0 means 100% reduction in incidence of disease due to Auto Disable syringe as compared to Normal syringe.

Forest Plot Showing Incidence of HIV

Study or Subgroup	Auto Disable Syringes Events	Total	Normal Syringes Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
C Sikora	0	1000000	0	1000000		Not estimable
Donatus Ekweueme	3	1000000	89	1000000	4.2%	0.03 [0.01, 0.11]
Dr. Annette pruss ustun	0	35702000	1000	35702000	47.5%	0.00 [0.00, 0.01]
Dwi Agustian	0	500000	18	500000	0.9%	0.03 [0.00, 0.45]
M A Miller	0	1000000	1000	1000000	47.5%	0.00 [0.00, 0.01]
Total (95% CI)		**39202000**		**39202000**	**100.0%**	**0.00 [0.00, 0.01]**
Total events	3		2107			

Heterogeneity: Chi² = 27.35, df = 3 (P < 0.00001); I² = 89%
Test for overall effect: Z = 13.03 (P < 0.00001)

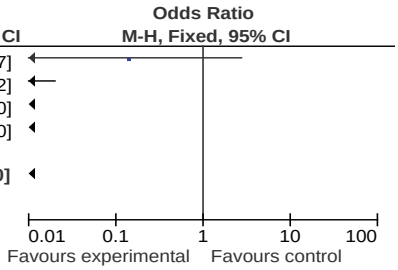


Interpretation
As per Forest plot,
RR = 0.0, which is less than 1.
RR of 0.0 means 100% reduction in incidence of disease due to Auto Disable syringe as compared to Normal syringe.

Forest Plot Showing Incidence of Hepatis C

Study or Subgroup	Auto-disable syringes Events	Total	Normal syringes Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
C Sikora	0	1000000	3	1000000	0.0%	0.14 [0.01, 2.77]
D Agustian	0	500000	399	500000	1.0%	0.00 [0.00, 0.02]
Dr Annette Pruss -Ustun	0	35702000	16400	35702000	41.2%	0.00 [0.00, 0.00]
M A Miller	0	1000000	23000	1000000	57.8%	0.00 [0.00, 0.00]
Total (95% CI)		**38202000**		**38202000**	**100.0%**	**0.00 [0.00, 0.00]**
Total events	0		39802			

Heterogeneity: Chi² = 33.38, df = 3 (P < 0.00001); I² = 91%
Test for overall effect: Z = 14.03 (P < 0.00001)



Interpretation
As per Forest plot, findings:
RR = 0.0, which is less than 1.
RR of 0.0 means 100% reduction in incidence of disease due to Auto Disable syringe as compared to Normal syringe.

Burden of disease-

Burden of disease due to unsafe injections =7.8 million persons annually

As per a study 7.8 million populations suffers from disease due to unsafe injections annually in India. HIV, HCV, HBV burden has been estimated by the studies. Children become carrier of disease. Pregnant mothers transmit the disease to the fetus as a result the newborn are likely to suffer from disease.

Annual usage of syringes - It is determined that 3billion - 4billion syringes are used annually in India.

H) Cost effectiveness analysis

Cost-effectiveness analysis is a method of comparing the cost and effectiveness of two or more alternatives. Such comparisons are useful when one of the alternatives being considered is standard care, as this allows the decision maker to consider whether an alternative is better or not. The standard care, however, could also be a placebo or "Do Nothing" scenario.

The **incremental cost-effectiveness ratio (ICER)** is an equation used commonly in health economics to provide a practical approach to decision making regarding health interventions. ICER is the ratio of the change in costs to incremental benefits of a therapeutic intervention or treatment. The equation for ICER is:

ICER = (C1 – C2) / (E1 – E2)

DALY

DALY is disability adjusted life years. DALY indicates number of years of life lost due to disability, ill health or death. The modeled incidence of blood borne viruses suggests that introducing AD Syringes will impose an incremental cost of $46-$48 per disability adjusted life years (DALY) averted. The epidemiological evidence suggests that incremental cost of introducing the AD Syringes for all medical injections is between $39 and $79 per DALY averted. Worldwide, the reuse of injection equipment in the year 2000 accounted for 32%, 40%, and 5% of new HBV, HCV and HIV infections, respectively, leading to a burden of 9.18 million DALYs between 2000 and 2030. Interventions implemented in the year2000 for the safe (provision of single-use syringes, assumed effectiveness 95%) and appropriate (patients–providers interactional group discussions, assumed effectiveness 30%) use of injections could reduce the burden of injection-associated infections by as much as 96.5% (8.86 million DALYs) for an average yearly cost of I$ 905 million (average cost per DALY averted, 102; range by region, 14–2293). (#)

Reference-(#)

A cost benefit assessment of the auto-disable syringe in a country with low blood borne virus prevalence, 2012

Gerald Dziekan,Daniel Chrisholm,Benjamin Johns,Juyan Rovira,Yvan J.F Hutin,The cost effectiveness of policies for safe and appropriate use of injections in healthcare settings Bulletin of WHO 2003

Discussion

The boon of introducing AD Syringes is prevention of re-sale. Transmission of Blood borne Virus (BBV) due to re-use will decline. The burden of disease in near future will reduce and as a result the cost incurred on treating these diseases will definitely go down. The decline in financial implications of future disease will be a boosting factor towards growth and progress. Vaccine Wastage will be less. Coverage rate in immunization program is likely to increase. The hidden cost of disease and unsafe injections are enormous. In some countries one out of five disposable syringes many of them supplied for vaccination are reused .It is likely that bulk of infection from injections arises from re-use of injecting equipment.(#)

Recommendation

The use of AD Syringes must be incorporated in the national health policy. Laws and regulations should be formulated regarding the same. Regular visits to the facilities and inspection to keep a check .This will be a beneficial initiative in the long run for the present and the future generations. The nation will be free from the brunt of transmission of diseases acquired through NSI (needle stick injuries) and re-use.

(References: #

http://www.who.int/bulletin/archives/77 (10)789.pdf

http://www.who.int/bulletin/archives/77 (10)808.pdf

http://www.scielosp.org/scielo.php?script=sci_arttext&pid=S0042-96862002001100005)

Bibliography

1. *J .S Lyod, J.B Milstein Auto-disable syringes for immunization-issues in technology transfer1999Bulletin of WHO.*
2. *Savanna Reid, Estimating the burden of disease from unsafe injection in India: A cost benefit assessment of the auto-disable syringe in a country with low blood borne virus prevalence, 2012*
3. *Pilot testing the WHO tools to assess and evaluate injection practices –WHO2003*
4. *Safety of injections-WHO-UNICEF-UNPA joint statement on the use of auto-disable syringes in the immunization services .Geneva, World Health Organization 1999*
5. *Sudesh Gyawali, Devendra S Rathore , Bhuvan KC, P Ravi Shankar Study of status of safe injection*

practice and knowledge regarding injection safety among primary health care workers in Baglung district western Nepal 2013.

6. *Dwi Agustian,Sri Yusnita,Herman Susnato, Hadyana Sukandar,Antoon De Schryver, Andre Meheri An estimation of the occupational risk of HBV,HCV,HIV among Indonesian healthcare workers .*
7. *C Sikora, AU Chandran, AM Joffe, D Johnson Population risk of syringe reuse: Estimating the probability of transmitting blood borne virus 2010.*
8. *Murakami H,Kobayashi M, Zhu X,Li Y,Wakai S,Chilia Y Risk of transmission of Hepatitis B virus through childhood immunization in north west China 2003 Soc Scie Med.*
9. *Donatus U Ekweune , Bruce G weniger Robert T Chen Model based estimates of risk of disease transmission and economic cost of seven injection devices in Sub-African Countries Bulletin OF WHO 2002*
10. *Dr Annettee Prus-Ustun ,Dr Elisabetta Rapiti,Dr Yvan Hutin Estimation of GlOBAL Burden of disease attributable to contaminated sharp injuries among health care workers2005*
11. *M A Miller,E Pisani.Cost of unsafe injections Bulletin of WHO 1999.*
12. *Syringes that lock after use to be launched in India Sonal Matharu2012*
13. *Healthcare to get a shot with Auto-disable syringes Nina et al ET bureau 2009*
14. *Parthasarthy Textbook of Paedetrics,Jaypee Publishers2005*
15. *Gerald Dziekan,Daniel Chrisholm,Benjamin Johns,Juyan Rovira,Yvan J.F Hutin,The cost effectiveness of policies for safe and appropriate use of injections in healthcare settings Bulletin of WHO 2003*
16. *Paul K Drain,Josoa S.Ralaivio,Alexander Rokatonandrasana,MarryAKarnell Introducing auto-disable syringes in the National Program in Madagascar Bulletin of WHO 2003*
17. *GPV declares war on Unsafe injections Vaccine and Immunization use 1997World health Organization.*
18. *Simonsen L etal Unsafe injections in the developing world and transmission of blood borne pathogens bulletin of WHO 1999.*

CHAPTER 8

Iron Fortification of Drinking Water

Introduction:

Water is an essential nutrient for all known forms of life and the mechanism by which fluid and electrolyte homeostasis is maintained in humans A 65 kg man contains about 40 liters of water. Of this, 25 liters are intracellular and 15 liters are extracellular. These fluids are in continuously balance, being turned constant by a water intake and output. Several substances are found in drinking water that significantly contributes to health and well being. Water acts as a building material, in thermoregulation and body metabolism. It has been shown it could be a carrier of numerous macro and micronutrients as Ca, F, Cu, Mg, Se, K and particularly low in iron and iodine, source of health problems.

Globally, an estimated two billion lives are affected by a deficiency of essential micronutrients, known as hidden hunger. Worldwide, the most widespread micronutrient deficiencies are iron; iodine, zinc; vitamin A and folate, four of them are water soluble. Iron deficiency anaemia is the most common disorder in the world. Even mild to moderate deficiencies of micronutrients lead to impaired intellectual and growth development, increased morbidity from infectious diseases in infants and young children and decreased work productivity in adults.

Iron deficiency and iron anaemia are known today as the main, the most frequent worldwide nutritional deficiency problem in the world. Millions of children are still anaemic or becoming anaemic today in the world. It is generally considered to be the result of low iron intake from local diets. It is the most common health problem of children and pregnant women of underdeveloped and developing countries, in spite of the large amount of attention and effort carried out by national and international organizations. The best way to prevent iron deficiency anaemia is to increase the intake of iron; the iron fortification of water can be a viable option. As, drinking water, being available everywhere, daily consumed by everyone, children, adults and old people have been shown to be effective for the prevention of iron anemia. (#)

(#) - Drinking Water as Iron Carrier for the Prevention of Iron Deficiency Anaemia: The Brazilian Experience

Description of the condition

Micronutrients' deficiency is a major public health challenge. This may be due to low dietary intake, poor iron (less than 20 mg /day) and folic acid intake (less than 70 micrograms/day), poor bio-availability of iron (3-4 percent only) in phytate fibre-rich Indian diet and chronic blood loss due to infection such as malaria and hookworm infestations (Department of woman and child development Report, n. d.), there is a high prevalence of anaemia in India especially in pre-school children. Anaemia contributes to poor scholastic performance and increased susceptibility to infection. Pre-school children were one of the target groups to receive IFA tablets under the National Nutritional Anaemia Prophylaxis Programme. But both access to and intake of Iron Folic Acid tablets by children have been very poor; as a result there has been very little impact in terms of reduction in anaemia in childhood.

This Health Technology Assessment Report gives us an eagle's eye view on this topic covering clinical effectiveness, regulatory, safety and cost effectiveness analysis.

Clinical Effectiveness of Iron Fortified water for prevention of Anaemia in Preschool Children

Objective:

- Does Iron Fortified water prevents Anaemia in Pre – school Children?

Search Methods:

- We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, MEDLINE, PUBMED Science Direct, British Medical Journal, SCOPUS and Google Scholar for relevant studies. We also conducted secondary referencing by manually reviewing reference lists of key articles and searching citations by using Web. We also conducted specific searches for primary studies published more recently than the included systematic reviews and meta-analyses. Studies were included or excluded on the basis of our exclusion and inclusion criteria.

Key Words:

- The keywords used for literature search were "Iron fortification in drinking water, Iron fortification in drinking water pre-school, Water as iron carrier preschool children, Anaemia prevention using iron fortified water".

Selection Criteria:

Below mentioned selection criteria was used:-

- Population: - Preschool children
- Intervention :- Iron Fortified water
- Control :- No fortification group
- Primary Outcome :- Hemoglobin level

Criteria for considering studies for this review:

Types of studies

- Randomized clinical trials, Non-Randomized clinical trials, Case control and cohort studies which were available on this subject are included in this review.

Data Collection and Analysis:

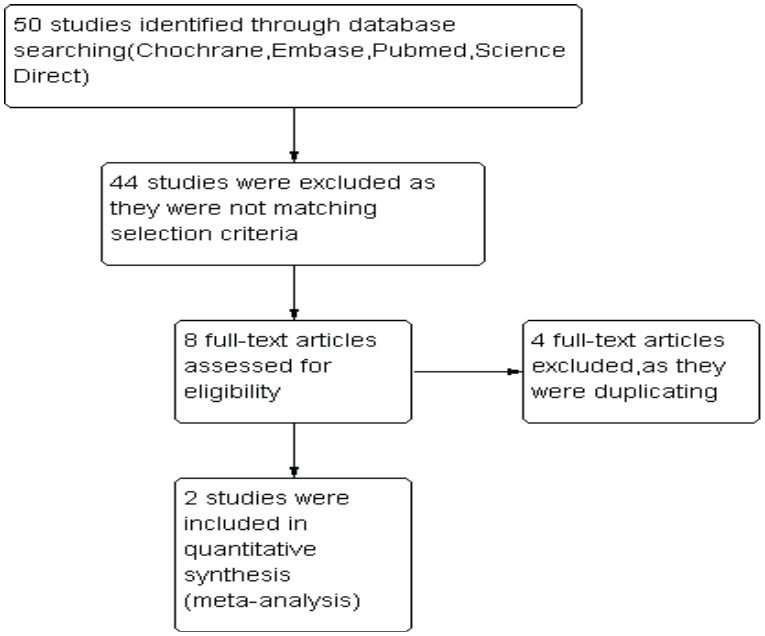
Data extracted was categorised in two groups:-

1. Studies based on water fortification only with iron without Vitamin C.

In this group 50 studies were available among these 44 studies were excluded as they were not matching our selection criteria. Remaining 6 studies were checked for duplicates and 4 duplicated articles were removed. Hence, only 2 studies were included in Quantitative synthesis (Meta – Analysis).

As shown in the Study Flow diagram below:

Study Flow Diagram



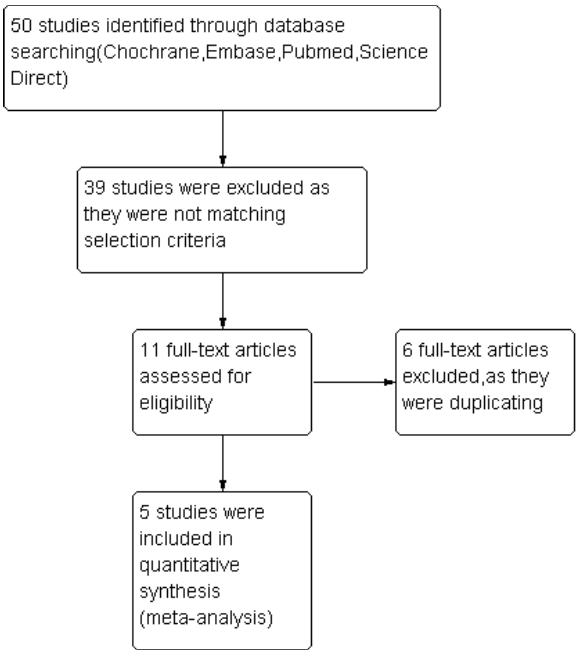
Note: This table is applicable for studies based on water fortification only with Iron without Vitamin C

2. Studies based on water fortification with Iron and Vitamin C

In this group 50 studies were available among these 39 studies were excluded as they were not matching our selection criteria. Remaining 11 studies were checked for duplicates and 6 duplicated articles were removed. Hence, 5 studies were included in Quantitative synthesis (Meta – Analysis).

As shown in the Study Flow diagram below:

Study Flow Diagram



Note: This table is applicable for studies based on water fortification with Iron and Vitamin C

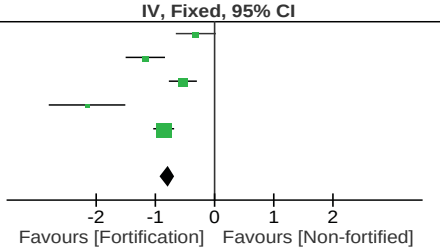
Table of Included Studies:

S. NO	STUDY NAME	AUTHOR	YEAR
IFW1	Randomized Controlled Trial of Iron-Fortified Drinking Water in Preschool Children	Francisco Pla´cido Nogueira Arcanjo, PhD, Olga Maria Silverio Amancio, PhD, Josefina Aparecida Pellegrini Braga, PhD, Vicente de Paula Teixeira Pinto, PhD	2010
IFW2	Drinking water as an Iron carrier to to control anemia in preschool children in a day care center	J.E.Dutra-de-Oliveira,MD. Jacob B. Ferreira, BS, Valeria P. Vasconcellos, BS, and J. Sergio Marchini MD	1994
IFW3	Effectiveness of fortification of drinking water with iron and vitamin C in the reduction of anemia and improvement of nutritional status in children attending day-care centers in Belo Horizonte, Brazil	Daniela da Silva Rocha, Flávio Diniz Capanema, Michele Pereira Netto, Carlos Alberto Nogueira de Almeida, Sylvia do Carmo Castro Franceschini, and Joel Alves Lamounier	2011
IFW4	Effect of fortification of drinking water with iron plus ascorbic acid or with ascorbic acid alone on haemoglobin values and anthropometric indicators in preschool children in day-care centres in Southeast Brazil	Carlos Alberto Nogueira de Almeida, José Eduardo Dutra-de-Oliveira, Gerson Claudio Crott, Alessandro Cantolini, Rubens Garcia Ricco, Luiz Antonio Del Ciampo, and Marina Elisa Costa Baptista	2005
IFW5.	Assessment of Drinking Water Fortification with Iron Plus Ascorbic Acid or Ascorbic Acid Alone in Day care Centres as a Strategy to Control Iron-Deficiency Anaemia and Iron Deficiency: A Randomized Blind Clinical Study	Carlos A. N. de Almeida, Elza D. De Mello, Adriana P. R. Ramos, Camila A. João, Carolina R. João José E. Dutra-de-Oliveira	2013
IFW6	Domestic drinking water--an effective way to prevent anemia among low socioeconomic families in Brazil.	Dutra-de-Oliveira JE, de Almeida CA.	2002
IFW7	Effect of iron-fortified drinking water of day care facilities on the haemoglobin status of young children.	Beinner MA, Lamounier JA, Tomaz C.	2005

Forest Plot showing Haemoglobin level after fortification

Study or Subgroup	Before Mean	Before SD	Before Total	After Mean	After SD	After Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Almeida 2005	11.54	1.35	74	11.95	1.22	74	11.9%	-0.32 [-0.64, 0.01]
Arcanjo 2010	10.5	0.8	89	11.5	0.9	89	12.4%	-1.17 [-1.49, -0.85]
Beinner M A 2005	11.8	1.3	160	12.4	0.9	160	25.2%	-0.54 [-0.76, -0.31]
Oliveira 1994	10.6	1.1	31	13	1.1	31	3.1%	-2.15 [-2.79, -1.52]
Rocha 2011	11.84	1.3	318	12.98	1.35	318	47.4%	-0.86 [-1.02, -0.70]
Total (95% CI)			**672**			**672**	**100.0%**	**-0.79 [-0.90, -0.68]**

Heterogeneity: Chi² = 37.14, df = 4 (P < 0.00001); I² = 89%
Test for overall effect: Z = 13.87 (P < 0.00001)



All the study showed a significant increase in mean haemoglobin level after fortification. The increase in the mean Hb level itself shows there is increase in the iron deposition in the body.

However, this increase could not show if it averted cases of anemia or not and upto what extent it is effective as it is a continuous outcome.

The effect size shown here is not in form of Risk ratio, which could be interpreted in terms of risk reduction with such intervention. However, considering holistically, it could be easily understood that there is no harm doing iron fortification as compared to no fortification as it is supported by forest plot findings.

This plot shows that the mean Hb was lower by 0.79 g/dL (95% CI -0.90 to -0.68 g/dL) in the no fortification group compared to fortification group.

Hence, Meta-analysis favours the Iron fortification in terms of clinical benefit as compared with no fortification.

Cost Effectiveness Analysis:

Cost-effectiveness analysis is a method of comparing the cost and effectiveness of two or more alternatives. Such comparisons are useful when one of the alternatives being considered is standard care, as this allows the decision maker to consider whether an alternative is better or not. The standard care, however, could also be a placebo or "Do Nothing" scenario.

Cost of iron fortification:

- The fortification criteria was given in one of selected study, which was there should be 20 mg/l iron in fortified water.
- The tank capacity is 8000 Ltrs. (Data from National Rural Drinking Water Plan(NRDWP- Ministry of Drinking water and Sanitation Govt. of India site)
- Content of Ferrous Sulphate in a tablet as per Essential Drug list- National Health Mission = 200 mg
- Thus for fortifying one tank with iron, total 200 tablets would be required.
- Thus, considering iron content required for one tank = 16,000 mg =800 tablets required per day
- Cost of one tablet of iron sulphate = 0.05472
- Thus cost of daily iron fortification in one tank = 43.77 Rs.
- For whole coverage , daily iron fortification cost = 43.77 x 84,612 = 37,03,467 Rs

- ❖ Approximately Rs1 lakh /state/day.
- ❖ The mean annual economic loss due to Iron deficiency anaemia is assumed to be $16.78 per capita. (Pasricha S R et al. 2012) =Rs 1006.8/ person

Iron fortification of drinking water in schools could thus be clinically effective and cost saving intervention, if provided in schools. Hence, it dominates the alternative scenario of not providing iron-fortified water.

Regulatory and Commercial Status:

Iron tablets are included in essential drug list for each states and UTs under National Health Mission, India. It is regulated by Drug Controller General of India. However, being a novel concept, the process of fortification of drinking water is not separately regulated.

Being a generic version, it would be easier to implement such fortification at lower cost.

Safety Issues:

Solubility of iron is the biggest challenge in case of water unlike vitamin C tablets. Excess amount of iron in body may result in a serious chronic condition known as hemochromatosis. Thus, it should be conducted in very cautious manner along with Ascorbic acid or easily water-soluble forms of irons like Ferric Ammonium Citrate, Ferrous Lactate, Ferrous Sulfate or our soluble Ferric Pyrophosphate. (Lohman P n.d.)

Way forward more studies of fortification of drinking water is retained. With the limited evidence it would be difficult to say that fortification could be achieved safely. Smaller efforts may be done to gather contact based results. Only after such results have been analyzed decision on water fortification is suggested.

Conclusion/ Recommendations:

This is an innovative concept to prevent iron deficiency anaemia in India. It is still in experimental phase. Without robust trials evidence, it is not advisable to introduce it at public health level. Though statistically significant difference is seen as per presented analysis, it could be only considered in terms of its implications for research and not for its implication for practice.

However, if it is identified to be positive and effective intervention, it could be introduced in health system via joint efforts of Ministry of Health and Ministry of Drinking water and sanitation with their National Health Mission and National Rural Drinking Water Programme.

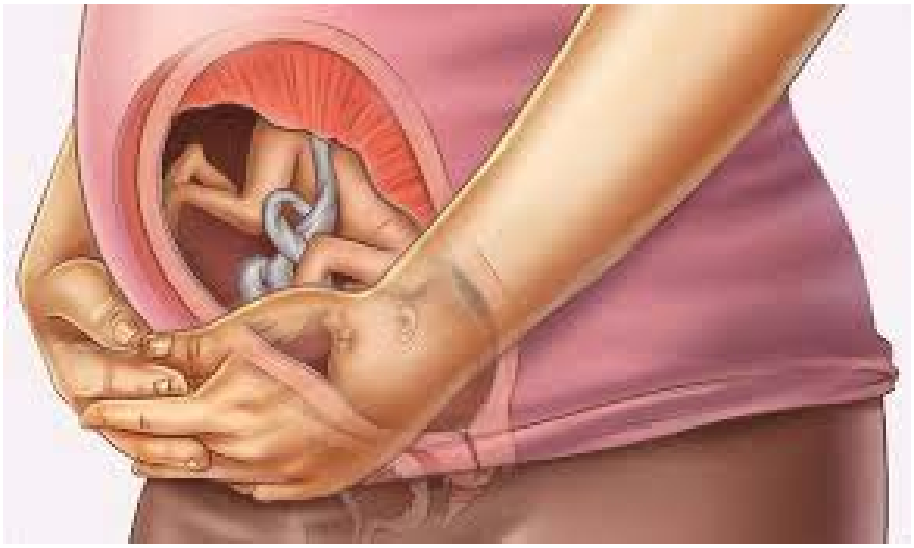
Bibliography:

1. *http://bloodjournal.hematologylibrary.org/content/121/14/2607.long.*
2. *http://www.unicef.org/india/10._National_Iron_Plus_Initiative_Guidelines_for_Control_of_IDA.pdf*
3. *http://www.academia.edu/4276449/Prevalence_of_Iron-Deficiency_Anaemia_in_India_Results_from_a_Large_Nationwide_Survey)*
4. *http://www.almat.ca/pressrelease/Beverage%20Fortification_EN_DNR%20152_RevA.PDF*

CHAPTER 9 Role of Multi-Micronutrient (MMN) in Ante-Natal Period

A) Introduction:

Antenatal period is the period where the foetus is in developmental stage and also there are many physiological hormonal changes in mother's body. As a result, it is recommended that woman should be provided with adequate nutritional supplementation apart from diet. In pregnancy, maternal health is compromised with anaemic conditions due to lack of proper iron amount in the body. On the other side, there is risk of low –birth –weight babies, children with neural tube defects resulting from improper nutrition apart from Iron supplements. Thus, one consideration is to supplement IFA (Iron folic acid) tablets. Whereas other consideration is to provide pregnant woman with the multivitamin tablets, which includes other micronutrient, vitamin B complex, vitamin C ,D, zinc with folic acid. However, commonly pregnant women are more inclined towards IFA as they are more concerned about potential risk of anaemia. Thus compliance issues with multi vitamin tablets have been observed. Moreover, side effects and adverse drug reactions in case of either intervention may impact the overall use and thereby public health. Thus, from policy point of view, there is requirement of evidence based comprehensive assessment of these both antenatal interventions. This HTA report explains the findings on clinical efficacy, safety, cost-effectiveness, regulatory and marketing aspects with evidence.



B) Clinical Effectiveness of Iron Folic Acid versus Multivitamin/Multi micronutrient in Antenatal Period:

Objective:

- Effect of Iron Folic Acid versus Multivitamin/Multi micronutrient in Antenatal Period in reduction in low birth weight infants.

Search Methods:

- We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, MEDLINE, PUBMED Science Direct, SCOPUS and Google Scholar for relevant studies. We also conducted secondary referencing by manually reviewing reference lists of key articles and searching citations by using Web of Science. We also conducted specific searches for primary studies published more recently than the included systematic reviews and meta-analyses. Studies were included or excluded on the basis of our exclusion and inclusion criteria.

Key Words:

- The key words mainly used for article search were :"iron folic acid supplementation", "antenatal multivitamin supplementation", "antenatal multivitamin supplements randomised controlled trials ","iron folic supplementation", "antenatal folic acid efficacy RCT", "antenatal supplementation and efficacy", "IFA in pregnancy".

Selection Criteria:

Below mentioned selection criteria was used:-

- Population: - All Pregnant ladies.
- Intervention :- Multivitamin/Multi micronutrient
- Comparator :- Iron Folic Acid
- Primary Outcome :- Low birth weight infants

Criteria for considering studies for this review:

Types of studies

- Randomized clinical trials, Non-Randomized clinical trials, Case control and cohort studies which were available on this subject are included in this review.

Types of interventions:

- Experimental :- Multivitamin/Multi micronutrient
- Control :- Iron Folic Acid

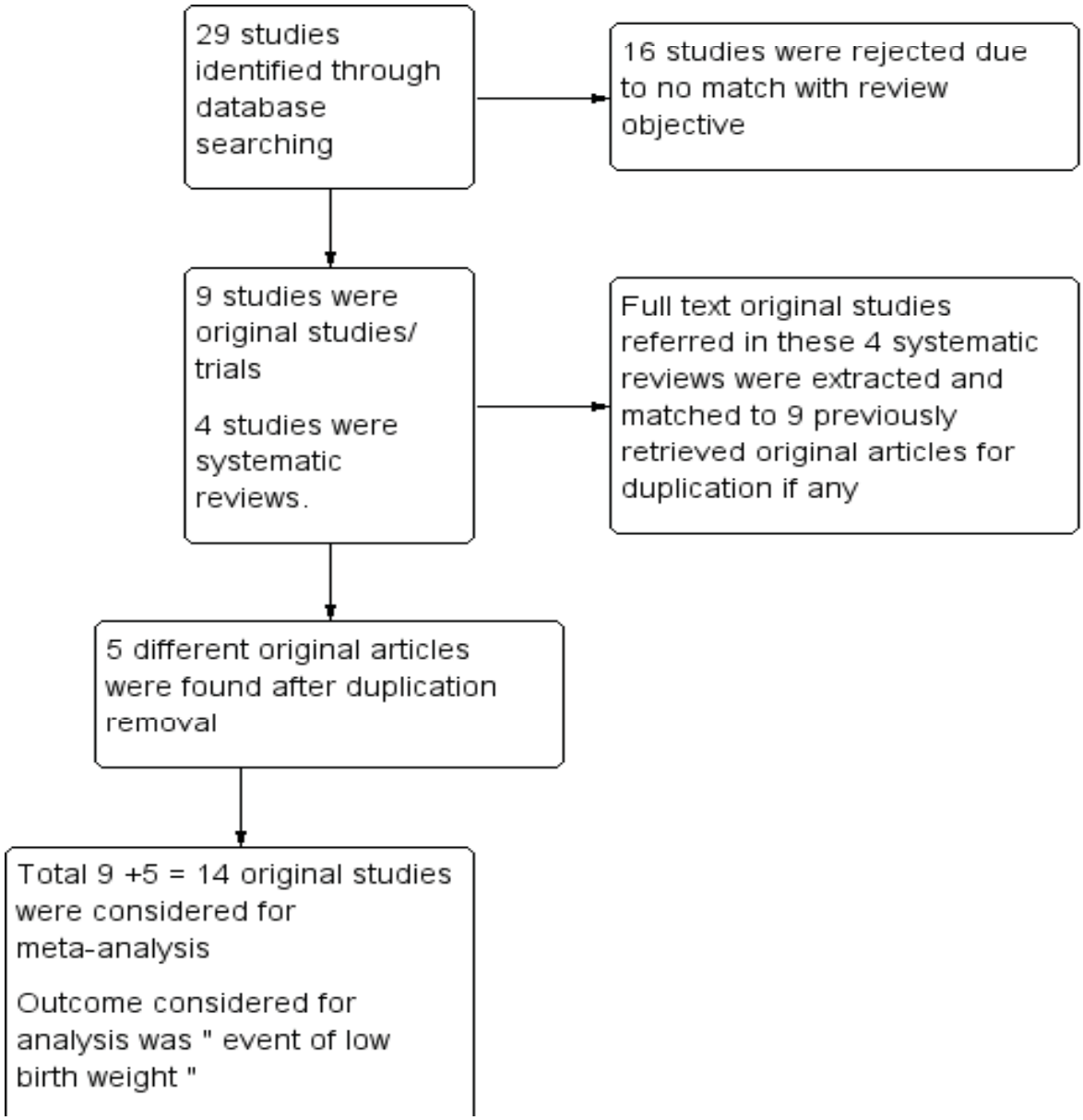
Outcome:

Low birth weight infants were assessed in both experiment and control group.

I) Data Collection and Analysis:

Total 29 studies were selected among them 16 studies were rejected as they were not matching with our objective, 9 were original studies and 4 were systematic reviews. Full text studies referred in systematic reviews were also extracted. All full text studies were critically appraised and rated as per Critical Appraisal Skills Programme (CASP) tool for randomized controlled trials. Due to difference in scientific design of randomised trials and systematic reviews, separate formats were used for data extraction for both the types of studies. The extracted data is tabulated as below:

C) Study Flow Diagram



D) Data from studies no. 1-4; Table -1

Study No.	1	2	3	4
Author's names	Roberfroid et al.	Christian P.et al.	Roberfroid D.et.al.	Hanieh et.al.
Study Aim/Objective	Effect of MMN on cord blood hormones	Effect of alternative MMN on low birth weight	Impact of prenatal MMN on survival and growth during infancy	Effect of intermittent antenatal iron supplementation on maternal and infant outcome
Sample size	1246 pregnant women with subsample of 294 live singleton birth	4296 pregnant women +4130 live born infants	1294 pregnant women	1258 in 104 countries
Study Design	Randomised Controlled Trial	Randomised Community Trial	Randomised Controlled Trial	Cluster Randomised Controlled Trial
Primary Outcome	Level of IGF-1,leptin ,insulin , free tyroxine,cortisol	Birth weight, anthropometric measures within 72 hours of birth	Anthropometric measures and safety measures	Birth weight ,infant mortality and gestational age at birth
Secondary Outcome	Anthropometric measures	-	-	Head circumference,maternal and infant Hb,ferritin level, cognitive development,infant length -for-age z score,still births ,miscarriages

Table 2

Randomisation Method (if any)	-	Cluster randomised	Computer generated block randomisation	Cluster randomised
Statistical Method	Bi-variate Analysis,Multivariate analysis,matrix of co-variance decomposition of dependent variables ,exploratory apoian test	Intention to treat,Estimating equation linear model	Intention-to -treat ,Poission's regression model,mixed effect	Per-protocol analysis
Blinding	Double blind	Triple blind but mid-study testing unblinding done	Triple blind	Double blind
Study Score based on CASP tool (out of 24)	19	24	18	23

Inclusion Criteria	-	Likely to be pregnant women after urine test and other verifying measures	Pregnant women	Residence in trial commune,age >16y ,confirmed pregnancy at< 16 wk gestation,registration with commune health system
Exclusion Criteria	-	Currently pregnant,menopausal,widow,breast feeding <9month and sterile	-	High risk pregnancy,Multi fetal pregnancy(confirmed on palpation or ultrasound or a significant medical condition or if they had severe anemia (Hb<80 g/l)
Study Limitation /Bias	Weak statistical power	Survival analysis not done	Adverse event severity not measured	Type -1 error driven results (possible incorrect association of mean cognitive score in infant to women)
Statistical Power	80%	80%	-	-

Outcomes	Baseline observation		Mother-infant characteristics similar in both group except primiparity rate which was significantly low in control(IFA)	Maternal characteristics similar in both group	Similar baseline characteristics in both groups	Similar baseline characteristics in both group
	After intervention	Safety	●perinatal mortality increased in primiparous women significantly with MMN	-	●No difference in IFA or MMN groups in infant mortality ●14% lower risk of fever in MMN compared to IFA group● No difference in risk of diarrhea or cough episodes in any group	●No clinically significant difference in risk of premature birth, still birth and early neonatal death in both groups ●prevalence of nausea and vomiting higher in twice weekly MMN group
		Efficacy/Effectiveness	●Gender,parity and height's influence on level of hormones ●overall no evidence of effect of UNIMMAP versus IFA on cord blood hormone concentrations	●Disproportionate weight gain due to MMN●lower incidence of Small -for - Gestational Age- infants in IFA group●No reduction in pre-term birth incidence in either intervention(IFA OR MMN)	●Prenatal UNIMMAP reduced stunting rate by 27% during infancy●Modest improvement in infant growth due to UNIMMAP compared to IFA●Time bound impact of MMN on birth length , length-for-age and other anthropometric measures	●Distribution of infant birth weight similar in case of daily IFA , twice weekly IFA and twice weekly MMN ●Head circumference significantly lower in twice weekly IFA compared to daily IFA whereas no difference in outcomes for daily IFA and twice weekly MMN ●No clinically significant difference in gestational age ●No difference in maternal Hb in both groups after 32 wk gestation and also same status with infant Hb ● Lower ferritin in twice weekly IFA compared to daily IFA ●Prevalence of iron deficiency more in twice weekly IFA and even more in twice weekly MMN ●No difference in length for age for all groups ●Higher composite cognitive scores in twice weekly IFA compared to daily IFA but no difference in case of daily IFA versus twice weekly MMN
		Limitation of outcome	Small sample size in determining association between UNIMMAP supplementation and cord blood hormones levels and fetal growth.	-	-	Paucity of high quality data
Primary Outcome Effect (score between -2/-1/0/+1/+2)			1	2	2	1
Study Finding on Birth Weight			-	No. of Low birth weight events reduced by 3% more in case of MMN versus IFA	No. of low birth weight events reduced by 0.6%more in case of MMN vesus IFA	No. of low birth weight events reduced by 0.2 % more in case of twice weekly MMN versus daily IFA

Data from studies no. 5-9: Table - 3

Study No.	5	6	7	8	9
Author's names	Ramakrishnan et al.	Roberfroid D et al.	Friss H. Et al.	Prado et. Al.	Shankar A et al.
Study Aim/Objective	Effect of MMN versus iron on birth size	Effect of IFA + MMN versus IFA on dose response of maternal Hb	Effect of MMN on gestational length and birth size	Effect of MMN on cognition and mood during pregnancy and post partum	Effect of MMN versus IFA on fetal loss and infant death
Sample size	873 pregnant women	1426 pregnant women	1106 pregnant women	2369 pregnant women	31290 pregnant women
Study Design	Randomised Controlled Trial	Randomised Controlled Trial	Randomised Placebo Controlled Trial	SUMMIT design	Cluster Randomised Trial
Primary Outcome	Anthropometric measures and biochemical analyses of micronutrients concentration in blood,Hb	Maternal Hb level	Birth weight, length and head circumference	overall cognition and performance on individual test	Early infant mortality
Secondary Outcome	-	Anthropometric measures	no. of tablets as compliance measure	-	neonatal mortality, fetal loss and birth weight

Table 4

Randomisation Method (if any)	-	Computer generated pemuted block sequence	Computer generated sequence replaced by permuted block combination	-	Computer generated permuted blocks
Statistical Method	Intention-to-treat ,Student's t-test,Chi-square test ,adjusted analyses with multivariate technniques	Multivariate mixed effect model -logistic regression, covariance,restricted maximum likelyhood test	Intention to treat ,2 sample student's t-test ,chi-square test , HIV infection status based stratification ,multiple and linear logistic regression analysis	Mixed effect model ,multiple regression analysis	Intention-to-treat,Hierarchial logistic regression analysis,estimating equations, mixed effect model, survival analysis
Blinding	Double blind	Double blind	Double blind	Double blind	Double blind
Study Score based on CASP tool (out of 24)	23	22	24	21	23

Table 5

Inclusion Criteria	**women with assured pregnancy technically**	**Pregnant women after pregnancy test positive results**	**Any women between 22 and 36 wk of gestation**	**Pregnant women after pregnancy confirmation**	**Pregnant women for any gestational age after pregnancy confirmation**
Exclusion Criteria	**Being >13 wk of pregnancy,previoius use of MMN and refusal to participate**	-	-	-	-
Study Limitation /Bias	**Less severe effect produced due to less MMN deficiencies and poor birth outcome,high level of loss to follow up -presumed effect on sample ,poor availability of supplements and poor compliance**	**No surety about saturation point for appropriate dose response curve, no measure of ferritin concentration thus no assessment of effect of MMN on iron stores,compliance data reliance issue (no proper allocation of iron in both MMN and IFA group),less statistical power in Hb analysis**	**High lost-to-follow-up,compliance data measurement taken in only half of the patients i.e. Treatment arm**	**Reliance on inconsistent data for cognition positive results and for motor dexterity and mood score, links between maternal intervention, maternal cognition specific care giving behaviours to be confirmed**	**Not specific -general more rigorous study design is required**
Statistical Power	-	-	**80%**	-	**80%**

Table 6

Outcomes	Baseline observation		Similar baseline characteristics in both group	Similar baseline characteristics in both groups	Similar characteristics in both groups	Similar baseline characteristics in both groups	Similar baseline characteristics in both groups	Apparently similar baseline characteristics in both groups
	After intervention	Safety	●No clinically significant difference in risk of premature birth, still birth and early neonatal death in both groups ●prevalence of nausea and vomiting higher in twice weekly MMN group	●Apparently Similar number of still birth in both group	No safety outcome mentioned	No safety outcome mentioned	No safety outcome mentioned	●18% and 30% reduction in early infant mortality and post natal deaths respectively in case of MMN compared to IFA ●persistent tend in mortality reduction in case of MMN observed from Kaplan meier survival analysis ●25% reduction and 38% reductionin early infant mortality resulted from MMN in case of malnourished and anemic women respectively●15% and 29% reduction in combined fetal loss and neonatal death due to MMN in case of undernourished and anemic women.
		Efficacy/ Effectiveness	●Distribution of infant birth weight similar in case of daily IFA , twice weekly IFA and twice weekly MMN ●Head circumference significantly lower in twice weekly IFA compared to daily IFA whereas no difference in outcomes for daily IFA and twice weekly MMN ●No clinically significant difference in gestational age ●No difference in maternal Hb in both groups after 32 wk gestation and also same status with infant Hb ● Lower ferritin in twice weekly IFA compared to daily IFA ●Prevalence of iron deficiency more in twice weekly IFA and even more in twice weekly MMN ●No difference in length for age for all groups ●Higher composite cognitive scores in twice weekly IFA compared to daily IFA but no difference in case of daily IFA versus twice weekly MMN	● No difference in birth weight, gestational age,incidence of low birth weight,intrauterine growth retardation,intra uterine stunting,ponderal index, birth length and preterm birth .	Identical dose response curve in both group after dose administration ●Same effect in case of 30 mg Fe or 60 mg Fe + other micronutrients on maternal Hb ●Effect produced by micronutrient supplementation in strong correlation of baseline Hb	Except 49 g increase in birth weight in case of MMN , effect on gestational length, birth length ,ponderal index and head circumference was same	●Improvement shown in only case of women who were identified malnourished and/or anemic ●No difference in maternal Hb and mid-upper arm circumference ●Improvement in overall cognition and reading efficiency after MMN supplementation ●No improvement in maternal motor dexterity and mood during pregnancy and post partum in case of MMN versus IFA	●Non -significant increase in mean birth weight of 21 g with 14% reduction in low birth weight in MMN group compared to IFA group in case of women with non anemic status ●Increase of 52 g in mean birth weight with 33% reduction in low birth weight in MMN group in case of women with anemic status
		Limitation of outcome	Paucity of high quality data	-	Safety outcome not measured	Paucity of data due to high loss to follow up	-	-
Primary Outcome Effect (score between -2/-1/0/+1/+2)			1	1	2	2	2	2
Study Finding on Birth Weight			No. of low birth weight events reduced by 0.2 % more in case of twice weekly MMN versus daily IFA	No. of low birth weight events reduced by 0.4% more in case of MMN versus Iron .	-	Mean birth weight increased by 49 g in case of MMN versus placebo	-	No. of low birth weight events reduced by 2% more in case of MMN versus IFA

Table 7

Data from Systematic Reviews:

Systematic Review No.	1	2	3	4
Total no.of studies included	17	7	13	17
Review author	Zerfu T A and Ayele H T	Carroli G et al.	Shah P S et al	Kawai K et al.
Review objective	Effect of micronutrient supplementation on pregnancy and pregnancy outcome	Comparison of new model of antenatal visits and standard model of antenatal visit programme	Effect of prenatal multimicronutrient supplementation on pregnancy outcomes	Maternal multiple micronutrient supplementation and pregnancy outcomes in developing countries
Methodological Quality Assessment	No mention	Quality of randomisation,allocation concealment,masking with respect to outcome assessment ,care providers and treatment recipients,contamination in control group ,cointervention ,protocol deviation and intention-to-treat analysis were assessed and represented in 4 catergories : met, unmet, clear and unclear .	Checklist suggested for Cochrane Database of Systematic Reviews was used for methodological quality assessment which included risk of bias identification in sequence generation , allocation concealment,blinding,attrition ,selective reporting and was responded in form of either of 4 categories : Yes,No, Can't tell and Unclear.Sensitivity analysis for exclusion of studies with high likelyhood of bias in 3 or 4 domains.	Criteria for assessing methodological quality included randomization, allocation concealment, blinding, completeness of follow-up and compliance with study regimens

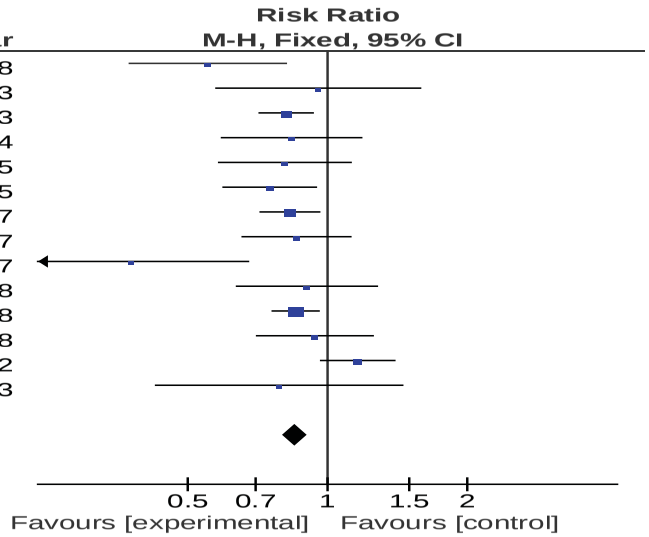
Table 8

Limitation of systematic review	less valid due to unavailability about method of methodologic quality assessment of studies included ,no measure about minor adverse evvent -prime safety data missing	Inconsistency of outcomes between apriori selected outcomes for review and actual outcome of included stduy - may be reason for biased conclusion ,no graphical presentation available i.e .forest plot or bar graph	-	Unclear information about association of treatment effect and time with time of treatment initiation,justification needed with evidence
Study score based on CASP tool (out of 24)	18	24	24	24
Results in context of birth-weight	3 studies showed "no difference" in terms of mean birth weight or no. Of low birth weight events where as 3 studies unanimously showed beneficial effect of MMN in reducing number of low birth weight events and also improving the mean birth weight	151 g increase in mean birth weight in standard model (regular frequency of antenatal visits)as compared to new model(few less antenatal visits), no difference in no.of events in low birth weight in both models	No. of low birth weight events reduced by 19 %in placebo in case of MMN as compared to placebo .**No.of low birth weight events reduced by 15% in case of MMN versus IFA.**Moreover, 54 g mean birth weight incrased also in case of MMN compared to IFA.	44 g increase in mean birth weight in case of MMN , No. Of low birth weight events reduced by 14%

E) Forest Plot Showing Clinical Benefit: Table 9

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Fawzi 1998	36	410	62	390	3.0%	0.55 [0.38, 0.81]	1998
Ramakrishnan 2003	27	318	28	315	1.3%	0.96 [0.58, 1.58]	2003
Christian 2003	249	705	297	685	14.2%	0.81 [0.71, 0.93]	2003
Friss 2004	54	564	62	542	3.0%	0.84 [0.59, 1.18]	2004
Kaestel 2005	83	750	51	373	3.2%	0.81 [0.58, 1.12]	2005
Osrin 2005	101	529	133	523	6.3%	0.75 [0.60, 0.94]	2005
Fawzi 2007	306	3937	368	3929	17.3%	0.83 [0.72, 0.96]	2007
Zagre 2007	96	1328	103	1222	5.1%	0.86 [0.66, 1.12]	2007
Gupta 2007	12	74	31	72	1.5%	0.38 [0.21, 0.67]	2007
Zeng 2008	57	1406	66	1470	3.0%	0.90 [0.64, 1.28]	2008
Shankar 2008	510	5695	567	5406	27.4%	0.85 [0.76, 0.96]	2008
Roberfroid 2008	77	526	82	526	3.9%	0.94 [0.71, 1.25]	2008
Roberfroid 2012	239	5611	211	5756	9.8%	1.16 [0.97, 1.39]	2012
Hanieh 2013	26	787	16	381	1.0%	0.79 [0.43, 1.45]	2013
Total (95% CI)		**22640**		**21590**	**100.0%**	**0.86 [0.81, 0.91]**	
Total events	1873		2077				

Heterogeneity: Chi² = 26.33, df = 13 (P = 0.02); I² = 51%
Test for overall effect: Z = 5.27 (P < 0.00001)



As per Forest plot,

RR= 0.86 % <1

This means there is 14% risk reduction of low birth weight infants in case of Experimental Group i.e. Multi micronutrient Group.
Moreover it is also observed that Risk Ratio (RR) is less than 1, means that experimental intervention is more effective than control.

F) Cost Effectiveness Analysis:

Cost-effectiveness analysis is a method of comparing the cost and effectiveness of two or more alternatives. Such comparisons are useful when one of the alternatives being considered is standard care, as this allows the decision maker to consider whether an alternative is better or not. The standard care, however, could also be a placebo or "Do Nothing" scenario.

Cost per Low Birth Weight infants associated deaths averted:

Calculation of total Low Birth Weight associated neonatal deaths that could be averted by Multivitamin/Multi micronutrient:

Total number of beneficiaries = 2, 15, 00,000 (HMIS NRHM data 2013)

Neonatal mortality rate in India = 32 per 1000 live births=3.2%

(WHO health statistics report 2013)

Low birth weight associated deaths = 35% of total neonatal deaths

(UNICEF 2010)

Reduction in Risk of Mortality due to MMN supplementation is 14%

(From forest plot)

Considering partial coverage i.e. 80%, 60%, 40% and 20% and corresponding mortality can be calculated and tabulated as below.

Coverage (%)	Number of pregnancies	Neonatal Deaths = 3.2% of total births	LBW associated deaths =35% of total neonatal deaths	Reduction in mortality (RD)= 14% of LBW associated deaths
100	21500000	688000	240800	33712
80	17200000	550400	192640	26970
60	12900000	412800	144480	20227
40	8600000	275200	96320	13485
20	4300000	137600	48160	6742

Table: 4 Coverage wise Reduction in Mortality due to MMN supplementation

Cost per tablet C_T:

A. Ferrous Sulphate (Iron):

Rs. 54.45+5% CST for 1000 tabs (Gujarat approved drug rate)

$C_{T\ (Fe)}$ = 54.5/1000 = Rs. 0.0545

B. Folic Acid

Rs. 45 +5 % VAT for 1000 tabs (Gujarat approved drug rate)

$CT_{(FA)}$ = (45+0.05)/1000 = Rs. 0.04505

C. Iron Folic Acid

Cost of iron folic acid = Cost of Iron + Cost of folic acid

$C_{T\ (IFA)} = C_{T\ (Fe)} + C_{T\ (FA)}$

$C_{T\ (IFA)}$ = 0.0545 + [(45+0.05)/1000] = 0.0545+0.04505 =Rs. 0.09955 (Gujarat approved drug rate)

D. Multivitamin/Multimicronutrient

Rs. 244+5% CST for 1000 tabs (Gujarat approved drug rate)

$C_{T\ (MMN)}$ =244.05/1000=0.244=Rs. 0.24

However considering country's generic production capacity, MMN could be procured at much lower rates.

Moreover, as per recommendation from UNICEF WHO UNU workshop report 1999 (page-7) mention of iron is found in list of "agreed upon nutrients to be included".

Thus, MMN could be considered to be iron and folic acid. Thus providing for multi –micronutrient would not mean reduction in iron folic acid dosage.

Cost per death averted:

Considering mortality data from table -4, cost per deaths averted due to MMN supplementation can be tabulated as follows for 1. Cost of IFA= Cost of MMN and 2. Cost of MMN = Rs. 0.24

1. Cost of IFA= Cost of MMN: Due to same cost of both interventions, reduction in mortality due to MMN supplementation would be without any extra cost.

Cost /Tablet(INR)		Annual cost/ beneficiary= Cost/ tablet X 365 days (INR)		Beneficiaries in target population		Budget (INR)		Reduction in mortality (RD)= 14% of LBW associated deaths without extra cost
IFA	MMN	IFA	MMN	% coverage	Absolute numbers	IFA	MMN	
0.09	**0.09**	**32.85**	**32.85**	**100**	21500000	**7062,75,000.00**	**7062,75,000.00**	33712
0.09	**0.09**	**32.85**	**32.85**	**80**	17200000	**5650,20,000.00**	**5650,20,000.00**	26970
0.09	**0.09**	**32.85**	**32.85**	**60**	12900000	**4237,65,000.00**	**4237,65,000.00**	20227
0.09	**0.09**	**32.85**	**32.85**	**40**	8600000	**2825,10,000.00**	**2825,10,000.00**	13485
0.09	**0.09**	**32.85**	**32.85**	**20**	4300000	**1412,55,000.00**	**1412,55,000.00**	6742

Thus if genuine MNM could be procured at the cost of IFA, then it would be 6742 to 3371 neonatal deaths averted depending upon coverage levels from 20% to 100%

2. Cost of MMN = 0.24

Cost / Tablet(INR)		Annual cost/ beneficiary= Cost/tablet X 365 days (INR)		Beneficiaries in target population		Budget (INR)		Difference in Budget(ΔB)(INR)	Reduction in mortality (RD)= 14% of LBW associated deaths	Incremental Cost/death averted = ΔB/RD(INR)
IFA	MMN	IFA	MMN	% coverage	Absolute numbers	IFA	MMN			
0.09	0.24	32.85	87.60	100	21500000	7062,75,000.00	18834,00,000.00	11771,25,000.00	33712	34,917.09
0.09	0.24	32.85	87.60	80	17200000	5650,20,000.00	15067,20,000.00	9417,00,000.00	26970	
0.09	0.24	32.85	87.60	60	12900000	4237,65,000.00	11300,40,000.00	7062,75,000.00	20227	
0.09	0.24	32.85	87.60	40	8600000	2825,10,000.00	7533,60,000.00	4708,50,000.00	13485	
0.09	0.24	32.85	87.60	20	4300000	1412,55,000.00	3766,80,000.00	2354,25,000.00	6742	

ICER -

compares the differences between the costs and health outcomes of two alternative interventions that compete for the same resources, and Is generally described as the additional cost per additional health outcome. When comparing two competing programs incrementally, one program should be compared with the next-less-effective alternative. The ICER numerator includes the differences in program costs, averted disease costs, and averted productivity losses if applicable. Similarly, the ICER denominator is the difference in health outcomes.

Thus incremental cost effectiveness ratio of Rs.34917/neonatal death averted could be achieved by providing MMN instead of just IFA at current market cost of MMN.

The incremental cost per neonatal death averted is less than the GDP per capita of our country and hence MMN can be considered cost effective in Indian context. A major limitation of our analysis is that the cost of procurement and distribution system for IFA or MMN; and the cost of delivery IFA/ MMN supplementation is not included in our analysis.

G) Regulatory Aspects and Market Status:

Both Iron folic acid (IFA) and Multivitamin / Multi-micronutrients are off-patent drugs. There are many generic manufacturers in Indian and global market. In India, both drugs are regulated by Drug Controller General of India (DCGI). Iron supplements are not reviewed for safety or efficacy and are not approved for sale as medications by the Stringent Regulatory Authorities (SRAs) in United States (Food and Drug Administration, FDA), Australia (Therapeutic Goods Administration, TGA) and the United Kingdom (Medicines and Healthcare products Regulatory Agency, MHRA). Rather supplements are registered as food supplements and are held to good manufacturing practices for purities only. Therefore, no additional specific analysis of regulatory status of iron or folic acid supplements was warranted. However, manufacturers of supplements must be registered entities and certified to adhere to good manufacturing practices. In India, IFA supplementation is well-incorporated in National Iron Supplementation Programme known as WIFS (Weekly Iron Folic Supplementation Programme).However, MMN supplementation is yet expected to be translated in policy.

H) Results and Recommendations:

Total consumption of IFA tablet in current supplementation program is 7847500000 tablets. (2, 15, 00,000 beneficiaries x1 tablet daily for year)(NRHM HMIS 2013 data).Thus, considering clinical impact of MMN,

1. The decline in low birth weight event associated deaths by supplementing MMN would be 33712 cases per year as per this assessment.

2. If MMN is supplemented instead of IFA considering full coverage.....

   - 33712 LBW associated deaths would be averted at no extra cost. (When price of IFA =price of MMN) at coverage levels of 100%.
   - Incremental cost per death averted would be Rs. 34,917.09(When price of MMN =0.24 rupees.

Bibliography:

1. *Roberfroid D et al.,Effect of maternal multiple micronutrient supplements on cord blood hormones: a randomized controlled trial, Am J Clin Nutr 2010;91:1649–58.*
2. *Christian P et al .,Effects of alternative maternal micronutrient supplements on low birth weight in rural Nepal: double blind randomised community trial,Br Med J 2003;326:1-6.*
3. *Roberfroid D et al.,Impact of prenatal multiple micronutrients on survival and growth during infancy: a randomized controlled trial, Am J Clin Nutr 2012;95:916–24.*
4. *Hanieh S et al.,The effect of intermittent antenatal iron supplementation on maternal and infant outcomes in rural Viet Nam: a cluster randomised trial. PLoS Med 2013 ;10(6): e1001470.*
5. *Ramakrishnan U et al., Multiple micronutrient supplementation during pregnancy does not lead to greater infant birth size than does iron-only supplementation: a randomized controlled trial in a semirural community in Mexico, Am J Clin Nutr 2003;77:720–5.*
6. *Roberfroid D et al., Randomized controlled trial of 2 prenatal iron supplements: is there a dose-response relation with maternal hemoglobin?, Am J Clin Nutr 2011;93:1012–8.*
7. *Friss H et al., Effect of multimicronutrient supplementation on gestational length and birth size: a randomized, placebo-controlled, double-blind effectiveness trial in Zimbabwe, Am J Clin Nutr 2004;80:178–84.*
8. *Prado E L et al., The effect of maternal multiple micronutrient supplementation on cognition and Mood during pregnancy and postpartum in Indonesia: a randomized trial. PLoS ONE 2012; 7(3): e32519.*
9. *Shankar A, Effect of maternal multiple micronutrient supplementation on fetal loss and infant death in Indonesia: a double-blind cluster-randomised trial, Lancet 2008; 371: 215–27.*
10. *Zerfu and Ayele, Micronutrients and pregnancy; effect of supplementation on pregnancy and pregnancy outcomes: a systematic review. Nutr J 2013 ;12:20.*
11. *Carroli G et al.,WHO systematic review of randomised controlled trials of routine antenatal care, Lancet 2001; 357: 1565–70.*
12. *Shah P S et al., Effects of prenatal multimicronutrient supplementation on pregnancy outcomes: a meta-analysis, Can Med Assoc J 2009;180(12):E99-E108.*
13. *Kawai K et al., Maternal multiple micronutrient supplementation and pregnancy outcomes in developing countries: meta-analysis and meta-regression, Bulletin of the World Health Organization 2011;89:402-411B.*

14. *UNICEF,Improving new born survival in India:status of new borns,UNICEF fact sheet 2010.Available at : http://www.unicef.org/india/Newborn_Fact_sheet_Final_21_june_2010.pdf*
15. *UNFPA, UNFPA India profile, The state of the world's midwifery 2011, Part 4: Country Profiles; 88-89.*
16. *Gujarat Government Approved Drug rate*
17. *NICE antenatal care guidelines document*
18. *WHO iron supplementation guideline document*
19. *WHO intermittent folic acid supplementation in pregnancy guideline document*
20. *Laing R et al., 25 years of the WHO essential medicines lists: progress and challenges. Lancet. 2003; 361(9370):1723-9.*
21. *World Health Statistics Report 2013.*

CHAPTER 10 Magnetic Resonance Imaging (MRI)

A) Background

Magnetic resonance imaging (MRI), nuclear magnetic resonance imaging (NMRI), or magnetic resonance tomography (MRT) are medical imaging techniques used in radiology to investigate the anatomy and to some extent function of the organs in both health and disease. MRI scanners use strong magnetic fields and radio waves to form images of the body. The technique is widely used in hospitals for medical diagnosis, staging of disease and for follow-up without exposure to ionizing radiation.

B) Description of the technology

How does MRI works?

A strong magnetic field is created by passing an electric current through the wire loops. While this is happening, other coils in the magnet send and receive radio waves. This triggers protons in the body to align themselves. Once aligned, radio waves are absorbed by the protons, which stimulate spinning. Energy is released after "exciting" the molecules, which in turn emits energy signals that are picked up by the coil. This information is then sent to a computer which processes all the signals and generates an image. The final product is a 2-D or 3-D image representation of the area being examined.

Unlike CT scanning or general x-ray studies, no ionizing radiation is involved with an MRI

Hence, Magnetic Resonance Imaging is considered as competent alternative to radiography for visualization of lesions and vasculatures in the human body.

(Reference - http://www.medicalnewstoday.com/articles/146309.php)

C) Clinical Applications of MRI

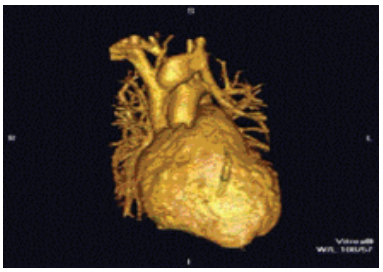
1. Clinical Neurology

MRI is the investigative tool of choice for neurological cancers as it is more sensitive than CT for small tumors and offers better visualization of the posterior fossa. The contrast provided between grey and white matter makes it the optimal choice for many conditions of the central nervous system including demyelinating diseases, dementia, cerebrovascular disease, infectious diseases and epilepsy.

MRI image of white matter tracts

2. Cardiovascular

Cardiac MRI is complementary to other imaging techniques, such as echocardiography, cardiac CT and nuclear medicine. Its applications include assessment of myocardial ischemia and viability, cardiomyopathies, myocarditis, iron overload, vascular diseases and congenital heart disease.



MR angiogram in congenital heart disease

Cardiac MRI is complementary to other imaging techniques, such as echocardiography, cardiac CT and nuclear medicine. Its applications include assessment of myocardial ischemia and viability, cardiomyopathies, myocarditis, iron overload, vascular diseases and congenital heart disease.

3. Musculoskeletal

Applications in the musculoskeletal system include spinal imaging, assessment of joint disease and soft tissue tumors.

4. Liver and gastrointestinal MRI

Hepatobiliary MR is used to detect and characterize lesions of the liver, pancreas and bile ducts. Focal or diffuse disorders of the liver may be evaluated using diffusion-weighted, opposed-phase imaging and dynamic contrast enhancement sequences. Extracellular contrast agents are widely used in liver MRI and newer hepatobiliary contrast agents also provide the opportunity to perform functional biliary imaging. Anatomical imaging of the bile ducts is achieved by using a heavily T2-weighted sequence in magnetic resonance cholangiopancreatography (MRCP). Functional imaging of the pancreas is performed following administration of secretin. MR enterography provides non-invasive assessment of inflammatory bowel disease and small bowel tumors. MR-colonography can play a role in the detection of large polyps in patients at increased risk of colorectal cancer.

5. Oncology

MRI is the investigation of choice in the preoperative staging of rectal and prostate cancer, and has a role in the diagnosis, staging, and follow-up of other tumors.

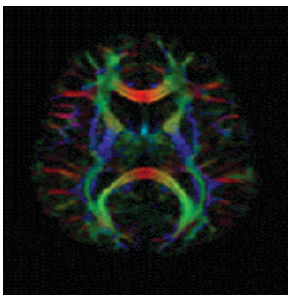
Specialized Applications

Diffusion MRI

Diffusion MRI measures the diffusion of water molecules in biological tissues. Clinically, diffusion MRI is useful for the diagnoses of conditions (e.g., stroke) or neurological disorders (e.g., multiple sclerosis), and helps better understand the connectivity of white matter axons in the central nervous system. In an isotropic medium (inside a glass of water for example), water molecules naturally move randomly according to turbulence and Brownian motion. In biological tissues however, where the Reynolds number is low enough for flows to be laminar, the diffusion may be anisotropic. For example, a molecule inside the axon of a neuron has a low probability of crossing the myelin membrane. Therefore the molecule moves principally along the axis of the neural fiber. If it is known that molecules in a particular voxel diffuse principally in one direction, the assumption can be made that the majority of the fibers in this area are parallel to that direction.

The recent development of diffusion tensor imaging (DTI) enables diffusion to be measured in multiple directions and the fractional anisotropy in each direction to be calculated for each voxel. This enables

researchers to make brain maps of fiber directions to examine the connectivity of different regions in the brain (using tractography) or to examine areas of neural degeneration and demyelination in diseases like multiple sclerosis.



Magnetic resonance angiography

Another application of diffusion MRI is diffusion-weighted imaging (DWI). Following an ischemic stroke, DWI is highly sensitive to the changes occurring in the lesion. It is speculated that increases in restriction (barriers) to water diffusion, as a result of cytotoxic edema (cellular swelling), is responsible for the increase in signal on a DWI scan. The DWI enhancement appears within 5–10 minutes of the onset of stroke symptoms (as compared with computed tomography, which often does not detect changes of acute infarct for up to 4–6 hours) and remains for up to two weeks. Coupled with imaging of cerebral perfusion, researchers can highlight regions of "perfusion/diffusion mismatch" that may indicate regions capable of salvage by reperfusion therapy.

Like many other specialized applications, this technique is usually coupled with a fast image acquisition sequence, such as echo planar imaging sequence.

Magnetic resonance angiography (MRA) generates pictures of the arteries to evaluate them for stenosis (abnormal narrowing) or aneurysms (vessel wall dilatations, at risk of rupture). MRA is often used to evaluate the arteries of the neck and brain, the thoracic and abdominal aorta, the renal arteries, and the legs (called a "run-off"). A variety of techniques can be used to generate the pictures, such as administration of a paramagnetic contrast agent (gadolinium) or using a technique known as "flow-related enhancement" (e.g., 2D and 3D time-of-flight sequences), where most of the signal on an image is due to blood that recently moved into that plane, (FLASH MRI). Techniques involving phase accumulation (known as phase contrast angiography) can also be used to generate flow velocity maps easily and accurately. Magnetic resonance venography (MRV) is a similar procedure that is used to image veins. In this method, the tissue is now excited inferiorly, while the signal is gathered in the plane immediately superior to the excitation plane—thus imaging the venous blood that recently moved from the excited plane.

Magnetic resonance spectroscopy

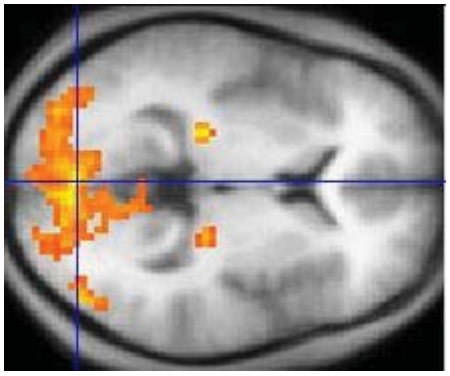
Magnetic resonance spectroscopy (MRS) is used to measure the levels of different metabolites in body tissues. The MR signal produces a spectrum of resonances that corresponds to different molecular arrangements of the isotope being "excited". This signature is used to diagnose certain metabolic disorders, especially those affecting the brain, and to provide information on tumor metabolism.

Magnetic resonance spectroscopic imaging (MRSI) combines both spectroscopic and imaging methods to produce spatially localized spectra from within the sample or patient. The spatial resolution is much lower (limited by the available SNR), but the spectra in each voxel contains information about many metabolites. Because the available signal is used to encode spatial and spectral information, MRSI requires high SNR achievable only at higher field strengths (3 T and above).

Functional MRI

Functional MRI (fMRI) measures signal changes in the brain that are due to changing neural activity. Compared to anatomical T1W imaging, the brain is scanned at lower spatial resolution but at a higher temporal resolution (typically once every 2–3 seconds). Increases in neural activity cause changes in the MR signal via T* 2 changes, this mechanism is referred to as the BOLD (blood-oxygen-level dependent) effect. Increased neural activity causes an increased demand for oxygen, and the vascular system actually overcompensates for this, increasing the amount of oxygenated hemoglobin relative to deoxygenated hemoglobin. Because deoxygenated hemoglobin attenuates the MR signal, the vascular response leads to a signal increase that is related to the neural activity. The precise nature of the relationship between neural activity and the BOLD signal is a subject of current research. The BOLD effect also allows for the generation of high resolution 3D maps of the venous vasculature within neural tissue.

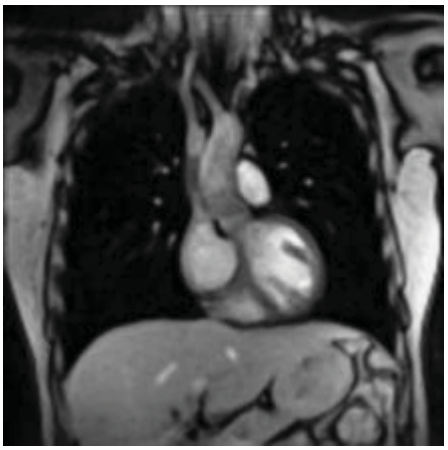
While BOLD signal analysis is the most common method employed for neuroscience studies in human subjects, the flexible nature of MR imaging provides means to sensitize the signal to other aspects of the blood supply. Alternative techniques employ arterial spin labeling (ASL) or weighting the MRI signal by cerebral blood flow (CBF) and cerebral blood volume (CBV). The CBV method requires injection of a class of MRI contrast agents that are now in human clinical trials. Because this method has been shown to be far more sensitive than the BOLD technique in preclinical studies, it may potentially expand the role of fMRI in clinical applications. The CBF method provides more quantitative information than the BOLD signal, albeit at a significant loss of detection sensitivity.



A fMRI scan showing regions of activation in orange, including the primary visual cortex

Real-time MRI

Real-time MRI refers to the continuous monitoring ("filming") of moving objects in real time. While many different strategies have been developed over the past two decades, a recent development reported a real-time MRI technique based on radial FLASH and iterative reconstruction that yields a temporal resolution of 20 to 30 milliseconds for images with an in-plane resolution of 1.5 to 2.0 mm. The new method promises to add important information about diseases of the joints and the heart. In many cases MRI examinations may become easier and more comfortable for patients.



Real-time MRI of a human heart at a resolution of 50 ms

Interventional MRI

The lack of harmful effects on the patient and the operator make MRI well-suited for "interventional radiology", where the images produced by an MRI scanner are used to guide minimally invasive procedures. Of course, such procedures must be done without any ferromagnetic instruments.

A specialized growing subset of interventional MRI is that of intra-operative MRI in which the MRI is used in the surgical process. Some specialized MRI systems have been developed that allow imaging concurrent with the surgical procedure. More typical, however, is that the surgical procedure is temporarily interrupted so that MR images can be acquired to verify the success of the procedure or guide subsequent surgical work.

Magnetic resonance guided focused ultrasound

In MRgFUS therapy, ultrasound beams are focused on a tissue—guided and controlled using MR thermal imaging—and due to the significant energy deposition at the focus, temperature within the tissue rises to more than 65 °C (150 °F), completely destroying it. This technology can achieve precise ablation of diseased tissue. MR imaging provides a three-dimensional view of the target tissue, allowing for precise focusing of ultrasound energy. The MR imaging provides quantitative, real-time, thermal images of the treated area. This allows the physician to ensure that the temperature generated during each cycle of ultrasound energy is sufficient to cause thermal ablation within the desired tissue and if not, to adapt the parameters to ensure effective treatment.

Multinuclear imaging

Hydrogen is the most frequently imaged nucleus in MRI because it is present in biological tissues in great abundance, and because it's high gyro magnetic ratio gives a strong signal. However, any nucleus with a net nuclear spin could potentially be imaged with MRI. Such nuclei include helium-3, lithium-7, carbon-13, fluorine-19, oxygen-17, sodium-23,phosphorus-31 and xenon-129. 23Na and 31P are naturally abundant in the body, so can be imaged directly. Gaseous isotopes such as 3He or 129Xe must be hyperpolarized and then inhaled as their nuclear density is too low to yield a useful signal under normal conditions. 17O and 19F can be administered in sufficient quantities in liquid form (e.g. 17O-water) that hyper polarization is not a necessity.

Multinuclear imaging is primarily a research technique at present. However, potential applications include functional imaging and imaging of organs poorly seen on 1H MRI (e.g., lungs and bones) or as alternative contrast agents. Inhaled hyperpolarized 3He can be used to image the distribution of air spaces within the lungs. Injectable solutions containing13C or stabilized bubbles of hyperpolarized 129Xe have been studied as contrast agents for angiography and perfusion imaging. 31P can potentially provide information on bone density and structure, as well as functional imaging of the brain. Multinuclear imaging holds the potential to chart the distribution of lithium in the human brain, this element finding use as an important drug for those with conditions such as bipolar disorder.

Molecular imaging by MRI

MRI has the advantages of having very high spatial resolution and is very adept at morphological imaging and functional imaging. MRI does have several disadvantages though. First, MRI has a sensitivity of around 10−3 mol/L to 10−5 mol/L which, compared to other types of imaging, can be very limiting. This problem stems from the fact that the difference between atoms in the high energy state and the low energy state is very small. For example, at 1.5 teslas, typical field strength for clinical MRI, and the difference between high and low energy states are approximately 9 molecules per 2 million. Improvements to increase MR sensitivity include increasing magnetic field strength, and hyper-polarization via optical pumping or dynamic nuclear polarization. There are also a variety of signal amplification schemes based on chemical exchange that increase sensitivity.

To achieve molecular imaging of disease biomarkers using MRI, targeted MRI contrast agents with high specificity and high relaxivity (sensitivity) are required. To date, many studies have been devoted to developing targeted-MRI contrast agents to achieve molecular imaging by MRI. Commonly, peptides, antibodies, or small ligands, and small protein domains, such as HER-2 affibodies, have been applied to achieve targeting. To enhance the sensitivity of the contrast agents, these targeting moieties are usually linked to high payload MRI contrast agents or MRI contrast agents with high relaxivities. A new class of gene targeting MR contrast agents (CA) has been introduced to show gene action of unique mRNA and gene transcription factor proteins. This new CA can trace cells with unique mRNA, microRNA and virus; tissue response to inflammation in living brains.

D) How to perform an MRI on patient?

To perform a study the patient is positioned within an MRI scanner which forms a strong magnetic field around the area to be imaged. Most medical applications rely on detecting a radio frequency signal emitted

by excited hydrogen atoms in the body (present in any tissue containing water molecules) using energy from an oscillating magnetic field applied at the appropriate resonant frequency. The orientation of the image is controlled by varying the main magnetic field using gradient coils. As these coils are rapidly switched on and off they create the characteristic repetitive noises of an MRI scan. The contrast between different tissues is determined by the rate at which excited atoms return to the equilibrium state. Exogenous contrast agents may be given intravenously, orally or intra- articularly.

MRI requires a magnetic field that is both strong and uniform. The field strength of the magnet is measured in tesla – and while the majority of systems operate at 1.5T commercial systems are available between 0.2T–7T. Most clinical magnets are superconducting which requires liquid helium. The lower field strengths can be achieved with permanent magnets, which are often used in "open" MRI scanners for claustrophobic patients.

However, there are several considerations in terms of the magnetic field strength used in it. It is assumption that increases in magnetic field strength would enhance the image quality.

There is also dilemma associated while procurement of MRI in healthcare centres regarding trade-off between image quality and lower cost 1.5 T MRIs compared to 3.0 tesla MRIs. This Health Technology Assessment report provides details on comparative analysis between diagnostic accuracy, cost effectiveness, safety issues and also challenges before adoption in health system.

E) Clinical Effectiveness of 1.5 Tesla versus 3.0 Tesla Magnetic Resonance Imaging

Objective:

- ❖ Diagnostic superiority of 1.5 Tesla versus 3.0Tesla Magnetic Resonance Imaging

Search Methods:

We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, MEDLINE, PUBMED Science Direct, SCOPUS and The International Society of Radiology for relevant studies. We also conducted secondary referencing by manually reviewing reference lists of key articles and searching citations by using Web of Science. We also conducted specific searches for primary studies published more recently than the included systematic reviews and meta-analyses from 1st January 2014 to 1st June 2014. Types of studies included during search were: Randomized controlled trial, observational analytical studies, Case control and cohort studies.

Keywords:

- ❖ The key words used were 1.5T MRI versus 3T MRI, 1.5T versus 3T MRI diagnostic accuracy, 1.5 Tesla versus 3 Tesla MRI systematic reviews, 1.5T and 3T sensitivity specificity, safety of MRI, MRI acquisition.

Study Outcomes:

1. **Diagnostic Test accuracy (Sensitivity and Specificity)**

a) Sensitivity - The sensitivity of a test is defined as the proportion of people with disease who will have a positive result. If we apply Test A to our hypothetical population, and 8 of the 10 people with Disease A test positive, then the sensitivity of the test is 8/10 or 80%.

b) Specificity - The specificity of a test is the proportion of people without the disease who will have a negative result. We can see from our hypothetical population that 90 people do not have Disease A. If we apply Test A to these 90 people and 85 of them test negative, then the specificity of the test is 85/90 = 94%

2. Number of lesions detected

Means number of lesions detected by using 1.5 Tesla MRI and 3 Tesla MRI Technology

3. Signal to Noise Ratio (SNR)

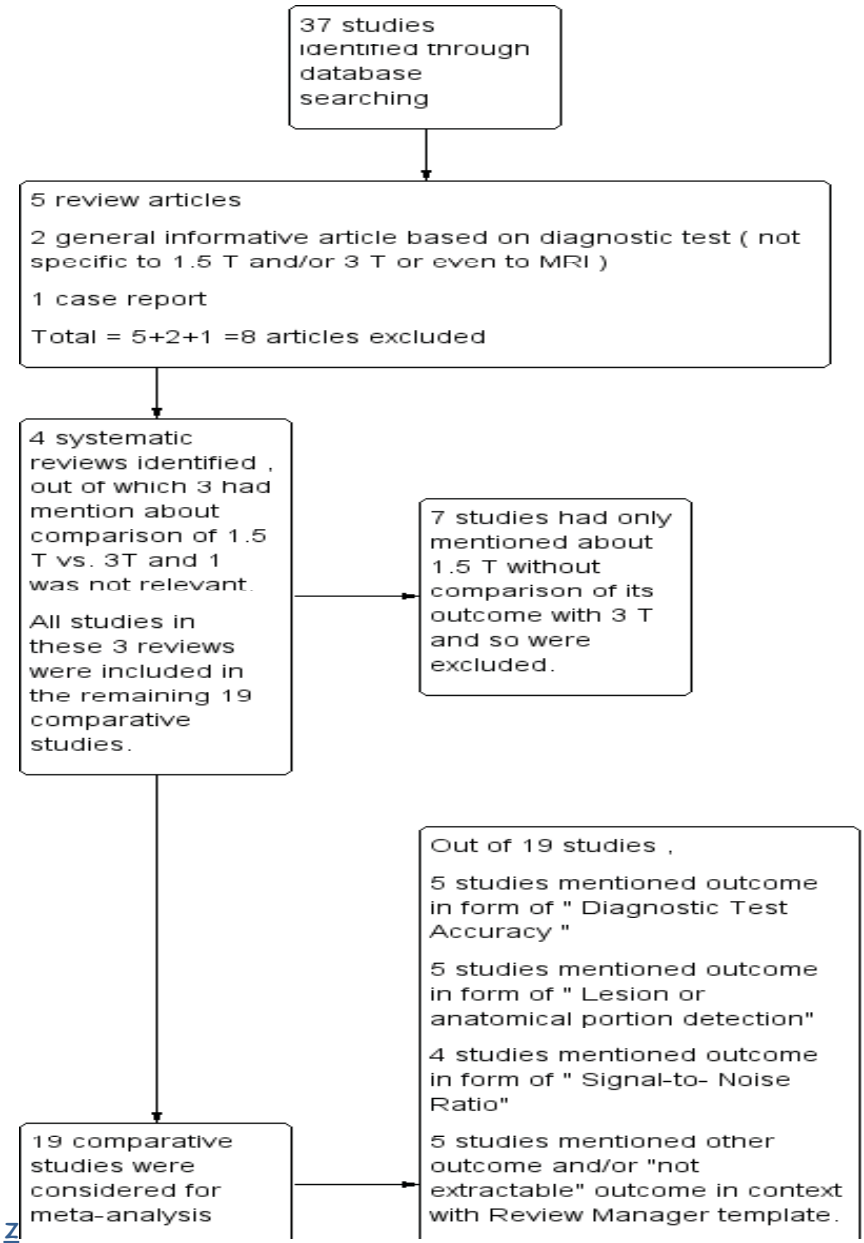
It is an objective quality measure for biomedical images nevertheless; the SNR is the most popularly used measure both for assessing the quality of images and for evaluating the effectiveness of image enhancement and signal processing techniques.

DTA extraction:

Total number of images was extracted with sensitivity and specificity data. In reverse way, TP (True Positive), TN (True Negative), FP (False Positive), FN (False negative) were calculated from these 3 data. (One study did not mention data on specificity)

Explained by below mentioned Study flow diagram

F) The study flow diagram is shown below



G) Results:

1. Diagnostic Accuracy:

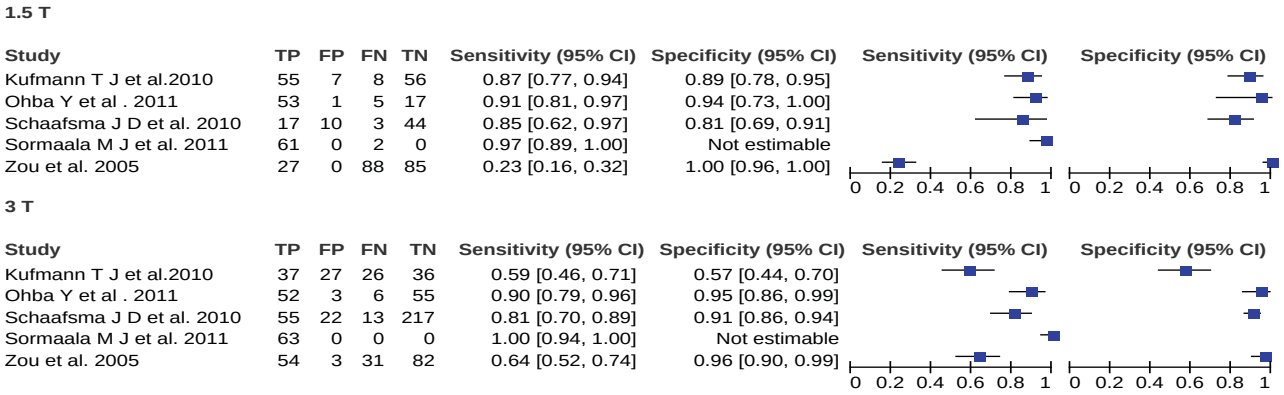
Wider range in sensitivity was observed from in case of 1.5 T (32% to 97%) as compared to 3T (58% to 100%). This could be justified in relation with Signal to Noise Ratio. As lower magnetic strength is susceptible to more noise, there may be such range in case of diseased/abnormal cases detection.

Data extraction table for outcome - Diagnostic Accuracy

Study Number	Name of First Author_Year	Title	Sensitivity of 1.5 T	Specificity of 1.5 T	Sensitivity of 3 T	Specificity of 3 T	N
1	Zou et al 2005	Reproducibility of Functional MR Imaging : Preliminary Results of Prospective Multi-Institutional Study performed by Biomedical Informatics Research Network	0.32	0.996	63.5	96	85
2	Ohba Y 2011	Diffusion weighted Magnetic Resonance for pulmonary nodules :1.5 vs 3 tesla	0.91	0.94	0.9	0.94	58
3	Sormala M J 2011	Comparison of 1.5T and 3T MRI Scanners in evaluation of acute bone stress in the foot	0.97	not given	100%	not given	63
4	Schafsmaa J D 2010	Intracranial Aneurysms treated with coil placement : Test Characteristics of Follow-up MR Angiography - Multicenter Study	0.85	0.81	0.81	0.91	17/20,44/ 54,55/68, 217/239
5	Kaufmann 2010	A Prospective Trial of 3 T and 1.5 Time-of-weight and Contrast Enhanced MR Angiography in the follow-up of coiled intracranial aneurysms	0.875	0.89	0.585	0.58	63

Above mentioned table explains that both machines were found to be apparently equally efficient in terms of detection of absence of any abnormality i.e. specificity.

H) Forest plot showing Diagnostic Test Accuracy of 1.5T and 3T MRI



Sensitivity = TP/(TP+FN) ,Specificity = TN/(FP + TN), Positive predictive value = TP/(TP + FP), Negative predictive value = TN/(FN + TN)

Likelihood ratio positive = Sensitivity/(1 – Specificity), Likelihood ratio negative = (1 – Sensitivity)/ Specificity,

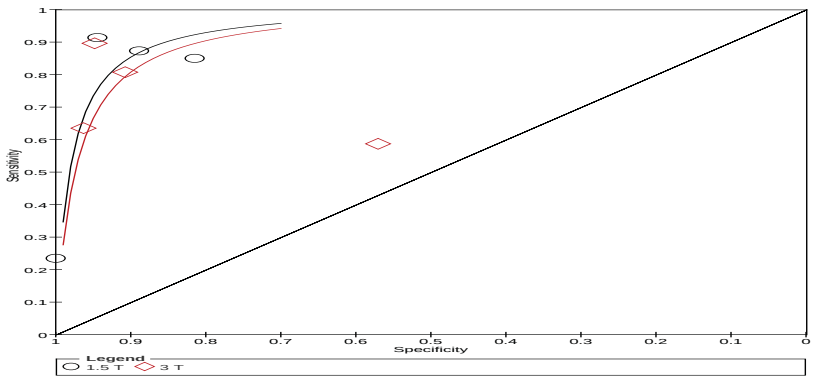
Prevalence (proportion of people with disease in population to whom the test has been applied) = TP + FN/ (TP + FP + FN + TN)

Likelihood Ratios: +LR = Sensitivity/ (1-specificity), -LR= (1-sensitivity)/specificity

I) Table showing the Measures of test accuracy for 1.5 Tesla MRI

FOR 1.5 T MRI				
Study ID	**Sensitivity**	**Specificity**	**Positive LR**	**Negative LR**
Kufmann T J et al.2010	0.87	0.89	7.91	0.15
Ohba Y et al . 2011	0.91	0.94	15.17	0.10
Schaafsma J D et al. 2010	0.85	0.81	4.47	0.19
Sormaala M J et al. 2011	0.97	Not estimable	n.a	n.a
Zou et al. 2005	0.23	1	Not Practical	0.77
FOR 3 T MRI				
Kufmann T J et al.2010	0.59	0.57	1.37	0.72
Ohba Y et al . 2011	0.9	0.95	18.00	0.11
Schaafsma J D et al. 2010	0.81	0.91	9.00	0.21
Sormaala M J et al. 2011	1	Not estimable	n.a.	0.00
Zou et al. 2005	0.64	0.96	16.00	0.38

J) Graph showing Receiver Operating Characteristics for 1.5T vs. 3T MRI



The above mentioned curve explains that 1.5 T had higher area under Receiver Operating Characteristics curve thereby depicting better Diagnostic Test Accuracy as compared to 3 T.

2. Lesion Detection:

Due to heterogeneity in the outcomes in studies, it was not possible to construct forest plot out of the extracted data. The heterogeneity was observed in terms of type of lesion numbers. Except one study *(Phal PM 2008),* none of studies had mentioned outcome in form of "no. of patients with lesion detected /no. of total patients i.e. Risk Ratio or Odds Ratio. However, the extracted data from all studies along with study with odds ratio is presented in the table below:

Data extraction table for outcome - lesion detection

Study Number	Name of First Author_Year	Title	No. of participant/no. of images observed in(with) 1.5 T	No. of participants/ images observed in(with) 3T	No. of more lesions and abnormalities detected in 1.5T	No. of lesions and abnormalites detected in 3 T
1	Simon B 2010	Improved in vivo detection of cortical lesions in multiple sclerosis using double inversion recovery MR imaging at 3 Tesla	102	102	17	77
2	Haacke E M 2009	Characterising iron deposition in multiple sclerosis lesions using susceptibility weighted imaging	14	7	189	111
3	Kuhl C K 2005	Acute and subacute Ischemic Stroke at High Field Strength (3.0 T) Diffusion weighted MR Imaging- Intraindividual comparative study	25	25	36	47
4	Willineck W A 2003	Time-of-flight MR Angiography : Comparison of 3.0 T Imaging and 1.5 T Imaging- initial experience	130	130	94	116
5	Phal P M 2008	Qualitative comparison of 3-T and 1.5-T MRI in the evaluation of Epilepsy	74	74	55	65

2. Signal-to-Noise Ratio:

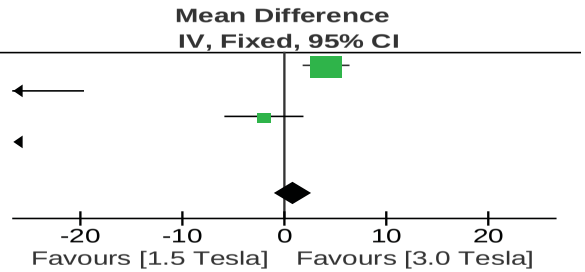
There was net improvement in Signal to Noise ratio observed in case of 1.5 Tesla MRI as compared to 3T MRI .This in turn reflects in improved signal strength in case of 1.5T MRI.The results from studies on Signal to Noise ratio are summarized below:

Data extraction table for outcome - Signal-to-Noise Ratio						
Study Number	**Name of First Author_Year**	**Title**	**No. of participant/no. of images observed in(with) 1.5 T**	**No. of participants/ images observed in(with) 3T**	**SNR for 1.5T**	**SNR for 3 T**
1	Willinek W A 2003	Time-of-flight MR Angiography : Comparison of 3.0 T Imaging and 1.5 T Imaging- initial experience	15	15	224.63± 39.10	411.96± 36.85
2	Sohn C H 2010	Fluid Attenuated Inversion Recovery (FLAIR) Imaging of the normal brain : Comparisons between under the conditions of 3.0 and 1.5 Tesla	11	11	25.9 ± 4.01	27.9 ± 7.47
3	Kuhl C K 2005	Acute and subacute Ischemic Stroke at High Field Strength (3.0 T) Diffusion weighted MR Imaging- Intraindividual comparative study	25	25	49.0± 12.6	83.5± 23.5
4	Bachmann R 2006	FLAIR Imaging for multiple sclerosis: a comparative MR study at 1.5 and 3.0 Tesla	22	22	11.9± 4.5	7.8 ± 2.2

K) Forest Plots Showing Signal-to-Noise Ratio of 1.5 Tesla MRI versus 3T MRI

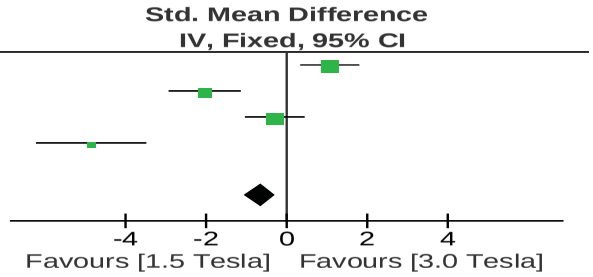
	1.5 T			3 T				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Bachmann 2006	11.9	4.5	22	7.8	2.2	15	73.2%	4.10 [1.91, 6.29]
Kuhl 2005	49	12.6	25	83.5	23.5	11	1.6%	-34.50 [-49.24, -19.76]
Sohn 2010	25.9	4.01	11	27.9	7.47	25	24.6%	-2.00 [-5.77, 1.77]
Willinek 2003	224.63	39.1	15	411.96	36.85	22	0.6%	-187.33 [-212.40, -162.26]
Total (95% CI)			**73**			**73**	**100.0%**	**0.91 [-0.96, 2.78]**

Heterogeneity: Chi² = 249.18, df = 3 (P < 0.00001); I² = 99%
Test for overall effect: Z = 0.96 (P = 0.34)



	1.5 T			3 T				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Bachmann 2006	11.9	4.5	22	7.8	2.2	15	34.3%	1.07 [0.36, 1.77]
Kuhl 2005	49	12.6	25	83.5	23.5	11	22.7%	-2.04 [-2.90, -1.17]
Sohn 2010	25.9	4.01	11	27.9	7.47	25	33.5%	-0.29 [-1.01, 0.42]
Willinek 2003	224.63	39.1	15	411.96	36.85	22	9.5%	-4.85 [-6.19, -3.51]
Total (95% CI)			**73**			**73**	**100.0%**	**-0.65 [-1.07, -0.24]**

Heterogeneity: Chi² = 71.33, df = 3 (P < 0.00001); I² = 96%
Test for overall effect: Z = 3.10 (P = 0.002)



L) Cost Effectiveness Analysis:

Cost-effectiveness analysis is a method of comparing the cost and effectiveness of two or more alternatives. Such comparisons are useful when one of the alternatives being considered is standard care, as this allows the decision maker to consider whether an alternative is better or not. The standard care, however, could also be a placebo or "Do Nothing" scenario.

Below mentioned is the cost data collected from market research:

Price of single unit 1.5T (INR)	Price of single unit 3T (INR)
Less than 5 Crore	Less than 9 -11 Crore

Rate of conducting MRI (AIIMS revised rate for all hospital procedures) –

S. No.	Type of Investigation & Category of patients	Fee Rs.
1	Plain MRI OPD/Indoor (Pvt. Wards)	3000/- Plus Rs.500/- (for films)
2	Plain MRI Indoor (General ward)	2500/- Plus Rs.500/- (for films)
3	Plain MRI Outside (Medico-legal cases and other exceptional cases)	3500/- (with films)
4	Additional clinical studies like MRA, MRS and/or additional parts being scanned during the same sitting. Additional payment is required. (applicable to each category of S.N. 1,2 & 3)	1500/-
5	Extra cost for contrast MRI. Applicable to each category of S.N. 1, 2 3 & 4.	A) 2600 For patients of age 12 years and above. B) 1500 For children less than 12 years of age.
6	MRS for research	3000/-(no films will be issued)

The true incremental cost effectiveness of 3-T MRI versus 1.5-T MRI will involve estimation all the costs involved in the delivery of care for patients using the alternating diagnostic technologies. One of the challenges in such situations is computing the cost of a wrong diagnosis as a result of less than 100% sensitivity and specificity. Each case which is wrongly diagnosed false positive or false negative using a given diagnostic test has costs associated with the same, both for the provider as well as for the individual. Such costs are most often poorly defined, and often underestimated.

Secondly, the effect size, i.e. sensitivity and specificity of the diagnostic test such as 3-T MRI might well be different in various health conditions. Moreover, simply stating the effectiveness in terms of improved diagnostic accuracy might be too premature to lead to a conclusion about the cost effectiveness. How much of this improved diagnostic accuracy lead to overall improved outcomes for treatment, in terms of patient survival and improved quality of life, is more relevant.

Any conclusion on cost effectiveness of diagnostic modalities such as MRI should thus be viewed in light of these limitations.

M) Safety Aspects:

Unlike radiography based imaging technologies, there is no radiation hazard associated with any MRI technology. However, it utilizes strong magnetic field .Thus, subjects with pacemakers and other implanted electronic medical devices are not advised to undergo through it as there are several reported cases of device malfunctions and life-threatening conditions aroused from electromagnetic interference(EMI).There is another psychological condition that may encounter in some patients undergoing MRI scan called " claustrophobia". It is phobia of "being confined in closed space". This may result in increased sympathetic response. However, it could be resolved by counselling prior to scan.

N) Commercial and Regulatory Aspects:

MRI is not listed in notified medical devices which are regulated by DCG (I). Most MRI devices are imported from overseas imaging technology market and its authenticity is tested with CE/FDA approvals.

O) Suggestions:

Contrast and its enhancement in MRI depends less on magnetic field strength as much as on skills of the technician performing the scan procedure. Setting of echo time, relaxation time, various modes of imaging like susceptibility weighted imaging and diffusion weighted imaging are several confounding factors which have significant impact in resultant image. From general public health point of view, this could be efficiently and effectively handled with 1.5 Tesla MRI. Moreover, contrast in MR is very context specific. The region of interest to be visualised along with the fluid and tissue density affects the contrast. Looking at Cost Benefit, it is suggested that 3.0 Tesla MRI may not be really required at district and sub district level. For Research institutions it may be beneficial to have MRI with field greater than 1.5T, however for most government medical colleges and district hospitals 1.5 T MRI would suffice the Clinical requirements.

P) Bibliography:

1. *"Magnetic Resonance, a critical peer-reviewed introduction". European Magnetic Resonance Forum.*
2. *Hollingworth W, Todd CJ, Bell MI, Arafat Q, Girling S, Karia KR, Dixon AK (2000). "The diagnostic and therapeutic impact of MRI: an observational multi-centre study". Clin Radiol . PMID 11069736.*
3. *"Manufacturer and User Facility Device Experience". Food and Drug Administration. Wang PI, Chong ST, Kielar AZ, Kelly AM, Knoepp UD, Mazza MB, Goodsitt MM (2012). "Imaging of pregnant and lactating patients: part 1, evidence-based review and recommendations", PMID 22451541.*
4. *Smith-Bindman R, Miglioretti DL, Johnson E, Lee C, Feigelson HS, Flynn M, Greenlee RT, Kruger RL, Hornbrook MC, Roblin D, Solberg LI, Vanneman N, Weinmann S, Williams AE (2012). "Use of diagnostic imaging studies and associated radiation exposure for patients enrolled in large integrated health care systems, 1996-2010".JAMA , PMC 3859870.PMID 22692172.*
5. *"ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 Appropriateness Criteria for Cardiac Computed Tomography and Cardiac Magnetic Resonance Imaging". Journal of the American College of Radiology*
6. *Helms, C (2008). Musculoskeletal MRI.*
7. *Frydrychowicz A, Lubner MG, Brown JJ, Merkle EM, Nagle SK, Rofsky NM, Reeder SB (2012). "Hepatobiliary MR imaging with gadolinium-based contrast agents". J Magn Reson Imaging, PMID 22334493.*

8. *Sandrasegaran K, Lin C, Akisik FM, Tann M (2010). "State-of-the-art pancreatic MRI".PMID 20566796.*

9. *Masselli G, Gualdi G (2012). "MR imaging of the small bowel". Radiology 264*

10. *Zijta FM, Bipat S, Stoker J (2010). "Magnetic resonance (MR) colonography in the detection of colorectal lesions: a systematic review of prospective studies". PMID 19936754.*

11. *Giussani C, Roux FE, Ojemann J, Sganzerla EP, Pirillo D, Papagno C (2010). "Is preoperative functional magnetic resonance imaging reliable for language areas mapping in brain tumor surgery? Review of language functional magnetic resonance imaging and direct cortical stimulation correlation studies". PMID 19935438.*

12. *Carr, Herman (1952). Free Precession Techniques in Nuclear Magnetic Resonance(PhD thesis). Cambridge.*

13. *Carr, Herman Y. (July 2004). "Field Gradients in Early MRI". Physics Today (American Institute of Physics).*

14. *Encyclopedia of Nuclear Magnetic Resonance 1. Hoboken, NJ: Wiley and Sons.*

15. *Damadian R (March 1971). "Tumor detection by nuclear magnetic resonance". PMID 5544870.*

16. *"Scan and Deliver". Wall Street Journal.*

17. *"Apparatus And Method For Detecting Cancer In Tissue". United States Patent and Trademark Office.*

18. *"NSF history". Sri.com.*

19. *"Scientist Claims Exclusion From Nobel Prize for MRI".*

20. *"Does Dr. Raymond Damadian Deserve the Nobel Prize for Medicine?". The Armenian Lauterbur PC (1973). "Image Formation by Induced Local Interactions: Examples of Employing Nuclear Magnetic Resonance".*

21. *"Diffusion Inaging". Stanford University.*

22. *Filler A (2009). "The History, Development and Impact of Computed Imaging in Neurological Diagnosis and Neurosurgery: CT, MRI, and DTI". Nature*

23. *Moseley ME, Cohen Y, Mintorovitch J, Chileuitt L, Shimizu H, Kucharczyk J, Wendland MF, Weinstein PR (May 1990). "Early detection of regional cerebral ischemia in cats: comparison of diffusion- and T2-weighted MRI and spectroscopy". Magn Reson Med, PMID 2345513.*

24. *Haacke, E Mark; Brown, Robert F; Thompson, Michael; Venkatesan, Ramesh (1999).Magnetic resonance imaging: Physical principles and sequence design. New York: J. Wiley & Sons.*

25. *Golder W (June 2004). "Magnetic resonance spectroscopy in clinical oncology". Onkologie . PMID 15249722.*

26. *Thulborn KR, Waterton JC, Matthews PM, Radda GK (February 1982). "Oxygenation dependence of the transverse relaxation time of water protons in whole blood at high field". Biochim. Biophys. Acta . PMID 6275909.*

27. *Nelson F, Poonawalla AH, Hou P, Huang F, Wolinsky JS, Narayana PA (October 2007). "Improved identification of intracortical lesions in multiple sclerosis with phase-sensitive inversion recovery in combination with fast double inversion recovery MR imaging". AJNR Am J Neuroradiol .PMID 17885241.*

28. *Guadalupe Portal; Aliosvi Rodriguez Whole body magnetic resonance imaging in early diagnosis in Trinidad BMJ (2010) url = http://www.bmj.com/rapid-response/2011/12/19/re-whole-body-magnetic-resonance-imaging*

29. *Royal Institution Lecture – MRI: A Window on the Human Body*

30. *How MRI works explained simply using diagrams*

31. *U.S. Food & Drug Administration*

32. *http://www.medicalnewstoday.com/articles/146309.php*

33. *Zou et al 2005, Reproducibality of Functional MR Imaging : Preliminary Results of Prospective Multi – Institutional Study performed by Biomedical Inform Informatics Research Network*

34. *Ohbay 2001, Diffusion weighted Magnetic Resonance for pulmonary nodules: 1.5 Tesla v 3 Tesla*

35. *Sormala MJ 2001, Comparision of 1.5 T and 3T MRI Scanners in evaluation of acute bone stress in the foot.*

36. *Schasmaa, Intracranial Aneurysms treated with coil placement: Test Characteristic of Follow – up MR Angiography – Multicentre Study.*

37. *Kaufmann 2010, A prospective Trial of 3 Tesla and 1.5 Time of weight and contrast enhanced MR Angiography in the follow up of coiled intra cranial aneurysms.*

CHAPTER 11 Use of Mammography for Breast Cancer Screening:

A) Background

Breast cancer is a tumor that starts from cells of the breast tissue, either in cells that line the ducts that carry milk to the nipples (ductal cancer) and/or in cells that line the lobules, which are glands involved in milk production. Breast tumors can be benign or malignant, the former are not life-threatening, can usually be removed, do not invade adjacent tissues or spread to other parts of the body and can include fibrocystic tissue, fibroadenomas and benign breast disease. Malignant breast tumors are cancerous and can invade surrounding tissues or metastasize to other parts of the body via the lymphatic system (lymphatic vessels and lymph nodes), such as the liver and bone. If cancer cells have spread to the surrounding lymph nodes, there is a much higher probability that the tumor has entered the bloodstream and metastasized to other parts of the body.

Breast Cancer is a heterogeneous disease with different tumor types demonstrating variation in tumor growth rates and metastatic potential. Some tumors grow relatively quickly, others so slowly that they may never cause symptoms, and a number of tumors grow at a rate somewhere in between. Fast growing breast tumors may grow within a year from undetectably small to large enough to cause symptoms. Slow growing breast cancers are more likely to be detected by screening because they exist longer in an asymptomatic state.

B) Description of the condition:

Classification of breast cancer according to WHO-

- Benign Tumor
- Malignant Tumor

The histological classification of breast cancer includes adenocarcinomas, cancers that originate in the glandular tissue, which include the ducts and lobules and sarcomas, cancers that originate in the connective tissue of muscle, fat or blood vessels. Carcinoma in situ (CIS) is an early stage form of cancer where the tumor is confined to the layer of the cells where the cancer began and it has not invaded deeper breast tissue or spread to other areas of the body.

Breast cancer includes the following types of diseases:

1. Ductal carcinoma in situ (DCIS):

Is the most common type of non-invasive cancer in women, where cancer cells have not spread beyond the duct walls into surrounding breast tissue. The prevalence of DCIS is strongly correlated with mammographic screening and in countries such as the US, can be as high as 18% of all newly diagnosed cancers but in countries such as India, represents a very low proportion of total disease since most cases present in late stage. Thus, probability and benefit of it being diagnosed by a mammographic screening is substantially large.

2. Invasive or infiltrating ductal carcinoma:

It originates in the breast duct, has broken through the wall of the duct into surrounding fatty tissue of the breast and is capable of metastasizing to other organs of the body through the lymphatic system and bloodstream. This represents about 80% of breast cancers.

3. Lobular carcinoma in situ (LCIS):

It is not cancer but is sometimes classified as a non-invasive breast cancer and women who have this condition are more likely to develop invasive breast cancer in the future.

4. Invasive or infiltrating lobular carcinoma

It originates in the milk-producing glands or lobules of the breast and can spread to other parts of the body. This is less common and represents about 1 in 10 breast cancer diagnoses.

5. Other (less common) types of breast cancer

Inflammatory breast cancer (1-3% of all breast cancers), triple negative breast cancers, mixed tumors, medullary carcinoma (3-5% of all breast cancers), metaplastic carcinoma, mucinous carcinoma, paget disease of the nipple, tubular carcinoma, papillary carcinoma, adenoid cystic carcinoma (adenocystic carcinoma), phyllodes tumor and angiosarcoma.

C) Risk Factors for breast cancer:

Non-modifiable risk factors:

1. Age:

Older age increases the risk of breast cancer and most women are over the age of 60 when they are diagnosed although there is evidence that Indian women are more likely to develop breast cancer at earlier ages than their Western counterparts.

2. Height:

Adult height is positively associated with the risk of developing breast cancer; a pooled analysis yielded a relative risk = 1.02 (2% higher) for each 5 cm increase in height for pre-menopausal cancer and RR=1.07 (7% higher) for post-menopausal cancer. For other childhood growth patterns, including age at maximal height and growth velocity, the associations are less consistent because the biological pathways are more complex.

3. Personal history of benign breast or other breast disease:

A history of atypical hyperplasia, lobular carcinoma in situ or ductal carcinoma in situ (as determined by a breast biopsy) increases the risk of developing invasive breast cancer. This is usually measured by history of a biopsy, which have ranged from a 10% to more than 3-fold increase depending on the study.

4. Family history:

A family history of breast cancer in the mother, father, sister or daughter increases the risk of breast cancer and the risk is even stronger if the family member was diagnosed before the age of 50 years old and/or with pre-menopausal breast cancer. Specifically, if a woman has a first-degree relative >50 years diagnosed with post-menopausal breast cancer, her risk increases by 80% whereas a first-degree relative with pre-menopausal breast cancer increases a woman's risk by 330%. The risks increase for a higher number of

first- and second-degree relatives diagnosed with breast cancer. A history of ovarian cancer in other relatives (in the mother's or father's families) also increases the risk of breast cancer.

5. BRCA1/BRCA2:

Having mutations in BRCA1, a gene on chromosome 17 that controls cell growth or BRCA2, a gene on chromosome 13 that suppresses cell growth, are associated with a 40-80% increased risk of breast cancer (32). Mutations in these genes are also associated with increased risks of ovarian, prostate and other types of cancer as well.

6. Menstrual history:

Ages at menarche and menopause. Women who have an early age at menarche (<12 years) have a 30% increased risk of breast cancer while those who have a late age at menopause (>60 years) will have a 20-50% increased risk of disease.

7. Breast density on mammogram:

Women with higher breast density have a higher risk of being diagnosed with breast cancer (OR=5.23, 95% CI: 1.70, 16.13 (34)).

8. Medical history of Hodgkin's lymphoma:

Women diagnosed with Hodgkin's lymphoma who received a chest irradiation dose > 40 Gray between 25-55 years, have a 29% increased risk of development of breast cancer.

9. Age at first child:

Women who have never had children or those who are more than 30 years at the time of their first child's birth are twice as likely to develop breast cancer as women who had their first child before the age of 20 years. Moreover, women who have five or more children have half the risk of breast cancer as women who have never had a child. These associations are more consistently observed for hormone receptor-positive breast cancer.

10. Hormone replacement therapy:

Women who have taken menopausal hormone therapy (estrogen + progestin for at least 5 years) have a 20% greater risk of developing breast cancer.

11. Breastfeeding:

Women who do not breastfeed or breastfeed for shorter durations are at a higher risk of developing breast cancer. Specifically, a 4.3% reduction in risk has been observed for each additional year of breastfeeding. (*)

(*) - Breast Cancer Factsheet, Preeti K. Dhillon, 2011(Online Available from:-

https://www.google.co.in/search?q=breast+cancer+fact+sheet+by+preet+k+dhillon&rlz=1C1KMZB_enIN545IN545&oq=breast+cancer+fact+sheet+by+preet+k+dhillon&aqs=chrome..69i57.26905j0j7&sourceid=chrome&espv=210&es_sm=122&ie=UTF-8

D) Breast Cancer early detection and prevention:

Breast cancer screening includes three methods of early detection:

1. Breast self-exams (monthly) starting in the 20's
2. Clinical breast exams (every 3 years) starting in the 20's
3. Mammographic screening starting at the age of 30 years

1. A clinical breast exam (CBE) is performed by the clinician or other health professional and involves a systematic examination of the breast skin and tissue. The health professional is looking for signs and symptoms or if any changes occur, including development of a lump or swelling, skin irritation or dimpling, nipple pain or retraction (turning inward), redness or scaliness of the nipple or breast skin, or a discharge other than breast milk. In countries where mammography is widely practiced, the CBE does not provide additional efficacy in mortality reduction and in resource-poor countries.

2 A breast self-exam (BSE) is performed by the woman herself and involves a similar examination as the CBE of the breast skin and tissue based on palpations by her hands. The woman is examining the look and 10 feel of her breasts as well as any signs, symptoms or changes to the breasts. While the BSE is recommended so that women understand their breasts for detecting any suspicious changes over time, the epidemiological evidence does not support BSE as an effective screening tool for reducing breast cancer mortality.

3 A mammogram is an x-ray of the breast that uses very low levels of radiation (0.1-0.2 rads per picture). The images capture calcifications (benign) and masses, which include benign cysts that are fluid-filled, benign solid tumors and cancer. To confirm that an abnormal mass is cancer, a biopsy is undertaken and may be a fine-needle biopsy, core biopsy or surgical biopsy.

E) Should mammography be used as a tool for Breast cancer screening in India?

As per Indian population census data, the rate of mortality due to cancer in India was high and alarming with about 806000 existing cases by the end of the last century. Cancer is the second most common disease in India. This is owing to the poor availability of screening, prevention, diagnosis and treatment of the disease. All types of cancers have been reported in Indian population including the cancers of breast, skin, lungs, rectum, stomach, prostate, liver, cervix, esophagus, bladder, blood, mouth etc. The causes of such high incidence rates of these cancers may be both internal (genetic, mutations, hormonal, poor immune conditions) and external or environmental factors (food habits, industrialization, over growth of population, social etc.)

A Global breast cancer incidence increased from 641,000 (95% confidence intervals 610,000—750,000) cases in 1980 to 1,643,000 (1,421,000—1,782,000) cases in 2010, an annual rate of increase of 3·1%. This variation in incidence may be due to multiple factors, including geographic variation, racial/ethnic background, genetic variation, lifestyle, environmental factors, socioeconomic status, the presence of known risk factors, and utilization of screening mammography, stage of disease at diagnosis and the availability of appropriate care.

The health care burden related to breast cancer in India has been steadily mounting. Over 100,000 new breast cancer patients are estimated to be diagnosed annually in India. As per the ICMR-PBCR data, breast cancer is the commonest cancer among women in urban registries of Delhi, Mumbai, Ahmedabad, Calcutta and Trivandrum where it constitutes > 30% of all cancers in females. In the rural areas, breast cancer is the second most common cancer in women after cervical cancer. The age standardized incidence rates (AARs)

range from 6.2 to 39.5 per 100,000 Indian women. The AARs vary from region, ethnicity, religion, with the highest incidence reported at 48.3 per 100,000 women in the Parsi community of Mumbai.

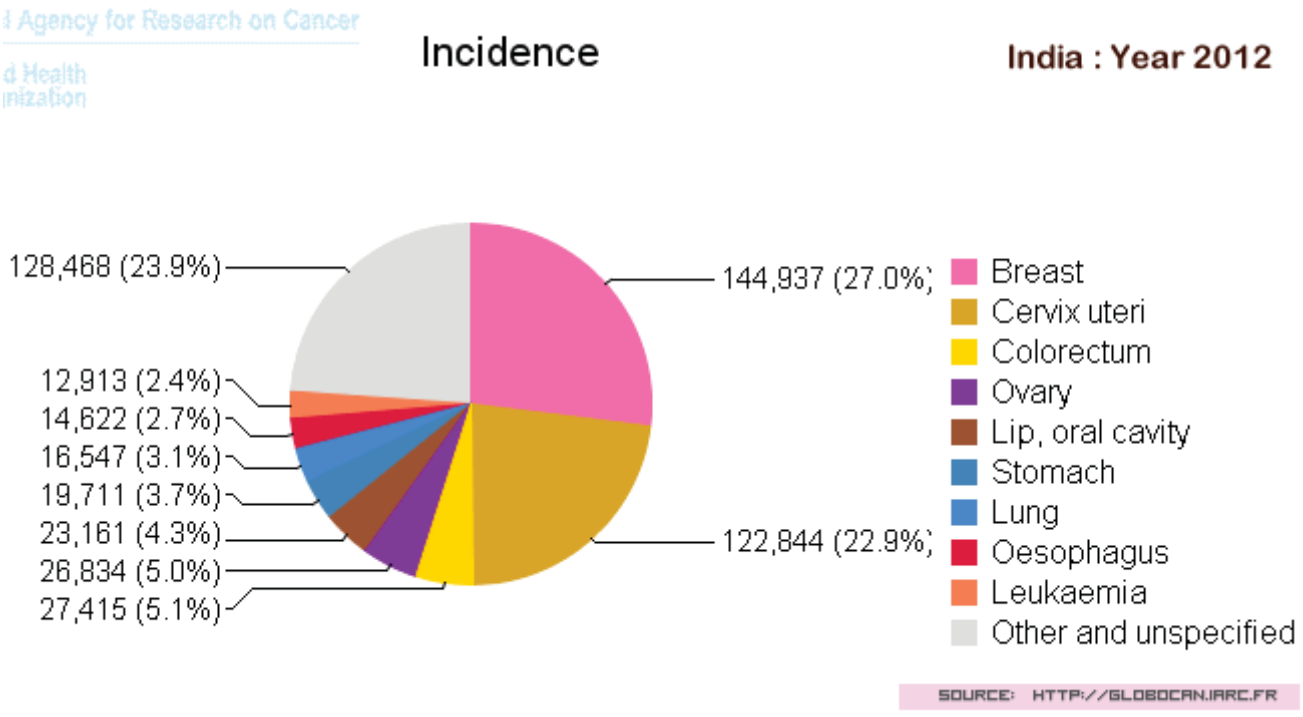
The quality of breast cancer treatment is dictated by many factors besides a patient's own outlook and may include where the patient lives, access to a medical institution, how much can she afford to spend on her treatment, whom does she trust etc. Few patients are treated at well-equipped centers in a protocol-based manner, with compromised multimodality therapy, based on factors such as the economics, tolerance, nutritional deprivation etc. In spite of having world class medical facilities and treatment options, patient access to these facilities remains a challenge. Furthermore, compliance with the treatment is hampered due to the social stigma associated with the disease.

The 5-year overall survival rate has been estimated to be 62%.

The 5-year actuarial patient survival has been:

- 90% for stage I
- 78% for stage II
- 57% for stage III
- 22% for stage IV

F) Burden of Disease in India for Breast Cancer for the year 2012,

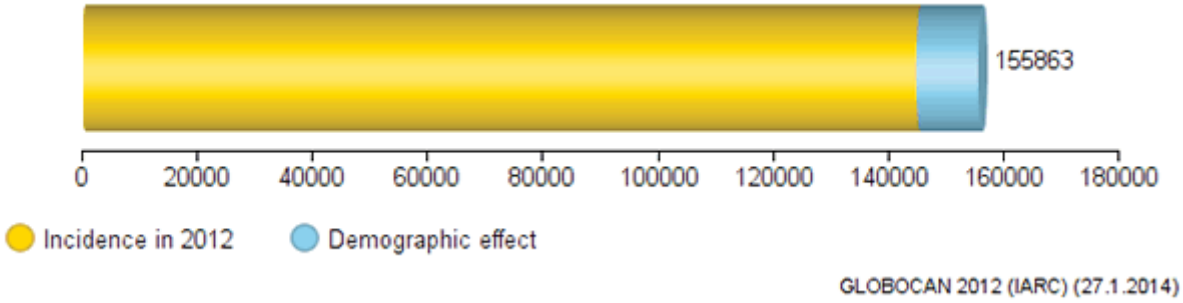


For decades together, cervical cancer was the most common cancer in women in India and more deaths in women in India were attributed to cervical cancer than any other cancer. This was the scene for almost 4 decades (or more). But over last ten years or so, breast cancer has been rising steadily, and for the first time now, breast cancer is the most common cancer in women in India, way ahead of cervical cancer. Both, the incidence, as well as deaths, due to breast cancer are more than cervical cancer. Part of it is due to an actual decrease in the incidence of cervical cancer. But most of it, will be because of rapid rise in the numbers of breast cancer cases.

International Agency for Research on Cancer
World Health Organization

SOURCE: HTTP://GLOBOCAN.IARC.FR

India
Breast
Number of new cancers in 2015 (all ages)



GLOBOCAN 2012 (IARC) (27.1.2014)

For the years 2015, there will be an estimated 1,55,000 new cases of breast cancer and about 76000 women in India are expected to die of the disease. The gap only seems to be widening, which means, we need to work aggressively on early detection.

India is experiencing an unprecedented rise in the number of breast cancer cases across all sections of society, as are also other countries. There is no way we can prevent breast cancer, but we can definitely detect it early and treat adequately. Only and ONLY with early detection, can we achieve a longer survival.

- 144,937 women were newel detected with breast cancer
- 70,218 women died of breast cancer
- 144,937 /70,218 =2.06
- **Hence, roughly for every 2 women newly diagnosed with breast cancer, one woman is dying of it. (*)**

(*) - Breast Cancer India, Global comparison of breast cancer, http://www.breastcancerindia.net/bc/statistics/trends.htm

G) Mammography as an intervention:

Mammography, as a diagnostic tool, was developed shortly after Roentgen's discovery of radiography in late 1800s. However, it has only been over the last two decades that mammography screening has become one of the principal techniques for detecting breast cancer. Screening procedures may include clinical breast examination (CBE), breast self - examination and mammography. This report focuses on mammography screening. By mammographic screening we understand radiographic examination of breasts for the purpose of identification of abnormalities that may be breast cancer. Modern mammography is done on dedicated imaging equipment designed to produce a high quality image of breast at a minimum radiograph dose. The screening examinations commonly involve two views of each breast: a craniocaudal (CC) view and a mediolateral oblique (MLO) view. Before taking the mammogram, a radiologic technologist positions the woman's breast in a compression device .Although breast compression results in discomfort and pain in some women, adequate compression

reduces radiation dose to the breast and is important to image quality by making the thickness of the breast more uniform, permitting even penetration, separating breast tissue that may obscure a lesion, limiting motion blur, and improving contrast.

H) Clinical Effectiveness of Mammography for Breast Cancer Screening

Objective:

- Does Mammographic screening reduce mortality in females by diagnosing breast cancer in the early stage?

Search Methods:

- We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, MEDLINE, PUBMED Science Direct, SCOPUS and Google Scholar for relevant studies. We also conducted secondary referencing by manually reviewing reference lists of key articles and searching citations by using Web of Science. We also conducted specific searches for primary studies published more recently than the included systematic reviews and meta-analyses. Studies were included or excluded on the basis of our exclusion and inclusion criteria.

Key Words:

- The key words used were "Breast Cancer" OR "Mammography" OR "Breast Cancer and Mammographic Screening".

Selection Criteria:

Below mentioned selection criteria was used:-

- Population: - Females above 30 years of age.
- Intervention :- Mammography
- Comparator :- No Screening
- Primary Outcome :- Mortality
- Secondary Outcome :- Detection of Breast Cancer

Criteria for considering studies for this review:

Types of studies

- Randomized clinical trials, Non-Randomized clinical trials, Case control and cohort studies which were available on this subject are included in this review.

Types of interventions:

- Experimental :- Screening with mammography
- Control :- No Screening with mammography

Outcome:

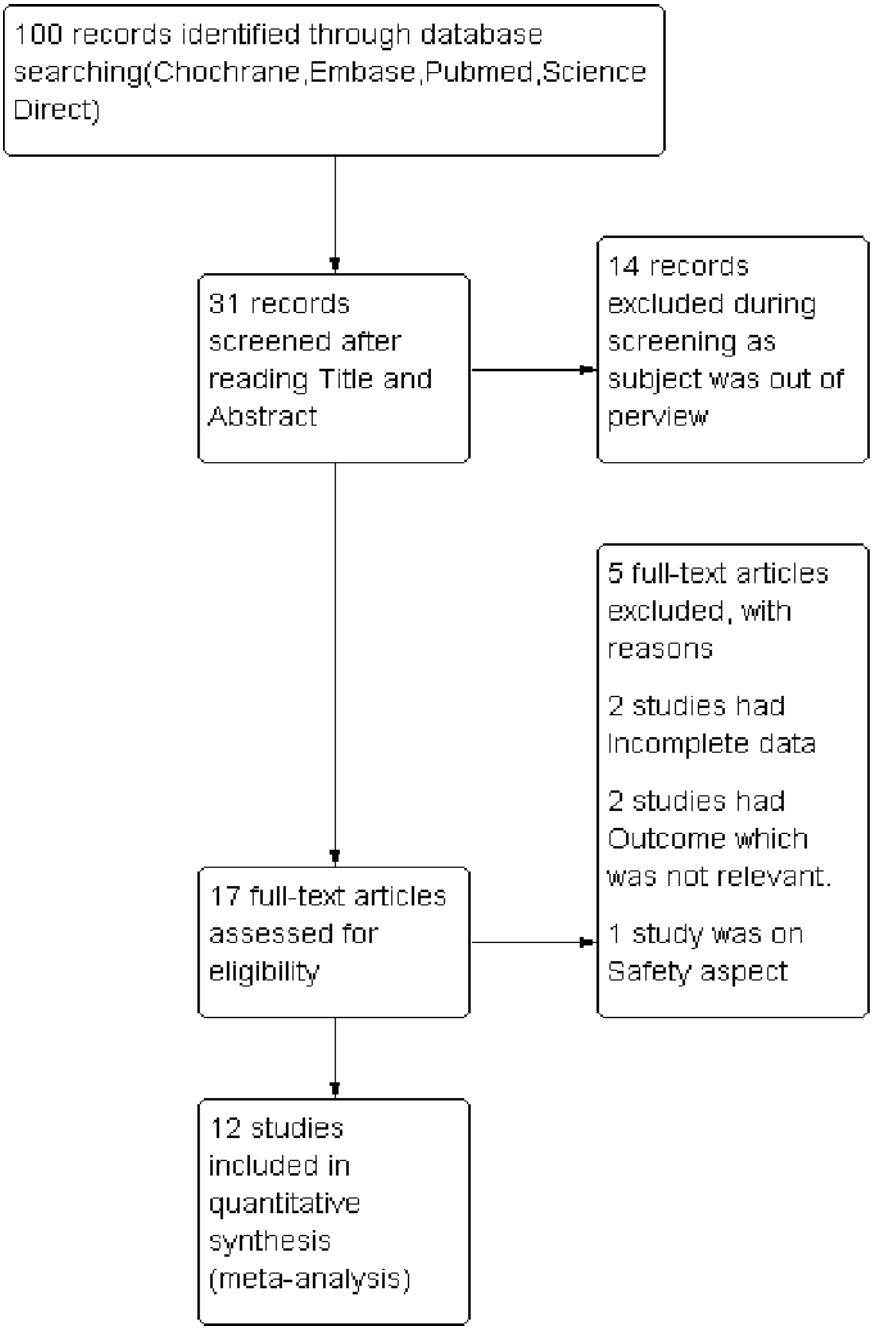
Mortality from breast cancer was assessed in both experiment and control group.

I) Data Collection and Analysis:

31 studies were selected, after reading the abstract 14 were rejected and 17 full text articles were assessed for eligibility. Among these 17 articles 5 articles were excluded with reasons and only 12 studies were included for quantitative synthesis. In addition to the studies we found ten Systematic Reviews and one HTA on this subject; all the studies were considered which were present in all the Reviews. Hence, giving us a comprehensive picture on this subject

As shown in the figure below:-

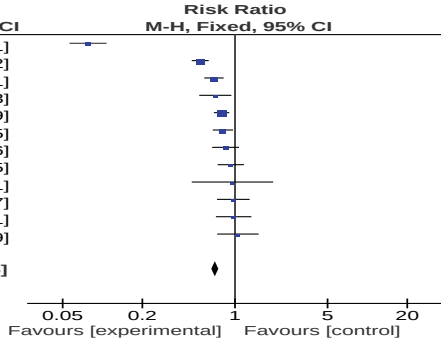
J) Study Flow Diagram



K) Forest Plot

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bjurstam Nils	63	21650	112	2991	7.1%	0.08 [0.06, 0.11]
Matte Kalager	423	7975	396	4081	19.0%	0.55 [0.48, 0.62]
S.W.Duffy	319	77080	334	55985	14.0%	0.69 [0.60, 0.81]
Sam Shapiro	91	3100	128	3100	4.6%	0.71 [0.55, 0.93]
Dr.Lennarth Nystrom	511	1864770	584	1688440	22.2%	0.79 [0.70, 0.89]
UK Trial	231	45607	396	63373	12.0%	0.81 [0.69, 0.95]
Alexander FE-1999	156	28628	167	26026	6.3%	0.85 [0.68, 1.06]
Allgood PC	86	284	185	568	4.5%	0.93 [0.75, 1.15]
Jan Frisel	24	14842	12	7103	0.6%	0.96 [0.48, 1.91]
Anthony B Miller	105	25214	108	25216	3.9%	0.97 [0.74, 1.27]
Anthony B.Miller	88	19711	90	19694	3.3%	0.98 [0.73, 1.31]
Andersson I - 1988	66	21088	63	21195	2.3%	1.05 [0.75, 1.49]
Total (95% CI)		**2129949**		**1917772**	**100.0%**	**0.71 [0.67, 0.75]**
Total events	2163		2575			

Heterogeneity: Chi² = 245.78, df = 11 (P < 0.00001); I² = 96%
Test for overall effect: Z = 12.13 (P < 0.00001)



As per Forest plot,

RR= 0.71 % <1

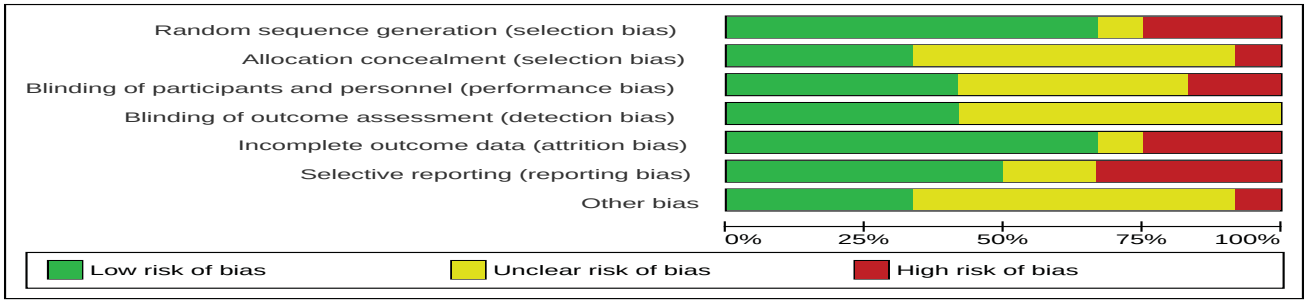
This means reduction in mortality due to breast cancer in mammography group as compared to no screening was 29%.

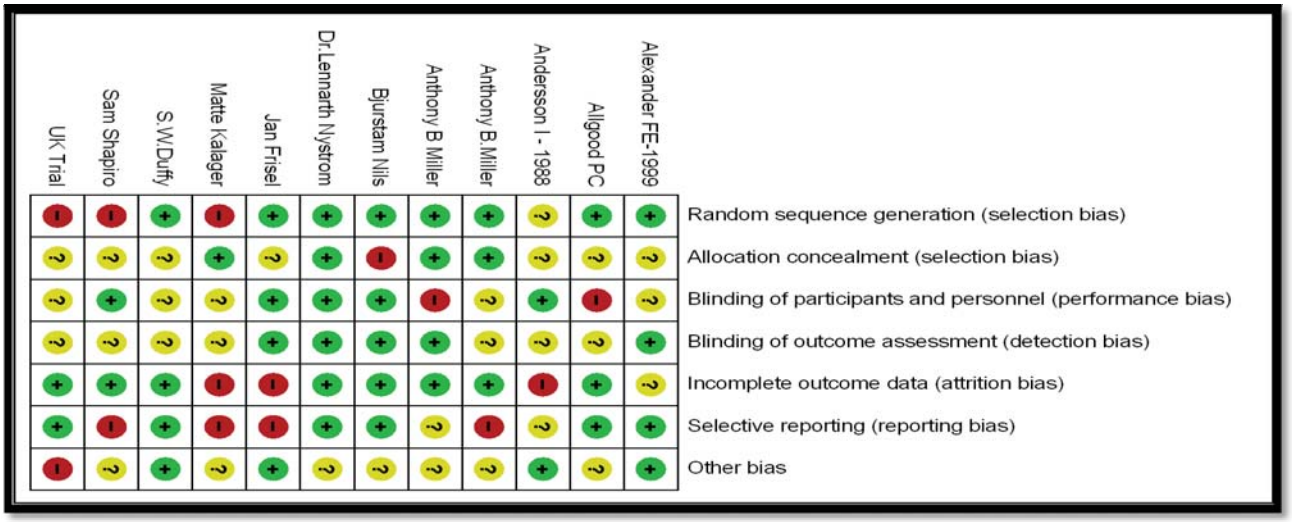
Moreover it is also observed that Risk Ratio (RR) is less than 1, means that experimental intervention is more effective than control.

Main Results:-

This Systematic Review shows 29% reduction in mortality by using mammography as a breast cancer screening tool for early detection.

L) Risk of Bias Table





Explanation of the above mentioned Table:-

Overall the studies show a low risk of any form of bias meaning that the findings of respective studies are of high scientific validity and credibility.

M) Cost effectiveness Analysis

Cost-effectiveness analysis is a method of comparing the cost and effectiveness of two or more alternatives. Such comparisons are useful when one of the alternatives being considered is standard care, as this allows the decision maker to consider whether an alternative is better or not. The standard care, however, could also be a placebo or "Do Nothing" scenario.

Disability-adjusted life year is a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death. It extends the concept of potential years of life lost due to premature death to include equivalent years of healthy life lost by virtue of being in states of poor health or disability - mortality and morbidity are combined into a single, common metric. Calculated by the below mentioned formula:-

DALYs = Disability-Adjusted Life Years lost = Years of life lost due to premature mortality (YLLs) plus years lived with disability (YLDs).

One DALY, therefore, is equal to one year of healthy life lost.

In this review,

Total number of females in India above 30 years = 281005344 (The World Fact Book, 2013)

Total number of breast cancers detected = 144,937 (Breast Cancer India, 2012)

Total number of women died of breast cancer =70218 (Breast Cancer India, 2012)

Cost of breast cancer treatment per patient/year is = Rs 120680 (Pakseresht S 2012)

Cost of Screening in Indian once per patient/year is = Rs 90 (Okonkwo Q L 2008)

1. Effect Analysis (where effect is lives saved)

- Total target population for screening = 281005344
- Total cost of screening = 281005344 X Rs. 90
  = Rs. 2529 crore

Total number of Breast cancer detected in 2012 = 144,937 *(Breast Cancer India, 2012)*

- Hence, 144,937 is the target population in treatment group.
- Total cost of treatment group (All stages) = 144,937 X Rs. 120680
  = Rs. 1749 crore

Although this cost does not cover HER2 positive cases for which treatment is 30 times more expensive.

- Total Mortalities due to Breast Cancer = 70218
- Total Mortalities in Screening group =49855

(As we know by screening we can reduce breast cancer by 29 %, hence total mortality if population is subjected to screening is 71% of 70218 that is 49855 deaths as per the findings of Forest Plot.)

- Total number of lives saved = 70218-49855 =20363
- Difference in total cost (Screening – Treatment) =Rs.2529 - Rs. 1749 =Rs. 780 crore

Cost for saving one additional life = $\frac{780 \text{ Crore}}{20363}$

= Rs.3.8 lacks

2. Effect Analysis (when effect is in life years gained)

Life Years gained is a modified mortality measure where remaining life expectancy is taken into account. Life years are calculated as the remaining life expectancy at the point of each averted death.

Total Number of life years gained by no screening = 1422 per million population per year. (Okonkwo Q L 2008)

$\frac{1422 \text{ life year/person}}{100,00,00}$

Total number of females in India above 30 years (Target population for screening)

= 281005344 *(The World Fact Book,2013)*

Total number of life years for target population = $\frac{1422 \text{ X } 281005344}{100, 00 ,00}$

= 3995896 life years

Incremental Cost of Screening=780 crore

= $\frac{780 \text{ X } 10,000,000}{3995896}$

=Rs. 19520 /life year gained, which is less than the GDP per capita in India, making mammographic screening an extremely cost – effective intervention by W.H.O standards. (Cost per life year gained <1GDP per capita then, it is very cost effective)

3. Total scans/machine/year=

$\frac{\text{No. of Hours/day X Total minutes/hour X Total No. of working days}}{\text{Total Time taken for 1 scan}}$

$=\frac{8x60x300}{15mts}$

=9600

Total number of females needs screening in 2012 = 281005344 *(The World Fact Book, 2013)*

Total no. of machines required $=\frac{\text{Total No. of screening required}}{\text{Total No. of scans/machine/year}}$

$=\frac{281005344}{9600}$

=29,271.39 mammography units

= 29, 271 units

Since it may not be infrastructurarly possible to provide a mammography unit at every PHC immediately, at least in CHC s, Mammography unit should be part of necessary medical technology infra structure, for the screening program on mammography to be successful.

Regulatory Aspect

Mammography utilizes ionizing radiation to image breast tissue. Age at the time of exposure and dose are predictors of risk. The concern for starting screening at a younger age would be the cumulative effect of radiation exposure over a lifetime due to mammography screening.

According to the article on Radiation Risk From Screening Mammography of Women Aged 40–49 Years by - Stephen A. Feig, R. Edward Hendrick-

The risk of breast cancer by radiation exposure due to mammography screening is very small. Annual screening of women age 40–49 years could save 36.5 (292/8) lives for every life potentially lost due to radiation-induced breast cancer, and biennial screening could save 48.5 (194/4) lives for every life potentially lost due to a radiation-induced cancer.

Subsequent screening after age 50			
	None	Biennial	Annual
Lives saved due to screening	194	194	194
Lives lost due to radiation	4	2.4	2.2
Net lives saved	190	191.6	191.8

As lives saved due to screening are 194 and lives lost due to radiation are 2.2, hence net lives saved are 191.8 (*)

[*]-Study -Radiation Risk From Screening Mammography of Women Aged 40 -49 years by- Stephen A. Feig , R Edward Hendrick, 2014. Journal of National Cancer Institute Monographs

Statutory Requirements for installation and safe operation of Mammography units:-

- Registration with Atomic Energy Regulation Board.
- Install AERB Type Approved mammography units.
- Get the plan of the Mammography machine installation approved by Atomic Energy Regulatory Board.
- Carry out Quality Assurance Performance Tests of Mammography units once in two years.
- Employ Quality Staff.
- Provide personnel monitoring badges for staff members associated with the operation of Mammographic unit.
- Comply with AERB Safety Codes No. AERB/SC/MED-2 (Rev-1)2001
- All the manufacturer or supplier of medical X-ray units shall install AERB approved X-ray units in AERB approved rooms.
- Medical Mammographic installations will be subjected to periodic inspection by personnel authorized under section 17 of the Atomic Energy Act, 1962, by Chairman, AERB who is the competent authority for enforcing provisions of radiation safety in the use of ionizing radiation.
- Non- compliance with the regulatory requirements could result in closure of the Mammographic installations.

Regulatory documents concerning requirements for safety operation of medical Mammographic units are:-

- Atomic Energy Act, 1962
- Atomic Energy (Radiation Protection) Rules,2004
- Radiation Surveillance Procedures for Medical Applications of Radiation, 1989
- AERB Safety Code No. AERB/SC/MED-2(Rev-1)2001

Basic guidelines for installations of Mammography unit recommended by AERB Guidelines:-

- No two Mammographic Equipments should be in the same room.
- Ideally the reception area should be away from ultrasound area (or pregnant patients/ baby areas)
- Power should be 3 phase for 200 mA units and above - Ideally separate electric line for Mammography is recommended
- Sonography room should be close by.
- Female Technicians are required as patient is more comfortable
- DICOM or Dark Room - so dark room arrangements should be done adjacent
- Changing room with small drawer for personal items
- For CR, cassettes should not be stored in the same room

O) Ethical and Social Aspect

Developing countries such as India face the brunt of the incursion due to such diseases which can be treated if diagnosed early and valuable lives could be saved .However, to generate more "health seeking behavior" towards mammographic screening in the target population, community based awareness strategies and financial initiatives to frontline health workers could be envisaged such as-

1. Providing small financial incentive Rs.25 per screening to ASHA/ANM to encourage getting eligible person for screening once every year.
2. Having mammography screening as essential component of NCD care.
3. Involving NGOs for community based awareness program for mammography screening for cancer prevention.

P) Recommendations and Suggestions

The aim of this Health Technology Assessment report is to show the efficacy of early detection of breast cancer through mammography. The advantage of screening an asymptomatic population of women is the benefit of identifying pre-clinical disease with sufficient lead time to potentially alter the natural and more adverse course of breast cancer.

Majority of breast cancers are diagnosed at a relatively advanced stage. Unlike other cancers, breast cancer is eminently treatable if detected at an early stage. However, there is a need for systematically implement breast cancer screening, education and intervention strategies.

Q) Bibliography

1. Breast Cancer Factsheet, Preeti K. Dhillon, 2011(Online Available from:-
https://www.google.co.in/search?q=breast+cancer+fact+sheet+by+preet+k+dhillon&rlz=1C1KMZB_enIN545IN545&oq=breast+cancer+fact+sheet+by+preet+k+dhillon&aqs=chrome..69i57.26905j0j7&sourceid=chrome&espv=210&es_sm=122&ie=UTF-8

2. Breast Cancer India, Global comparison of breast cancer(online)(2013).Available from : < http://breastcancer.about.com/od/mammograms/ig/Mammogram-Images/Breast-Tumor.htm >[accessed on 17 February ,2014]
http://www.breastcancerindia.net/bc/statistics/trends.htm

3. Study -Radiation Risk From Screening Mammography of Women Aged 40 -49 years by- Stephen A. Feig , R Edward Hendrick, 2014. Journal of National Cancer Institute Monographs No.22, 1997}

4. **Alexander FE-1999**
Alexander E F, Anderson J T, Brown H K, Forrest APM, Hepburn W, Kirkpatrick, Muir BB, Prescott R J, Smith A. 14 years of follow - up from the Edinburgh Randomised trial of breast - cancer Screening. Lancet 1999;353:1903-08.

5. **Allgood PC**
PC Allgood, J Warwick, RML Warren, NE Day and SW Duffy. A case–control study of the impact of the East Anglian breastscreening programme on breast cancer mortality. British Journal of cancer 2008;98:206 209.

6. **Andersson I - 1988**
Ingvar Andersson, Knut Aspegren, Lars Janzon, Torsten Landberg, Karin Lindholm, Folke Linell,Otto Ljungberg, Jonas Ranstam, Baldur Sigfusson. Mammographic screening and mortality from breast cancer: the Malmo mammographic screening trial. BMJ 1988;297:943-7.

7. **Anthony B.Miller**
Anthony B. Miller, Teresa To, Cornelia J. Baines, Claus Wall. Canadian National Breast Screening Study-2:13-Year Results of a Randomized Trial in Women Aged 50–59 Years. Journal of National Cancer Institute 2000;92:1490-97.

8. **Anthony B Miller**
Anthony B. Miller, MB, FRCP; Cornelia J. Baines, MD, MSc; Teresa To, PhD; Claus Wall, MSc. Canadian National Breast Screening Study:1. Breast cancer detection and death ratesamong women aged 40 to 49 years. Annals of internal Medicineof Internal Medicine 2002;137:305-15.

9. **Bjurstam Nils**
Nils Bjurstam,Lena Bjorneld,Jane Warwick,Evis Sala,Stephen W.Duffy,Lennarth Nystrom,Neil Walker,Erling Cahlin,Olof Eriksson,Lars-Olof Hsfstorm,Halvard Lingass,Jan Mattsson,Stellan Presson,Carl- Magnus Rudenstm,Hakan Salander,Jhon Save-Soderbergh,Torkel Wahlin. The Gothenburg Breast Screening Trial. American Cancer Society 2003;97:2387-96.

10. **Dr. Lennarth Nystrom**
Dr.Lennarth Nystorm PhD, Ingvar Andersson MD,Nils Bjurstam MD, Jan Frisell MD, Prof Bo Nordenskjold MD, Lars Erik Rutqvist MD. Long - term effects of mammography screening :update overview of the Swedish Randomised trials. Lancet 2002;359:909-19.

11. **Jan Frisel**

Jan Frisell,Elisabet Lidbrink. The Stockholm Mammographic Screening Trial: Risks and Benefits in Age Group 40-49 year. Journal of the National Cancer Institute 1997;22:49-51.

12. **Matte Kalager**

Mette Kalager,M.D,Marvin Zelen, Phd,Froydis Langmark,M.D and Hans - Olov Adami,M.D,Phd. Effect of Screening Mammography on Breast - Cancer Mortality in Norway. The New England Journal of Medicine 2010;363:1203-10

13. **S.W.Duffy**

S. W. Duffy, L. Tabar, B. Vitak, M. F. Yen, J. Warwick, R. A. Smith & H. H. Chen. The Swedish Two-County Trial of mammographic screening: Cluster randomisation and end point evaluation.

European Society for Medical Oncology.

14. **Sam Shapiro**

Sam Shapiro. Evidence on Screening for Breast Cancer from a Randomized Trial.

15. **UK Trial**

SM Moss, D A Coleman, J Chamberlain, TJ Mapp, PE Preece, FE Alexander, TJ Alexander, AE Kirpatric, AP Forrest. 16 year mortality from breast cancer in the UK Trial of Early Detection of Breast Cancer.