Strategies to increase the number of clinical trials that are recruiting children in India registered on the Clinical Trials Registry-India (CTRI)

Report submitted to HQ/RPC Research Policy and Cooperation: WHO

Prathap Tharyan

SOUTH ASIAN COCHRANE NETWORK & CENTRE

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1. Executive Summary of report

This report details the background scientific, ethical and regulatory issues that prevent full realization of the benefits of conducting clinical trials of the effects of interventions. It details strategies to overcome these obstacles and to increase prospective registration of clinical trials in India, particularly those recruiting children.

Section 2 details the critical issues that need to be considered in the design, conduct and reporting of clinical trials of the efficacy and safety of interventions used in healthcare and highlights the need for good quality trials and systematic reviews in addressing healthcare questions of local relevance in providing reliable information for evidence-based health decisions.

Section 3 details the scientific rationale for and the ethical issues involved in conducting clinical trials in children and provides an ethical framework by which these trials can be measured.

Section 4 provides an overview of the legal and ethical regulatory framework that governs research in India and clinical trials in particular.

Section 5 summarizes the importance of prospective clinical trials registration and its role in preventing publication bias and selective reporting and

contextualizes trials registration against the backdrop of the quality of design and conduct of clinical trials

Section 6 details the activities and progress of the Clinical Trials Registry- India CTRI) and its attempts to improve the registration of clinical trials and also improve the quality of design of such trials. It provides details of trials registration on the CTRI that are pertinent to this report

Section 7 discusses eight strategies and 14 options for action that will increase the number of trials, particularly those recruiting children in India, in the CTRI and a summary of these strategies and options with the likelihood of success and importance to this report are provided in **Appendix 6** in **Section 14.**

Section 8 provides a detailed reference list to articles cited in this report.

Section 9, Appendix 1 reproduces the terms of reference of this report

Section 10, Appendix 2 provides a draft of a proposed amendment in the ICMR bioethics guidelines endorsing trials registration in the CTRI that will increase the likelihood of clinical trials registration. This forms one of the proposed options to pursue among the list of suggested strategies aimed at increasing the number of trials recruiting children registered in the CTRI.

Section 11, Appendix 3 provides the draft of a performa for surveying ethics committees regarding approval for trials recruiting children

Section 12, Appendix 4 provides the draft of a performa for surveying researchers conducting clinical trials recruiting children

Section 13, Appendix 5 provides the contact details of key stakeholders that will improve the chances of success of this project and a list of web-addresses of key resources that will be essential for the activities under this project.

The views expressed in the report are entirely those of the author and do not necessarily reflect that of any of the organizations of individuals named in this report.

Prathap Tharyan

Vellore: October 25, 2009

2. Critical Issues in Interventional Research

In our attempts to determine the true effects of the interventions that we use in healthcare, we require experimental studies to confirm or refute impressions obtained from pre-clinical studies, laboratory experiments, and clinical observations. The strength of the evidence for the true benefits and harms of the intervention lies in the methods we use in these experiments in order to minimize the effects of bias (or systematic errors that impact on the results or conclusions of a trial), confounders (variables independent of the interventions that affect the outcomes), or the effects of chance variations in the course of a disease resulting in coincidental observation. The randomized controlled trial (RCT) is widely considered the best option we currently have available that fulfils these requirements and hence the findings generated by RCTs are likely to be closer to the true effects of the interventions we wish to evaluate than the findings generated by other experimental designs or natural observations.[1,2]

Why are randomized controlled trials necessary?

In an RCT, the process of randomization ensures that participants have an equal chance of getting one of the interventions through means independent of the investigators, thus balancing all known and unknown confounders such as age, sex, severity or duration of disease or lifestyle variations that may affect the outcome. Trials that do not have a controlled comparison are subject to individual biases and the effects of chance variations and even controlled clinical trials that are not randomized are not reliable in their estimates of effects due to bias in the selection of participants.[3, 4]

When are RCTs not possible or not necessary?

There are situations when randomizing people with illnesses could be unethical or logistically difficult. Rare conditions and urgent and life threatening situations cause difficulties with recruitment, consent, and randomization; for example, meningococcal meningitis is a condition may progress rapidly to produce death or serious neurological deficits. Many countries provide guidelines that mandate the administration of antibiotics, most commonly penicillin, as soon as the illness is suspected, usually penicillin, but contradictory benefits are reported in observational studies.[5,6] This is ideally best resolved through a well designed placebo controlled trial; but for ethical and logistic reasons, such trials are unlikely to be conducted. Some aspects of surgery also pose practical difficulties.

Patients' and surgeons' equipoise about the perceived effectiveness of two alternative interventions is an area of difficulty and in situations where adverse effects are likely to differ considerably (comparing surgical versus non-surgical treatments), people are unlikely to wish that their allotment to treatment should be decided by chance; for example- trials of aspirin versus carotid endarterectomy.[7]

RCTs are particularly appropriate for interventions for which it can be shown that there is treatment integrity — the intervention offered is no more and no less than what is intended and the patient receives the treatment. In many types of non-pharmacological treatments, complex interventions, or care packages that involve a learning curve to achieve standards of expertise, or resources for comparable service delivery, treatment integrity need not be uniform and are therefore difficult to evaluate through RCTs. In these situations, there is a need for study designs other than RCTs.

There are also situations where RCTs are considered unnecessary and these are situations where the effects of the intervention are so large that the need for RCTs is less compelling (e.g.: tracheostomy for tracheal obstruction, defibrillation for ventricular fibrillation), as bias *can* be reasonably ruled out.[8]

However, the majority of interventions in health care do not produce such dramatic benefits and only an RCT can provide reliable answers in such situations.

Since the RCTs form the building blocks of systematic reviews that are considered the highest level of evidence in the approach called evidence based medicine, it is important that clinicians and researchers understand the crucial elements required of an RCT to ensure that reliable evidence is generated.

Pre-requisites for an RCT

1) The need for the trial

Examples abound in the scientific literature of instances where interventions rushed into clinical practice based on insufficient evidence were proven to be ineffective, or even harmful, once the results of systematic reviews from good quality trials were made known, and where timely, cumulative meta-analyses of RCTs, establishing the efficacy of some interventions, might have averted subsequent unnecessary (and thereby unethical) trials.[9] It is now considered a scientific and ethical requirement by some medical journals that an RCT be preceded by justification from the results of a systematic review. [10]

2) A protocol with a well defined research question:

An important pre-requisite for an RCT is the competence of the team of investigators to undertake the trial. The other important pre-requisite is a good protocol that clearly identifies the research question in an answerable format. A focused question that contains the following elements (PICO): the patient or problem in question (P); the intervention (I); comparison intervention(s) (C); the outcome, or outcomes, of interest (I) [11] enables important aspects of the trial to be well defined beforehand. Methods of handling data and analyzing results also need to be described in adequate detail that would enable confidence in the trial's results and interpretations (see later).

3) Incorporation of elements of the CONSORT statement:

The protocol should also clearly delineate the methods that would used to improve the internal validity of a trial (see below) and that would aid transparency in the way the trial was conducted. The Consolidated Standards of Reporting Trials (CONSORT) statement, [12, 13] with its extensions for cluster RCTs, equivalence, and pragmatic trials, is an important source of information for investigators. The 22 items in the revised CONSORT checklist were developed using an evidence-based approach to improve transparency and validity of reporting the methods and results of randomized controlled trials to aid accurate

interpretation of the results. They were designed to help authors prepare, and reviewers assess, manuscripts that would reflect this aim. The International Committee of Medical Journal Editors (ICMJE) recommends in its *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* that these items and the CONSORT flowchart detailing participant progress though the phases of the trial are always reported.[14] If investigators were to incorporate these elements into *trial protocols*, then many of the problems in the design and conduct of trials, let alone reporting, could be averted.

4) Prospective Registration of the Trial:

The other requirement before commencement of the trial is the prospective registration of the trial in a publicly accessible database as required by the ICMJE and the World Health Organization (WHO).[15] The Indian Council of Medical Research (ICMR) has set up a clinical trials register for India at the National Institute for Medical Statistics, New Delhi that is a Primary Register of the WHOs stable of registers and all trials conducted in India would be expected to register prospectively before recruitment of the first participant and disclose a minimum data set of items pertaining to the trial.[16]

5) Ethical review and in issues regarding informed consent:

Since experiments conducted on humans are associated with risks, and considering the recent controversies concerning clinical trials conducted in India,[17] it is imperative that all trial protocols be subjected to peer review by appropriately constituted ethics committees [18] and follow international guidelines [19, 20] as well as local guidelines [21, 22] regarding the scientific and social merit of the trial, the risks and benefits of the trial, the anticipated benefits to trial participants including post-trial benefits, the methods used to ensure that participants were adequately informed of these and consented without duress, the responsibilities and roles of all involved in the trial, and measures to ensure that all outcomes are made publicly available. Protocols that combine the elements of CONSORT as well as ethical elements such as the ASSERT statement [23] are best suited to achieve these goals and the SPIRIT initiative that aims of define Standard Protocol Items for Randomized Trials will provide guidance on this, as well as other aspects of trial conduct not currently covered in the CONSORT guidelines, when made available. (http://www.equator-network.org/index.aspx?o=2910).

6) Methods to improve the internal validity of RCTs

There are four main types of biases that occur during the conduct of an RCT that affect internal validity: a) *Selection bias:* biased allocation to comparison groups, b) *Performance bias:* unequal provision of care apart from treatment under evaluation, c) *Detection bias:* biased assessment of outcome and d) *Attrition bias:* biased occurrence and handling of deviations from protocol and loss to follow up.[24]

There are four methods that are relatively easy to apply in most instances that are considered crucial to minimize these biases and improve the internal validity of RCTs. [25]

1) Method of generating the random sequence:

The main purpose of randomization is to eliminate selection bias and balance known and unknown confounding factors in order to create a control group that is as similar as possible to the treatment group. Methods for randomly assigning participants to groups, which limits bias, include the use of a table of random numbers and a computer program that generates random numbers. Methods of assignment that are prone to bias include alternating assignment or assignment by date of birth or hospital admission number or any method where it is possible to predict the allotment to interventional arms.

In very large clinical trials, simple randomization may lead to a balance between groups in the number of patients allocated to each of the groups, and in patient characteristics. This may not be the case in trials with smaller sample sizes. Block randomization ensures a balance in the number of patients allocated to each of the groups in the trial by randomizing participants in blocks of, say, four to eight at a time so that the difference in participant numbers between groups will be within the block size. Using varying block sizes prevents people from guessing allocation. While randomization may help remove selection bias, it does not always guarantee that the groups will be similar with regard to important patient characteristics, particularly when these characteristics are non-normally distributed. Stratification (or stratified block sampling) ensures that the groups are as identical as possible by generating separate block randomization lists for different combinations of known prognostic factors that might affect outcomes.[4]

2) Allocation concealment:

A crucial element of the randomization process in preventing selection bias is unpredictability. Concealment of the randomization sequence is critical to ensure this. Any method whereby allocation of the next participant is known beforehand, such as alternation or an open list of random numbers, may prompt

investigators to select the next participant according to conscious or unconscious needs that can seriously bias the selection process. Any selection bias in an RCT invalidates the study design and makes the results no more reliable than a non-randomized trial or an observational study. The ideal method would be to ensure that generating the randomization sequence and allocating participants are administered by someone who is not responsible for recruiting subjects, such as someone based in a central trial office or pharmacy. If such central randomization cannot be organized, then other precautions are required to prevent manipulation of the allocation process by those involved in recruitment, such as the use of pre-numbered or coded identical containers with the interventions, which are administered serially to participants; an on-site computer system combined with allocations kept in a locked unreadable computer file that can be accessed only after the characteristics of an enrolled participant have been entered; or the use of sequentially numbered, sealed, opaque (this has to be tested) envelopes with the allocated interventions described according to the randomization sequence.[25]

Allocation concealment takes place before the interventions are implemented and prevents selection bias that influences all aspects of trial outcomes, while blinding take place during the interventions and prevents performance and

detection bias that may affect only selected outcomes. Adequate allocation concealment is a pre-requisite for adequate blinding and can always be achieved, even in surgical interventional trials or other situations whereas blinding may not always be possible. Empirical research has shown that trials that lack adequate allocation concealment or do not report this are associated with bias, often overestimating treatment effects by as much as 41%.[3, 26] Indeed, concealment has been found to be more important in preventing bias than other components of allocation, such as the generation of the allocation sequence and blinding [23] and is the critical element used to judge the quality of a trial in many Cochrane systematic reviews. [24]

3) Blinding:

The perceptions of participants or investigators of the relative advantages or disadvantages of interventions may produce biased reporting of outcomes, especially when subjective outcomes, such as pain or depression scores, are involved as opposed to objective outcomes such as mortality. A *double-blind RCT* is a randomized trial in which two groups of individuals (participant and outcome assessor) involved in the trial do not know the identity of the intervention that is given to each participant.[26] In a *triple-blind RCT*, three groups of individuals (the

participants, the investigators giving the intervention, and those evaluating the outcomes are blind to interventions; or the participants, the investigators evaluating the outcomes, and the data analysts. If one more group is unaware of the identity of the intervention that is given to each participant, then the trial becomes a *quadruple-blind RCT.* Ideally, all properly conducted, so called, double blind trials should blind participants, investigators and outcome assessors (be triple blind trials) to ensure minimal observer bias. Since there is considerable confusion regarding the appropriate use of the terms 'double-blinding', [28] it is recommended that reports describe who exactly was blinded. Since it is not always possible to maintain blinding in clinical trials where the allocated interventions are difficult to mask adequately (differential side effects between the interventions), it is also recommended that the adequacy of blinding is tested, [12, 13] for example by asking participants and outcome assessors to guess allocation. Kappa statistics can be used to assess whether the degree of agreement (or disagreement) between the guessed and true allocation reveals whether blinding was actually preserved.

Adequate blinding prevents performance and detection biases. Blinding has also been shown to be an important attribute of study quality in producing reliable results, particularly when subjective outcomes are used. [3, 23]

Factors other than poor blinding can contribute to performance bias. Contamination (provision of the intervention to the control group) and co-intervention (provision of unintended additional care to either comparison group) can affect also study results.

4) Adequacy of follow up:

Not all participants randomized will complete trials in many situations. Patients not adhering to treatments in trials generally differ in respects that are related to prognosis.[23] If all participants randomized are not accounted for in the final analysis, attrition bias could result, especially if the number of drop-outs is substantial. It is recommended that authors of papers should state clearly which participants are included in their analyses. The sample size per group, or the denominator when proportions are being reported, should be provided for all summary information. [12, 13]

'Intention to treat' analysis is a strategy in the conduct and analysis of randomized controlled trials that ensures that all patients allocated to either the treatment or control groups are analyzed together as representing that treatment arm, whether or not they received the prescribed treatment or completed the study. This provides conservative estimates of treatment

outcomes and if these results do not differ significantly from that produced by an analysis of completers, confidence in the results is strengthened. Because of the variations in trial outcomes and numbers that complete trials, intention to treat is inconsistently associated with biased outcomes.[23]

7) Assessing the strength and significance of results

There are many issues that are important in handling data from trials and some of them include having pre-defined rules of interim analysis and for stopping early trials for harms or for benefits, having data monitors and procedures to ensure integrity of data etc. Stopping trials early for harms may be more justified than stopping early for perceived benefits of the intervention, since the latter often fail to adequately report relevant information about the decision to stop early, and show implausibly large treatment effects, particularly when the number of events is small. [29] Other issues include a pre-determined sample size, based on the primary (or an important secondary) outcome to ensure that adequate differences in treatments can indeed be detected to avoid Type II errors that occur from trials with small sample sizes.[12, 13] Sample size calculations are especially important when dealing with trials with designs different than the conventional group trials, such as cluster RCTs, factorial designs, and equivalence trials.[30-33] Extensions to the CONSORT statement for cluster randomized,

equivalence and non-inferiority trials have also been published, that deal with the issues relevant to increasing the reliability of evidence from these trial designs.[34,35]

In analyzing results, the magnitude and precision of the effects are especially important and are dealt with briefly here.

1. *The magnitude of treatment effects:*

It is important to know not only if the intervention works but also how effective the intervention is in comparison to the control intervention. Conventional methods test the hypothesis that there is no difference between interventions and use p values set at less than 0.05, derived from tests of proportions or from t tests or analyses of variance, to assess the significance of the results. This only tells us that the observed differences in outcomes cannot be accounted for by chance 95%% of the time.

An alternative, and more useful method, is to estimate the magnitude of treatment effects. Treatment effect in RCTs may be reported in various ways including relative risk, odds ratio, absolute risk and number needed to treat.[24] For unfavorable outcomes, an *odds ratio* or *relative risk* greater than 1 indicates increased likelihood of the outcome in the control group. If the odds ratio or

relative risk is less than 1, there is an increased likelihood in the treatment group. A ratio of 1 indicates no difference—that is, the outcome is just as likely to occur in the treatment group as it is in the control group. For favorable outcomes, the direction of effect is reversed, so that an odds ratio of greater than 1 favors the intervention over control. For unfavorable outcomes, an odds ratio of 0.65 also tells us that the treatment reduces the odds of the unfavorable outcome by 35% compared to the control intervention. The odds ratio will be close to the relative risk if the end point occurs relatively infrequently, say in less than 20%.[29] While odds ratios have better mathematical properties, they tend to be less intuitively understood by clinicians than relative risks; clinicians also often mistake odds ratios for relative risks. [24]

The risk difference describes the actual difference in the risk of events that was observed with treatment and with control; for an individual it describes the estimated difference in the probability of experiencing the event. However, the clinical importance of a risk difference may depend on the underlying risk of events. The *number needed to treat* is obtained from the risk difference and takes into account baseline risks as well; it is useful for policy makers and clinicians and reveals how many patients are needed to be treated to produce benefit (or prevent harm) to one additional patient compared to the control intervention. [24]

2. *Precision of treatment effects:*

Confidence intervals (CI) provide the likely range of values for the effect estimate (odds ratio, relative risk, risk difference) if the experiment were to be repeated a 100 times, in 95% of instances (95% CI) or even 99% of instances (99% CI). It is a measure of precision since if the confidence intervals are narrow (e.g.: relative risk 0.65; 95% CI 0.62 to 0.68) one has more confidence in the strength of the effect estimate. It is also a measure of uncertainty. If the confidence intervals are wide (relative risk 0.65; 95% CI 0.32 to 0.98), one has less confidence in the point estimate as the benefits may be as small as a 2% reduction in the likelihood of the outcome, which may not be clinically significant, or as great as 62%. If the confidence intervals includes 1, (e.g.; if the relative risk for an undesirable outcome is 0.65; 95% CI 0.32 to 1.20) then the intervention may be beneficial (reduce the likelihood of the outcome by 68%) or harmful (increase the likelihood of the outcome, compared to the control by 20%). Effect estimates should always be reported with their confidence intervals and if the upper and lower confidence intervals lie entirely on either side of 1, then the corresponding p values are likely to be low and statistically significant. If they include 1, then statistical significance is not reached. Confidence intervals therefore convey

more useful information than p values and should be reported along with (or instead of) p values. .

8) Interpreting results

In assessing the significance of the results of a trial, it is important to consider the direction and magnitude of effect as well as the precision of the confidence intervals. It is also important to not mistake 'evidence of no effect, 'with 'no evidence of effect,' when the confidence intervals for the effect estimate includes 1, the indicator of no significant difference.[24] The former indicates that the trial found the treatment to be inferior to the control treatment, which is not true in this instance, while the latter indicates that results, though not definitely favoring the intervention, were uncertain.

It is also important to differentiate statistical significance from clinical significance. Clinical significance reflects the value of the results to patients and includes judgments about how important the benefits and any adverse events of an intervention are likely to be in clinical practice.

9) Applying evidence to practice

In applying the results of clinical trials to practice, it is important to realize that results from *efficacy trials*, with strict inclusion and exclusion criteria that assess internal validity, may not necessarily generalize to one's own clinical practice and

pragmatic trials, that include participants similar to ones own patient population and assess external validity or generalizability, may be needed.[27, 36] Also, in trials of interventions where health care delivery systems impact on the outcomes, results of trials done in the developed world may not be applicable to the developing world. The crucial questions to consider in such instances include the similarity of participants in the trial report to one's own patient populations, the relative benefits and adverse effects of the intervention, when applied to one's patients, keeping in mind their co-morbid conditions; the wishes of the patient and their carers regarding the intervention, particularly the ease of availability, inconveniences and affordability.

Finally, it is important to consider, when evaluating the evidence for efficacy and safety of interventions, that the results of a single trial only rarely provide reliable estimates of effectiveness that are generalizable to multiple settings. Systematic reviews use explicit methods to limit bias in the assembly, search and retrieval, analysis and quantitative synthesis (meta-analysis) of relevant findings from research on a particular topic, and not just the results of one or two studies. They can be used to establish whether scientific findings are consistent and generalizable across populations, settings, and treatment variations, or whether

findings vary significantly by particular subgroups.[37] Moreover, the explicit methods used in systematic reviews limit bias and, hopefully, improve reliability and accuracy of conclusions.

For these reasons, systematic reviews of randomized controlled trials (RCTs) are considered to be evidence of the highest level in the hierarchy of research designs evaluating effectiveness of interventions. [38] Systematic reviews of good quality randomized controlled trials, with large sample sizes and with little variation in results (heterogeneity), offer the best available evidence of treatment effects.[39]

Access to the world's largest collection of systematic reviews and RCTs

The Cochrane Collaboration (www.cochrane.org) is an international organization devoted to preparing and maintaining systematic reviews of interventions used in health-care. The main output of this international organization is published electronically in *The Cochrane Library* (www.thecochranelibrary.com), which is a collection of seven databases pertaining to effects of interventions in health care and the science of systematic reviewing. Of these, *The Cochrane Database of Systematic Reviews* currently contains over 5000 regularly-updated systematic reviews and protocols of reviews in preparation; *The Cochrane Controlled Trials Register (CENTRAL)* currently contains references, mostly with abstracts, of more

than 500,000,000 controlled clinical trials- easily the largest collection of such trials in the world. All residents in India have complimentary access to the full contents of *The Cochrane Library*, thanks to sponsorship provided by the Indian Council of Medical Research (ICMR) that signed a three-year contract in 2007 for a national subscription with the publishers, John Wiley & Sons; this contract is due for renewal in 2010 and is likely to be renewed.

If health care in India is to be based on reliable evidence, then the conduct and reporting of RCTs done in India needs to include the crucial elements described herein. Moreover, all research planned and conducted need to be fully reported, so that their results may add to the knowledge base that will inform healthcare decision making. To achieve this, investigators, institutional ethics committees, medical journal editors and peer reviewers need to collaborate on ensuring that these elements are incorporated into trial protocols and reports and all results are published. Reliable evidence from trials conducted in India is especially important as locally generated results are necessary to contextualize the evidence. [40]

In addition, the availability of resources such as *The Cochrane Library* provide an additional source of reliable evidence that can be incorporated with clinical experience and the values of patients and their carers in the collaborative endeavor called evidence-based medicine. However, systematic reviews need to include trials from India, if these reviews are to be considered relevant to clinical care in India. Their exclusion from systematic reviews could bias conclusions, rendering them unreliable and potentially irrelevant to health care in these countries. Their quality needs to be high for this to occur, so that they are included in such systematic reviews, and to prevent their inclusion resulting in a diminution of the quality of the overall evidence. To achieve this, their existence should also be made known and their results made easily assessable.

3. Clinical Trials in Children

The need for clinical trials in children

Children are a unique population with distinct developmental and physiological differences from adults. The effects of drugs must be studied in children and adolescents to determine their safety and efficacy in them. Drug studies in adult humans may not adequately predict the pharmacokinetic, pharmaco-dynamic or toxic properties of drugs in children as growth, differentiation, and maturation can alter the kinetics, end organ responses, and toxicities of drugs in the newborn, infant, child, or adolescent as compared to the adult.[41] For most of the commonly used medications in children and adolescents no sound database about efficacy and safety is available and knowledge about adverse events and long-term safety remains poor. Only a small fraction of the drugs marketed and utilized as therapeutic agents in children have been clinically evaluated; the majority of marketed drugs are either not labeled, or inadequately labeled, for use in pediatric patients.[43] The absence of suitable medicines or critical safety and efficacy information poses significant risks to a particularly vulnerable patient population. This is due to a general lack of clinical trials in this population.

Participation in clinical trials involves the possibility of obtaining benefits but also of suffering risks. Those risks are often considered unacceptable for children but if clinical trials are not conducted in children, clinicians are forced to extrapolate study data from adults resulting in children being termed "therapeutic orphans" because of the lack of adequately tested and labeled drugs available in appropriate formulations.[42] Clinical trials in children are therefore essential in developing safe medications, age-specific formulations, clinical interventions and best practice pediatric treatment guidelines.[43] Thus, while we have a duty to protect children, we also have a duty to ensure that they receive the best available treatments.

Issues in conducting clinical trials in children

Differences exist in the definitions used delineate pediatric populations with the lower limit ranging from birth to two years of age and the upper limit ranging variably from 12 to 16 to 18 years of age.[44] For the purposes of this report, children will refer to individuals from birth to 18 years of age and include those termed pre-term or term newborn infants (birth to 27 days), babies, neonates, infants, adolescents and those referred to as minors or emancipated minors (16 to 18 years).

Research involving children entails specific difficulties due to the need to study children of different ages, the small number of children affected by certain diseases, and the numerous ethical issues that are associated with pediatric clinical trials. Some of these issues pertain to the benefits and risks to children due to trial participation; the specificity of pediatric trial design; ethical issues such as competency to consent, the need for assent and the age group where this becomes meaningfully possible; issues to do with pharmacokinetic studies; the use of placebos in pediatric trials, and the participation of healthy children and of neonates.[44] Hence, specific ethical and clinical concerns in this vulnerable population must be considered when designing and implementing clinical trials. Legislative efforts have tried to improve safety and labeling of medicines for children but these have been considered as barriers, by some, to conduct effective pediatric trials, [45, 46] while others opine that such legislation is likely to increase the recruitment and protection of children in clinical trials.[47]

Ethical issues in pediatric clinical trials

Pediatric trial design

Pediatric trials need to be designed by those with experience both in clinical trials and pediatric medicines and should include the views of parents and, where appropriate, children from the age groups to be included. This is particularly important with invasive study protocols, as when numerous blood samples are required for pharmacokinetic or other studies. These should be kept to the minimum, and alternative methods of sampling such as population pharmacokinetics, [48] or the use of non-invasive sources of samples such as urine, if feasible, should be explored. [44, 47] When multiple samples are required, their timing should coincide with therapeutic samples, wherever possible, and methods to minimize amounts drawn such as the use of microarrays. The use of indwelling catheters and analgesia should also be considered to minimize discomfort to children. Other methods to reduce sample size to the minimum should also be explored such as the use of sequential trial designs and the avoidance of equivalence and non-inferiority trial designs that require larger sample sizes.[44, 47, 49] However, trial designs that involve fewer children should be weighed against trials involving more children that could yield useful information but that use less invasive procedures.[44]

In evaluating efficacy, un-blinded and/or uncontrolled trials are subject to increased bias and should be avoided whenever possible. This applies to trials

evaluating safety as well, unless designed prospectively for longitudinal follow up or for pre-specified subgroups. As with trials in adults, all aspects of design detailed in section 3 of this report that will increase the internal validity of the trial need to be adhered to. In the case of open trials, where blinding is not possible, systematic assessment of outcomes by parents or other carers, and if possible, by the recruited children, should also be obtained. [44]

Risk- benefit analysis

A child's interests should always prevail over the perceived benefits to society and science. A proper risk-benefit analysis should form part of the protocol submitted for approval to Institutional Review Boards (IRB). Risk is defined as potential harm (real or theoretical) or potential consequence of an action.[44] Risks should be considered in conjunction with the severity of the condition or diseases to be studied, the age of the child and the risks and benefits of alternative treatments. Potential harms can be physical, psychological or social, may be immediate or delayed, and can take many forms, from the harms of the medicinal product tested, or from the control condition, to the invasiveness, inconveniences, and intrusiveness of the research protocol or the violation of privacy. Risks in pediatric trials also include those that may not usually be of

concern in adults due to adverse effects in children that have not been identified in adults. Current guidance also discourages enrolment in multiple clinical trials which can take place when a condition is rare in childhood.[44]

The level of risk may evolve over time, during the trial and with evolving knowledge, and risk should hence be continuously monitored with pre-defined stopping rules included in the protocol, especially for unscheduled or scheduled analyses in relation to safety or non-compliance. Age-appropriate formulations are recommended to reduce the risk of adverse reactions, and the risk of dosing errors due to inaccuracy .The use of a Data and Safety Monitoring Board (DSMB) that includes pediatric experts is recommended, and their absence, particularly in pharmacokinetic studies, should be justified.[44, 47]

Benefit from participation in a trial is defined as a tangible outcome experienced by the child participant with regard to progress in treatment, diagnosis, or prevention for the child or the group of children affected, or in contribution to patient care (for example, better route of administration, decreased frequency of dosing, improvement in relation to potential medication errors or compliance, reduced treatment duration, or a clinically relevant age-appropriate formulation).[44, 47, 50] This could result in either increased efficacy or safety resulting in a better risk-benefit balance, or through the provision of an

alternative to existing treatment with at least similar expected benefit risk balance.

Benefit could also include increased knowledge of the condition and /or treatment, which would possibly result in better diagnosis, treatment or prevention, measured by the importance of knowledge gained, severity of the issue to be addressed, the likelihood of obtaining valid results from the proposed research, and usefulness of benefits obtained.

In assessing the risk benefit ratio, the research could be classified as having:

- "Minimal risk with benefit for the individual or benefit for the group
- Minor increase over minimal risk, with benefit to individual or benefit to the group, and with the benefit to risk balance being at least as favorable as that of available alternative approaches.
- Greater than minor increase over minimal risk with benefit for the individual that is especially favorable in relation to available alternative approaches for the individual's condition".[44]

However, the appreciation of risk and benefits differs in various populations and according to the manner in which this information is conveyed; more research is required on strategies to better communicate the true risks versus benefits of

participation in research in information sheets for parents and children and for IRB members to aid their appreciation of the issues involved. [51, 52]

Consent and assent to participate

Valid, freely obtained and informed consent is the cornerstone of the ethical conduct of clinical trials in adults but in the case of trials recruiting children, as the child (or legal minor) is unable to provide legally binding consent, informed consent must be sought from the parents/ legal representative on the child's behalf. Consent should be viewed as a process (not an event) that allows for the expression of a free choice by a person to or not to participate in a research protocol. Therefore consent should not only be obtained prior to enrolling a child in a trial but should be assessed during the trial on a continuous basis by, for example, a brief discussion during each repeat visit that is documented. This is particularly important in the case of any new information that arises during the trial that might affect the willingness of the parent and child to continue.[44, 47, 50]

Financial inducements, particularly in economically deprived populations; the 'therapeutic misconception', whereby participants are unable to differentiate those elements of a research protocol from routine clinical care in situations where research is combined with care; and the unequal nature of the doctor

patient relationship wherein parents of children with chronic conditions, or less educated parents, or those overwhelmed by unfamiliar or seemingly dangerous medical conditions, may be reluctant to displease their doctors; may result in the consent given being not entirely free of coercion. [44,47, 50] Good practice therefore dictates that consent should obtained, or independently verified, by persons not involved in the routine clinical care of children.

Assent by the child to participate in a trial is also recommended in many ethical guidelines, particularly from children above the age of nine years, who have been shown to be capable of understanding the benefits and risks of research, while children below that age are unlikely to be able to consent or assent to participation in a meaningful way.[53,54] However, it is recognized that because of wide individual variations, one cannot depend on the subjects' age alone to ensure that sufficient understanding has occurred. The capacity to assent should also consider other factors such as developmental stage, intellectual capacities (especially in children with special needs and/or learning difficulties), life / disease experience, etc. This needs to be made after discussion of the parents / legal representative with the investigator, but the parents are usually in the best position to decide on whether the child has understood the information.

The minor's assent is not sufficient to allow participation in research unless supplemented by informed consent of the legal representative.[44, 47] If the child's assent is not obtained, this should ideally be respected and any exceptions documented along with the justification for continuance, particularly in situations where there is strong dissent or where the lack of assent may be detrimental to the health or welfare of the child, and the consent of the parent or legal representative.[44]

Adolescents belong to the pediatric age group, although they have the capacity to make adult decisions in many other areas of life. Most guidelines and publications recognize that adolescents are, under certain circumstances, able to make independent judgments, and this should be respected Seeking assent should put in balance the emerging capacity of an adolescent for independent decision-making, particularly in the case of 'emancipated minors,' with the need for continued special protection as provided by parents or legal representatives.

The use of placebo controls

In clinical trials involving consenting adults, there is general agreement that placebo or untreated controls are not appropriate in trials of therapy for life-threatening conditions if a treatment that prolongs or preserves life is available. However, it has also been argued that placebo-controlled trials are not uniformly

unethical when known effective therapies are available, since even the Declaration of Helsinki [19] acknowledges that, "Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality"; rather, their acceptability is determined by whether the patient will be harmed by deferring therapy. If patients are not harmed, such trials could ethically be carried out. Systematic reviews of the evidence do not indicate that, in general, participation in randomized controlled trials, even ones that include placebo arms, result in worse outcomes for participants than for those who refused participation. [56]

However, in trials involving children, the use of placebos is more problematic, since children cannot provide consent. The use of placebo is often needed for scientific reasons, including in pediatric trials. The use of placebo may be warranted in children as in adults when evidence for any particular treatment is lacking or when the placebo effect is known to be very variable (e.g. pain, hay fever). [44] Short term use of placebos in pediatric trials of some interventions, such as hypertension, appears to be safe. [56] It is as important to discuss the exclusion of placebo, as it is to discuss its inclusion for pediatric clinical trials.[44]

Including healthy children

Studies should ideally not be performed in children when they can be performed in adults. In some situations however, studies need to be performed in children who are healthy at the time of the trial, such as prevention trials or pediatric vaccine trials, including immunogenicity studies. Trials in children with intermittent diseases (e.g., seizures) are acceptable because even when asymptomatic the children are affected. Whenever possible the older age groups should be considered for inclusion before the younger ones.[44, 47]

4. Regulation and ethical oversight of research in India

Healthcare regulation in India

The Central Government's Ministry of Health and Family Welfare frames health policies and is involved with the regulation of the healthcare industry and management of Public Health initiatives and facilities. However, the implementation of health policies and delivery of services is the responsibility of State Governments though their Ministries of Health. Considerable variations exist between states within India on the quality, reach and management of public health facilities. The Indian Medical Council is responsible for the licensing and regulation of all medical professionals but is largely uninvolved with the delivery of care or setting of standards of healthcare delivery. Medical practice in India comes under the jurisdiction of the Consumer Protection Act (COPRA), 1986. [57]

The Drugs and Cosmetic Act & Rules

The Drugs and Cosmetics Act 1940 (Act 23 of 1940 as amended up to 30 June 2005) and the Drugs and Cosmetic Rules 1945 (as amended up to 30 June 2005) regulate the import, manufacture and sale of drugs and cosmetics in India, including those that are used in Ayurvedha, Siddha and Unnani systems of medicine. Schedule Y of the Drugs and Cosmetic Rules 1945 in conjunction with

rules 22 A to E of the Act provide the policies, requirements and procedures governing the import for new drugs for manufacture and undertaking clinical trials in India. [58]

Schedule Y requires that all applications for clinical trials should conform to the requirements of the Declaration of Helsinki,[19] the Ethical Guidelines for Biomedical Research on Human Participants of the Indian Council of Medical Research and the Good Clinical Practice Guidelines issued by Central Drugs Standard Control Organization (http://cdsco.nic.in/html/GCP1.html).[22] Schedule Y provides detailed requirements of the structure and content of study protocols, informed consent forms and documentation and the composition and functions of ethics committees and includes child patients as deserving special consideration as a vulnerable group.

The relevant sections of Schedule Y that covers pediatric drug trials are reproduced below (pages 509 to 510):

"(i) The timing of pediatric studies in the new drug development program will depend on the medicinal product, the type of disease being treated, safety considerations, and the efficacy and safety of available treatments. For a drug expected to be used in children, evaluations should be made in the appropriate age group. When clinical development is to include studies in children, it is

usually appropriate to begin with older children before extending the trial to younger children and then infants.

(ii) If the new drug is for diseases predominantly or exclusively affecting pediatric patients, clinical trial data should be generated in the pediatric population except for initial safety and tolerability data, which will usually be obtained in adults unless such initial safety studies in adults would yield little useful information or expose them to inappropriate risk.

(iii) If the new drug is intended to treat serious or life-threatening diseases, occurring in both adults and pediatric patients, for which there are currently no or limited therapeutic options, pediatric population should be included in the clinical trials early, following assessment of initial safety data and reasonable evidence of potential benefit. In circumstances where this is not possible, lack of data should be justified in detail.

(iv) If the new drug has a potential for use in pediatric patients – Pediatric studies should be conducted. These studies may be initiated at various phases of clinical development or after post marketing surveillance in adults if a safety concern exists. In cases where there is limited pediatric data at the time of

submission of application – more data in pediatric patients would be expected after marketing authorization for use in children is granted.

(v) The pediatric studies should include -

(a) clinical trials; (b) relative bioequivalence comparisons of the pediatric formulation with the adult formulation performed in adults; and (c) definitive pharmacokinetic studies for dose selection across the age ranges of pediatric patients in whom the drug is likely to be used. These studies should be conducted in the pediatric patient population with the disease under study.

(vi) If the new drug is a major therapeutic advance for the pediatric population – the studies should begin early in the drug development, and this data should be submitted with the new drug application.

(vii) Pediatric Subjects are legally unable to provide written informed consent, and are dependent on their parent(s)/ legal guardian to assume responsibility for their participation in clinical studies. Written informed consent should be obtained from the parent/ legal guardian. However, all pediatric participants should be informed to the fullest extent possible about the study in a language and in terms that they are able to understand. Where appropriate, pediatric

participants should additionally assent to enroll in the study. Mature minors and adolescents should personally sign and date a separately designed written assent form. Although a participant's wish to withdraw from a study must be respected, there may be circumstances in therapeutic studies for serious or life-threatening diseases in which, in the opinion of the Investigator and parent(s)/ legal guardian, the welfare of a pediatric patient would be jeopardized by his or her failing to participate in the study. In this situation, continued parental/ legal guardian consent should be sufficient to allow participation in the study.

(viii) For clinical trials conducted in the pediatric population, the reviewing ethics committee should include members who are knowledgeable about pediatric, ethical, clinical and psychosocial issues."

However, limitations in the punitive provisions of the Act have prevented effective enforcement of the provisions. Additional legislation to amend the Drugs and Cosmetics Act and provide for punitive actions from non-compliance and better regulate the conduct of clinical research in India is currently pending legislative approval.[59]

Ethical Guidelines for Biomedical Research on Human Participants of the Indian Council of Medical Research

The Indian Council of Medical Research (ICMR) first published a *'Policy Statement on Ethical Considerations involved in Research on Human Subjects'* in 1980 that was revised in 2000 and in 2006 as the '*Ethical Guidelines for Biomedical Research on Human Participants.'* [21]

While incorporating changes necessitated by the rapid growth of the globalization of research, the 2006 revision also addressed issues peculiar to the Indian cultural values and context, particularly in the application of informed consent and the primacy of individual autonomy. The eight chapters cover the general principles of ethics in research on human participants; ethical review procedures; general ethical issues such as informed consent, compensation to participants, conflicts of interest, confidentiality, post-trial access, international collaboration, etc; and specific principles related to interventional research, epidemiological studies, genetic research, research in transplantation and assisted reproductive techniques. Additional draft guidelines for compensation to participants for research related injury were made available on the ICMR website (http://icmr.nic.in/icmrnews/compensation_guide.pdf) in November 2008.

Under the section on general ethical issues, sub-section IV. *Selection of special groups as research participants*, the guidelines discuss the principles to be applied to involving children in research, particularly clinical trials, and these are reproduced below (page 28):

"*Children*: Before undertaking trials in children the investigator must ensure that –a) children will not be involved in research that could be carried out equally well with adults; b) the purpose of the research is to obtain knowledge relevant to health needs of children. For clinical evaluation of a new drug the study in children should always be carried out after the phase III clinical trials in adults. It can be studied earlier only if the drug has a therapeutic value in a primary disease of the children; c) a parent or legal guardian of each child has given proxy consent; d) the assent of the child should be obtained to the extent of the child's capabilities such as in the case of mature minors from the age of seven years up to the age of 18 years; e) research should be conducted in settings in which the child and parent can obtain adequate medical and psychological support; f) interventions intended to provide direct diagnostic, therapeutic or preventive benefit for the individual child participant must be justified in relation to anticipated risks involved in the study and anticipated benefits to society; g) the

child's refusal to participate in research must always be respected unless there is no medically acceptable alternative to the therapy provided/ tested, provided the consent has been obtained from parents / guardian; h) interventions that are intended to provide therapeutic benefit are likely to be at least as advantageous to the individual child participant as any available alternative interventions; i) the risk presented by interventions not intended to benefit the individual child participant is low when compared to the importance of the knowledge that is to be gained."

Good Clinical Practices for Clinical Research in India

Good Clinical Practice (GCP) guidelines for biomedical studies in India[22] were developed keeping in mind the need for specific guidelines to encompass the design, conduct, termination, audit, analysis, reporting and documentation of the studies involving human subjects in India to ensure uniform quality of clinical research throughout the country and to generate data for registration for new drugs before use in the Indian population. The Indian adaptation of GCP also aims to ensure that the studies are scientifically authentic and that the clinical properties of the investigational product are properly documented. It incorporates essential elements of Schedule Y as well as the ethical principles enumerated in the Declaration of Helsinki and the ICMR ethical guidelines.

Other Requirements

Regulations for export of biological materials are laid down by the Director General of Foreign Trade (http://dgftcom.nic.in/) and the material transfer agreement of the ICMR (http://www.icmr.nic.in/min.htm). All internationally funded research needs approval by the Health Minister's Screening Committee (HMSC; http://www.icmr.nic.in/icmrnews/OM_IHD.pdf); this is to screen such research for potential violations of national security and intellectual property rights. Additional guidance for international research collaborations can be obtained from http://www.icmr.nic.in/guide.htm.

5. Prospective Registration of Clinical Trials

The need for prospective registration of clinical trials

The World Health Organization and the International Committee of Medical Journal Editors (ICMJE) consider the prospective registration of clinical trials before enrollment of the first participant an ethical and scientific imperative.[60-63] There are many benefits that accrue from prospective registration of clinical trials. These include:

- *Preventing publication bias:* For clinical decisions to be adequately guided by reliable evidence, data from all clinical trials need to be available, not only data from trials that were written up and submitted for publication, or those that journal editors decided to publish (usually because the results were interesting, though not necessarily complete). [64, 65]
- *Preventing selective reporting*: Many high-profile examples of selective reporting (for example, failure to report all adverse events).[66] The results of empirical research demonstrating both the existence of publication bias and discrepancies in reporting outcomes between trial protocols and published reports. [67] led to calls for prospective registration of clinical trials and publication of detailed clinical trial protocols.[60-63] While the Ottawa Statement[68] calls for

registration of the complete trial protocol as well as any amendments, the WHO and ICMJE requirements currently stop short of this. The WHO 20-item Registration Data Set[69] is considered the minimum information required to be able to identify a trial and disclose crucial details of its objectives and methods, outcomes and funding sources.

- *Ethical imperative*: However, the fundamental and overarching reason to prospectively register trials and disclose important details is the ethical obligation to trial participants, who are subjected to potential personal risks in exchange for the accumulation of public scientific knowledge. If the existence of a clinical trial and its results remain unknown to anyone but the trial investigators then it could be argued that the trial is unethical.[70]
- *Recruiting participants*: Trials registers are also used by patients and healthcare providers to identify clinical trials they may wish to participate in.
- *Guiding evidence-based healthcare decisions*: They have other potential uses for policy-makers and funding agencies in research priority setting, resource utilization and capacity building for research, as well as for everyone involved in informed healthcare decision-making.[71]

There has been universal support among clinicians, researchers and consumer groups regarding prospective registration of trials, and prospective registration of clinical trials in a publically accessible database was specifically mentioned in clause 19 of the latest revision of the Declaration of Helsinki as an ethical imperative. However, dissenting voices from within the pharmaceutical industry continue to be heard. [72, 73]

The WHO International Clinical Trial Registry Platform and Search Portal

The WHO ICTRP was established under the authority of the call from the Ministerial Summit on Health Research (http://www.who.int/entity/rpc/summit) that took place in Mexico City, Mexico, in November 2004, and the subsequent resolution at the 58th World Health Assembly (Resolution WHA58.34; http://www.who.int/gb/ebwha/pdf_files/WHA58/WHA58_34-en.pdf). The main aim of the WHO ICTRP is to facilitate the universal prospective registration and the public accessibility of the WHO Trial Registration Data Set (http://www.who.int/entity/ictrp/network/trds/en/index.html) for all clinical trials.

There are 10 national or international registers that are currently listed as Primary Registers of the WHO ICTRP that meet specific criteria for content, quality and validity, accessibility, unique identification, technical capacity and administration (http://www.who.int/ictrp/network/primary/en/index.html; accessed October 15,

2009). WHO Primary Registries meet the requirements of the ICMJE. In addition, four registries that do not either have a national or regional remit or the support of government, or are managed by a not-for-profit agency, or are not open to all prospective registrants are listed as WHO Partner Registries (http://www.who.int/ictrp/network/partner/en/index.html; accessed October 15, 2009), but these do not meet the ICMJE requirements.

The ICTRP Trials Search Portal (http://www.who.int/trialsearch/; accessed October 12, 2009) aims to provide a single point of access to information about ongoing and completed clinical trials. It provides a searchable central database containing the trial registration data sets made available by data providers (currently the 10 Primary Registries) around the world meeting criteria for content and quality control. Many multinational, multicentre trials are registered in more than one registry. To aid in the unambiguous identification of trials, the ICTRP Search Portal matches the main trial identifiers to secondary trial identifiers found in trial records to identify and group the same trial record in different registers. Additionally, when a unique number, called a Universal Trial Number (UTN) is uniformly implemented, this will enable the global research and

publishing community to identify studies with reasonable confidence. (http://www.who.int/ictrp/unambiguous_identification/en/index.html).

The WHO ICTRP Search Portal and Clinical Trials in Children

The WHO ICTRP Search Portal has a search filter that enables the identification of clinical trials recruiting children (http://www.who.int/ictrp/child/en/index.html) that aims to improve awareness and make it easier to access accurate, up to date, understandable information relevant to the conduct of clinical trials in children. This will contribute to addressing the Millennium Development Goal of reducing child mortality. This two stage search filter was developed using relevant pediatric lexicon and associated synonyms in the Unified Medical Language System (UMLS) meta-thesaurus has been pilot tested but further work to determine the sensitivity and specificity of the filter.

6. The Clinical Trials Registry- India

The Clinical Trials Registry–India (CTRI; http://www.ctri.in) was launched at the National Institute of Medical Statistics, New Delhi, on 20 July 2007. The CTRI is a Primary Register of the WHO ICTRP and fulfils the requirements of the ICMJE. The CTRI is managed by a team based at the National Institute of Medical Statistics, New Delhi that is supported by the ICMR. Funding for the CTRI is from the Department of Science and Technology, the Indian Council of Medical Research and the World Health Organization- India Country Office.

The evolution of CTRI, the data-elements required for registration and the rationale for these particular data-elements of the CTRI that were chosen in keeping with its mission and vision, the activities that followed its launch, and a progress report of the CTRI were published in 2009.[74] Reproduced herein are some issues relevant to this report.

The mission and vision of the CTRI

From the outset it was thought important to utilize the opportunity of designing the CTRI to achieve more than compliance with international requirements for transparency in clinical research. The results of a survey undertaken to evaluate

editorial policies in Indian medical journals that facilitate better reporting of measures that improve internal validity, transparency and ethical conduct of randomized trials; and that also evaluated the quality of reporting of randomized trials in Indian medical journals found that only a third of medical journal policies endorsed reporting standards such as CONSORT in reporting trials and suggested that the deficiencies in reporting the results of clinical trials in Indian medical journals could be due to poor understanding of the importance of complete reporting of elements of trial design pertaining to minimizing bias and improving internal validity.[75] Equally possible was the notion that poor reporting could be due to poor study design. Also worrying was the poor reporting of ethical safeguards, funding sources and conflicts of interest.

The implications of these findings on reporting of trials in Indian journals have a direct bearing on evidence–informed health care in India. Systematic reviews of good quality RCTs form the highest level of evidence for the effects of interventions in healthcare. Inclusion of trials of good quality from resource-constrained settings such as India would help in generalizing the results of systematic reviews to healthcare in these settings. Publishing trials of poor quality could lead to erroneous results, if included in systematic reviews, or their exclusion from such reviews with the resultant lack of relevance of the results to

local clinical practice. Recent controversies regarding the ethical conduct of trials in India also mandated that trial reports are transparent about the ethical safeguards employed, sources of funding and conflicts of interest.[17]

Improving the quality of conduct and reporting of locally relevant research in order to generate reliable evidence that would enable the appropriate use of scarce resources, especially in resource-constrained settings such as India, and to better safeguard participants, was considered a necessary role for the CTRI. Hence, separate mission and vision statements were developed to reflect its scope (Table 1).

Table 1: Mission and Vision of the Clinical Trials Registry-India (CTRI)

Mission
To encourage all clinical trials conducted in India to be prospectively registered before the enrolment of the first participant and to disclose details of the 20 mandatory items of the WHO International Clinical Trials Registry Platform (ICTRP) dataset.

Vision

1. To improve transparency and accountability by encouraging full disclosure
2. To improve the internal validity of trials conducted in India by facilitating reporting of details of the method of random sequence generation, concealment of allocation of participants to interventions, and blinding of participants, investigators and outcome assessors.
3. To conform to accepted ethical standards by disclosing contact details of ethics committee (s) granting approval and providing approval document(s).
4. To facilitate reporting of all relevant results of all clinical trials in India and the region by working with the WHO ICTRP

The data elements in the CTRI

As a Primary Register of the WHO ICTRP, the CTRI is expected to, and does, require as mandatory, full disclosure at the time of registration of the WHO and ICMJE 20 item data-set. There are additional items required by the CTRI, some of which are mandatory if trial registration is to proceed to completion.

While the WHO ICTRP recognizes that prospective registration of clinical trials is an ethical and scientific imperative, the current 20-item dataset does not include

disclosure of ethics committee approval. In fact, the original item 11 titled *Research Ethics Review* was replaced by *Countries of Recruitment* as this was thought to provide more relevant information and because ethics review was considered already mandatory for clinical trials. While the latter may be true for clinical trials done in many parts of the world, the same cannot be assumed for all clinical trials done in India. One of the mandatory CTRI-specific data elements requires the names of all ethics committees from whom approval has been sought to be disclosed, the approval status at the time of registration, and a copy of the approval letter(s), when available (Table 2). The register also seeks disclosure of clearance from the Drug Controller General of India (for trials that require this) and a copy of the clearance letter. This information is being collected as a pre-requisite for registration in the hope that mandatory disclosure of the specific ethics committee that cleared the trial as well as proof of this approval may lead to more responsible conduct and supervision of the trial.[75]

Notwithstanding the attention that industry-sponsored trials receive, it is less often appreciated that numerous clinical trials of drugs, psychological interventions, devices and surgery are done every year in medical colleges and other institutions and non-governmental organizations, often with insufficient

ethical oversight or even valid research designs. These trials are often not reported once the requirements of theses submissions or conference attendance are fulfilled. Those that do make it to publication often reveal important deficiencies in reporting requirements that are likely to have been the result of poor trial design, and journal editorial policy and peer review do not necessarily prevent these trials of doubtful validity from achieving the perceived sanctity of published truth.[75]

Attempts to comply with CONSORT requirements (even if mandated by editorial policy of journals), at the time of reporting results may be too late, as these elements need to be considered when trials are designed. Recruiting participants in clinical trials that are likely to produce unreliable results is unethical even if the trials are prospectively registered. In an attempt to use prospective trials registration to drive better design and reporting of clinical trials conducted in India, the CTRI data set includes three items pertaining to internal validity that do not form part of the 20-item WHO Registration Data Set. Registrants are requested (though not mandated as yet) to describe the method used for generation of the random sequence, method used to conceal allocation to interventions, and exactly who will be blinded to interventions (Table 2). The drop down menu of options and a downloadable explanatory document provide

educational opportunities to help prospective trialists improve the design of the trial at the stage of registration and consequently improve the reliability of the trial's results.[70, 75-78]

Table 2: Data elements specific to the Clinical Trials Registry-India (CTRI)

Item	Rationale
Principal investigator or overall trial coordinator (multi-centre study) name and contact details	To improve transparency and accountability
Site/s of study	To improve transparency and accountability and to identify sites where trials are being conducted in order to facilitate ethical oversight
Name of ethics committee and approval status†	**To improve transparency and accountability and to facilitate ethical oversight**
Regulatory clearance	**Regulatory requirement; will improve**

obtained from the Drug Controller General of India†	**transparency and accountability and facilitate ethical oversight**
Brief summary	To improve transparency
Method of generating randomization sequence	To reduce risk of bias in trial design and improve transparency
Method of allocation concealment	To reduce risk of bias in trial design and improve transparency
Blinding and masking	To reduce risk of bias in trial design and improve transparency
Phase of trial†	**To improve transparency**
Estimated duration of trial	To improve transparency

† Mandatory CTRI items required for registration to proceed to completion

That this strategy appears to be working was apparent from the survey of trials registered on the CTRI that was conducted in January 2009.[74] Items pertaining to

internal validity were meaningfully reported in over 75% of trial protocols as opposed to less than 25% of published trial reports.[75]

The current status of trials registration on the CTRI

Even though the CTRI was launched in July 2007, technical difficulties delayed the commencement of registration. The first trial was registered on 29 August 2007. Trial registration was initially slow and by 31 March 2008 only 29 trials had been fully registered.[79] However, by 10 January 2009, 155 trials had been registered of which 144 trials met the registry's requirements and were assigned full registration numbers, while 11 were assigned temporary or provisional registration numbers. Of the 144 fully registered trials, 12 (7.7%) were registered in 2007, 137 (88.4%) in 2008 and 6 (3.9%) in the first 10 days of 2009.[74]

Mandatory registration of clinical trials in India

Since November 2008, the Drug Controller General of India (DCGI) has required all new drug approvals to register details of the trial in the Clinical Trials registry-India, but from June 15, 2009 the DCGI has made this mandatory for all new drug applications before recruitment of the first participant.[80] The number of trials registered in the CTRI since this announcement has increased dramatically and as of September 15, 2009, the number of trials registered in the CTRI stands at 475.

Since January 1st 2009, 298 trials have been registered of which 159 (64%) occurred since July 2009. (Table 3)

Table 3: Registration of trials in the Clinical Trials Registry: India

August 2007 to Sept. 15, 2009

All Trials N	2007 N (%)	2008 N (%)	2009 N (%)
475	32 (6.7)	145 (30.5)	298 (62.7)
Industry funded **N**	**2007** **N (%)**	**2008** **N (%)**	**2009** **N (%)**
338	19 (5.7)	71 (21)	248 (73.3)
Recruiting children	**2007** **N (%)**	**2008** **N (%)**	**2009** **N (%)**
Stated	3 (9.4)	25 (17.3)	27 (9.0)
Unclear	11 (34.4)	39 (26.9)	85 (28.5)

It is apparent that the number of industry funded trials has increased as a proportion of all registered trials and they now comprise 71% of all registered trials on the CTRI, with the most dramatic increase occurring in 2009.

Registering clinical trials recruiting children

Of the 475 trials registered in the CTRI, 57 (11.6%) were reported to be recruiting children; 38 (8%) recruited only children, 17 (3.6%) recruited adults and children and in 135 (28.4%) it was unclear whether children were being recruited (Table 3). Since the field for disclosing participant details in the CTRI is a free-text field, the onus is on registrants to disclose the age of participants; many records do not clarify the age groups or age ranges of prospective trial recruits.

As of July 2008, 12300 (18%) of all 68849 trials registered on the WHO Clinical Trials Search Portal were reportedly recruiting children.[81] It is unclear whether the proportions shown on the CTRI are a true reflection of the total number of registered trials that are recruiting children, let alone the total number of trials being conducted in India that are recruiting children.

7. Strategies to increase the registration of clinical trials in the Clinical Trials Registry- India

General strategy

It will be readily apparent that any strategy that hopes to increase the number of trials that are recruiting children will have to improve the overall registration of clinical trials. One reason for this is that many trials include adults as well as children. The other is that trials registration should never be seen as an end in itself but only as a means to improve the overall scientific and ethical conduct of clinical trials in order to provide meaningful information that can be used to inform health outcomes. The latter is the position that was taken by the CTRI when its mission and vision were being framed. Hence this section will discuss the general strategies to increase the prospective registration of clinical trials being conducted in India and also separate those elements of the strategy that will focus on increasing registration of trials recruiting children. It will also outline strategies that will facilitate the better design, conduct and reporting of these trials in order to ensure that those trials that are registered are also designed in a manner that will increase the chances of the trials producing valid results. An important element in this approach is that it could result in this endeavor to

ensure that all trials are prospectively registered being perceived as facilitatory, rather than purely regulatory.

Strategy 1: Establishing a baseline number of clinical trials conducted in the country and the proportion recruiting children

The most difficult aspect of any strategy to monitor improvements in prospective trials registration is to obtain an accurate baseline of the trials being conducted in India. While most trials being conducted in the country are funded by industry, the proportion of trials that are investigator driven and funded by local sources or other funding agencies is unclear as there is no single source from which this can be ascertained. The second problem is to be able to ascertain accurately whether these trials plan to recruit children. These two problems require parallel strategies.

A. Estimating the baseline number of all trials being conducted in India

1. Industry funded trials

The Central Drugs Standard Control Organization (CDSCO) (http://cdsco.nic.in/) is responsible for standards for drugs, devices, cosmetics and diagnostics, as well

as enforcing regulations and regulating clinical research, among other things, at a national level. The Head of CDSCO is the DCGI, or Drugs Controller General of India. In many cases, DCGI, or Office of the DCGI, is used when referring to the authority and/or roles and responsibilities of the overall organization. This organization is now headquartered at the Food and Drug Administration Building in New Delhi.

All applications for new drugs to be marketed in India or marketed drugs to be used for new indications, require to be approved by the office of the DCGI that has prescribed formats for approval of clinical trials under Section Y of the Drugs and Cosmetics Act.[58]

An interview with a senior member of the office of the DCGI revealed that in 2008, 16,945 applications concerning drugs, devices and vaccines were processed by the DCGI's office. From January to June 2009, 11061 applications had been processed. Not all of these were trials, though the office has access to the number the actual number of applications for clinical trials. However, this is not publically available due to reasons of confidentiality.

The officer clarified that with the prospective registration of clinical trials being made mandatory by the DCGI, all industry funded trials of new drugs or drugs with new applications that have commercial possibilities are likely to be

registered. While there is no official mechanism to ensure this, the current practice is that once approval has been granted with the proviso that registration in CTRI was mandatory before commencement of recruitment, any further correspondence required the registration number of the trial on the CTRI. While it needs to be determined whether all such industry approved trials are indeed registered in the CTRI, it is likely that the vast majority will now be prospectively registered; since drug approvals are expensive, non-compliance is likely to be expensive and not worth the omission or commission .

Option 1

One option worth considering to ensure that all trials approved by the DCGI are registered on the CTRI is to depute a person to follow up actively the DCGI approved trials to see if they are registered, and that what is registered is what was approved, though this may occur at variable periods after DCGI approval is granted. The DCGI's office currently does not have the staff to do this. This will require paying for the salary of a person that is acceptable to the DCGI and working out the complexities of where he/she will be stationed and how they will gain access to the DCGI's register of approved proposals that is currently not in the public domain etc.

Likelihood of success: Moderate

Likelihood of providing required information: Very High

Importance to the endeavor to increase registration of pediatric trials: Important

Non-industry funded trials

The mandatory registration of clinical trials by order of the DCGI does not extend to trials that are not seeking DCGI approval, as the DCGI has no jurisdiction over such trials. This exemption includes all drug trials involving drugs already marketed and not being evaluated for new indications; all non-pharmaceutical trials; and trials of many types of devices and biologicals. Getting an accurate denominator of the number of such trials being conducted will be more difficult due to the absence of a register of such trials or a central regulatory authority providing funding or granting approvals. This requires an accurate mapping of institutions and organizations that are conducting trials that is currently not available at the moment.

Identifying all medical colleges and research institutions in the country that are conducting trials and get a list of ongoing trials from the head of the organization are options to be considered. The former list can be readily obtained from the website of the Medical Council of India (MCI) (www.mciindia.org). As of 15 October 2009, there are 4552 medical colleges in the country listed on the MCI

website, out of which 3361 are recognized as fulfilling MCI requirements. The proportion involved in research and in clinical trials is not clear.

The list of non-governmental agencies will be more difficult to obtain as many non-governmental agencies are involved in trials but the exact number and the proportion of these against the overall number of trials with health related outcomes being conducted in the country are uncertain.

Option 2:

Through the ICMR, a survey of medical colleges could be undertaken to ascertain the number of institutions undertaking trials in children.

Likelihood of success: Low (response rate likely to be low)

Likelihood of providing required information: Moderate (will not identify other types of institutions conducting trials with health related outcomes)

Importance to the endeavor to increase registration of pediatric trials: Important

B. Identifying the proportion of trials in India recruiting children registered on the CTRI

The limitations of searching CTRI to ascertain the number of trials registering children have been described in the previous section of this report. The WHO ICTRP Search Portal's filter to identify clinical trials in children provides an

opportunity to fill this lacuna. Using the filter on the Search Portal to identify only trials in children and limiting the search to the field 'Countries of Recruitment' to India ,however, reveals many records where the age of participants to be recruited is stated as from 18 years and above.

Option 3

The limitations of the CTRI and the WHO ICTRP Search Portal's filter for clinical trials in children suggest that:

A) The filter in the WHO ICTRP Search Portal to identify clinical trials in children needs to be modified to search for trials where recruitment is below 18 years by modifying the search terms to avoid the number 18 as this is possibly the reason why trials that specify 18 years and above in the CTRI free text field are identified and misclassified as trials in children.

B) Coupled with this, the CTRI also needs to be modified to add fields for age of participants as an extension of the WHO 20-item dataset for inclusion and exclusion criteria and provide a drop down list of age bands that will enable better identification of trials recruiting children. The CTRI is currently planning to revise its software programme for the registry and in November / December will appoint a vendor to provide solutions to the lacunae in the current registry

process and this child-specific modification could easily be included in the revision process.

Likelihood of success: High

Likelihood of providing required information: Very High

Importance to the endeavor to increase registration of pediatric trials: Important

C. Identify ongoing clinical trials in India that are recruiting children through members of the Indian Academy of Pediatrics

The Indian Academy of Pediatrics (www.iapindia.org) is the official organization of pediatricians in India and has been in existence for the past 45 years. It is actively involved in Continuing Medical Education programmes and hosts an annual conference for its members called 'Pedicon.' It has 16053 registered members and a survey among them could identify those participating in clinical trials sponsored by pharmaceutical companies or non-industry trials. However, the response rate in surveys conducted in the country thus have not been very encouraging with response rates ranging from 10%-30% so this might not yield the comprehensive information that we seek.

Option 4: Conduct a survey among members of the Indian Academy of Pediatrics to ascertain the number of ongoing trials recruiting children in India

Likelihood of success: Low

Likelihood of providing required information: Moderate

Importance to the endeavor to increase registration of pediatric trials: Important

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Strategy 2: Legislative approaches to increasing the number of trials registered in the CTRI, especially ones recruiting children

The DCGIs directive for mandatory registration of trials approved by the Office of the DCGI does not carry with it any legal provisions to deal with non-compliance other than refusal of permission to commercially market the drug or device.

1. New Legislative approaches:

Other pending legislative steps are detailed below:

a) Drugs and Cosmetics (Amendment) Bill, 2007

The *Drugs and Cosmetics (Amendment) Bill, 2007* was introduced in the Rajya Sabha (the Council of States in the Indian Parliament) on 21 Aug 2007 and submitted to the Standing Committee on Health and Family Welfare on 23 Aug 2007 for review and recommendations.

The Standing Committee Report (http://prsindia.org/docs/bills/), which includes review comments as well as recommendations for changes, was approved and released to Parliament on 21 Oct 2008.

This Bill amends the *Drugs & Cosmetics Act and Rules, as Amended up to the 30th of June, 2005*[58] in several key areas.

This Amendment:

- Calls for the creation of a Central Drugs Authority (CDA) with the authority to issue licenses for the manufacturing, distribution, sale, and import and export of drugs and cosmetics at a national level, separate and apart from CDSCO, and with authority over Ayurvedic, Siddha or Unani drugs as well. In addition, the CDA, among other responsibilities, would recommend to the Central Government measures to regulate clinical trials.
- Expands the definition of "drug" to include medical devices.
- Adds and defines "clinical trial" as "systematic study of any drug or cosmetic in human subjects to generate data for discovering or verifying it's clinical, pharmacological (including pharmacodynamic and pharmacokinetic) or adverse effects with the objective of determining safety, efficacy or tolerance of the drug or the cosmetic."

The Amendment adds an entirely new chapter, Chapter IB to the *Drugs and Cosmetics Acts and Rules*, which addresses clinical trials. In particular, Section 5N states: "No person shall conduct clinical trials in respect of any drug or cosmetic except under, and in accordance with, the permission granted by the Central Drugs Authority."

Section 5O provides for punishments, including imprisonment and fines, for failure to comply with Section 5N, and Section 5Q allows the Central Government, with the help of the CDA, to makes rules for implementing the provisions of this new chapter.

The Standing Committee Report (http://prsindia.org/docs/bills/) recommendations for going forward with this Bill include the following:

6. Rather than create the Central Drugs Authority (a completely new government entity), expand the authority and role of CDSCO to encompass all that was to be addressed by the CDA.

7. Provide more applicable and appropriate guidance for medical devices. Do not group medical devices under the definition of drug as it pertains to the requirements for clinical trials.

8. Revise the definition of clinical trial to address "new drugs" and "dermatological" products, rather than "any drug or cosmetic".

Comment:

Since there is no timeline for enacting this amendment, it is unclear when it may come into effect. However, if it does come into effect, the punitive provisions in this amendment would considerably aid the DCGIs directive on mandatory prospective registration of clinical trials.

b) Clinical Establishments (Registration and Regulation) Bill, 2007

The *Clinical Establishments (Registration and Regulation) Bill, 2007* was introduced to the Lok Sabha (House of the People in Parliament) on 30 Aug 2007 and submitted to the Standing Committee on Health and Family Welfare on 28 Sep Aug 2007 for review and recommendations. A Legislative Brief on The Clinical Establishments (Registration and Regulation) Bill, 2007 dated 13 Nov 2007 is available from PRS Legislative Research (http://prsindia.org/docs/bills/). The Standing Committee Report, which includes review comments as well as recommendations for changes, was approved and released to Parliament on 24 Oct 2008.

The *Clinical Establishments Bill, 2007* implements a system of registration and regulation of clinical establishments and creates a new government entity, the National Council, to develop standards, to register and regulate clinical

establishments, and enforce requirements. While the provisions of this Bill do not directly implement requirements for registration of clinical trials, various news and journal articles have highlighted individuals from the Indian Council of Medical Research (ICMR) indicating that a bill pending in the Parliament would establish, in effect, a National Ethics Committee system, to develop standards, to register and regulate ethics committees, and enforce requirements. See *Biomedical Research on Human Participants (Promotion and Regulation) Bill 2007* in this report.

The *Standing Committee Report* (http://prsindia.org/docs/bills/) recommendations for going forward with this Bill include the following:

- Make this legislation applicable to research and development clinical establishments, including establishments conducting clinical trials, as well as "single doctor establishments".
- Do not exclude government (Army and other) clinical establishments.
- Encourage all States to adopt this Bill so that it will be reflected at a national level.
- Change the name of the Bill to *The Healthcare Establishments (Regulation and Registration) Act, 2007*

- Change the name of the National Council to the "National Council for Healthcare Establishments".

Comment:

One could anticipate the *Clinical Establishments Bill* stipulations regarding the authority of the National Council being used by the National Council to require a system of ethics committee approvals for clinical trials conducted at clinical establishments as part of the registration and regulation requirements for those clinical establishments. Going a step further, the National Council could even dictate specific requirements as part of the ethics committee approval requirements, including the prospective registration of clinical trials in CTRI or another public registry before approval is granted to conduct clinical trials in India. However, as with the previous bill, the date when this bill will be enacted is unclear.

c) Biomedical Research on Human Participants Bill, 2007

The *Biomedical Research on Human Participants (Promotion and Regulation) Bill, 2007* has a long history in India. Numerous news articles have addressed this bill over the course of four years, but it does not appear to have been introduced into Parliament as of this date. This bill is important, however, because if the

legislation is introduced, it will definitely impact registration requirements in India.

An article dated 28 Oct 2004 from the *Hindu Business Line* titled "Legislation soon to address 'patient safety' in research" quotes Dr. Vasantha Muthuswamy, Senior Deputy Director-General, Indian Council of Medical Research (ICMR) about the Bill: "Ethics committees would be made mandatory in organizations undertaking research on human subjects, be it for a herbal drug or an allopathic drug. The Bill also includes steps for prosecution, if the law is breached."

The bill which relies heavily on the "*Ethical guidelines for biomedical research on human subjects"* issued by the Indian Council of Medical Research (ICMR), aims to plug the holes and encompass all kinds of research on humans. This would include clinical trials - *both commercial and academic,* as well as the entire range of research, including genomics, gene mapping, foetal tissue transplant, and stem cell research.

The Bill proposes that the ethics committee of ICMR be designated as the national ethics committee, which will also be the technical adviser to the biomedical regulator. It also prescribes fines up to Rs 1 lakh and imprisonment of up to a year for norm violations.

A news item titled, "Medical ethics committees to be regulated" dated 21 Feb 2007 and is available on website of the news daily The Hindu (www.hinduonnet.com/). The article stated that, "The medical ethics committees of all institutions, which consider research trials involving human subjects for clearance, will be regulated by a National Ethics Committee once the Biomedical Research on Human Participants (Promotion and Regulation) Bill 2007 is passed in Parliament, according to Nandini Kumar, Deputy Director General of the Indian Council of Medical Research (ICMR). Once the Bill is legislated, it will pave way for the establishment of a National Ethics Committee, the authority empowered to register all the ethics committees, institutional and independent. The Central Ethics Committee of the ICMR would be advisory to such an authority."

Comment:

Based on the ICMR's involvement with the Clinical Trials Registry - India (CTRI), prospective registration of clinical trials in the CTRI will almost certainly be required, and extended to non-industry funded trials and ones not coming under the jurisdiction of the DCGI, once the legislation creating a National Ethics Committee with the ICMR as advisor is passed. However, as with the previous

two proposed legislative acts, the date of enactment, or whether it will be enacted at all, is uncertain.

Option 5

Lobby with parliamentarians to follow up on pending legislation

Likelihood of success: Uncertain

Likelihood of increasing the number of trials recruiting children that are registered in the CTRI: High

Importance to the endeavor to increase registration of pediatric trials: Important

2. Working within existing legislative frameworks

There is currently sufficient legislation in India to facilitate the prospective registration of clinical trials in India, though this currently extends only to industry-funded trials and others that require DCGI approval. Schedule Y of the Drugs and Cosmetics Act[58] requires researchers to abide by the World Medical Association's Declaration of Helsinki[19] and the ICMR's ethical guidelines for research.[21] Prospective trial registration was not an explicit requirement in the WMA Declaration and is still not in the ICMR guidelines.

The World Medical Association revised the Declaration of Helsinki on October 18th, 2008 at its General Assembly in Seoul, South Korea.[19] the WHO ICTRP had recommended that prospective trials registration be specifically mentioned as an

ethical imperative and this recommendation was incorporated in the 2008 revision. The home page of the WMA (http://www.wma.net/e/) states that "The current (2008) version is the only official one; all previous versions have been replaced and should not be used or cited except for historical purposes."

Of particular interest to the WHO International Clinical Trials Registry Platform and for this report are paragraphs 19 and 30:

"19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication."

Paragraph 19 is a significant change as it indicates that the World Medical Association believes that registration is mandatory in order to obtain ethics approval. This means that in some countries registration will become a legal requirement as the law compels researchers to obtain ethics approval, and in many countries ethics committees are required to comply with the Declaration of Helsinki.

To add to the moral and ethical duty to prospectively register clinical trials, at the steering group meeting of the CTRI in 2008 a proposal was made that the ICMR Bioethics guidelines should also specifically endorse registration of clinical trials in the CTRI. The reason for this endorsement to register in the CTRI even for multinational trials was two-fold: National registers are ideally placed to promote, identify and track clinical trials being conducted in a specific country, and are able to fully integrate into local ethics and regulatory processes thus ensuring complete and comprehensive registration of all trials conducted in their region of influence. Many multi-country trials registered in international registers in the home country of the sponsors do not provide details of the sites in India where trials are being conducted and reliance on only these registers will not permit opportunities for transparency and facilitation of ethical oversight.[71]

The draft for inclusion in the ICMR bioethics guidelines has been submitted to the ICMR and awaits action. The full draft of the proposed amendments that was submitted to the ICMR is available in Appendix: 2.

Since Schedule Y requires researchers to abide by the ICMR guidelines and the Declaration of Helsinki, regulators and ethics committees would then be obliged to support trial registration as a legal as well as an ethical requirement.

Option 6

Pursue the amendment to the ICMR bioethics guidelines to specifically include endorsement of prospective trials registration for all trials recruiting participants in India in the CTRI.

Likelihood of success: Very high

Likelihood of increasing the number of trials recruiting children that are registered in the CTRI: High (if coupled with endeavors to work with ethics committees)

Importance to the endeavor to increase registration of pediatric trials: Important

Strategy 3: Work with ethics committees and Institutional Review Boards in India to endorse prospective trials registration in the CTRI of all clinical trials that they approve.

Prospective registration of clinical trials is considered a scientific and ethical imperative for researchers and trial sponsors. Requiring prospective registration can also be considered an ethical imperative for ethics committees since safeguarding the rights of trial participants and weighing risks and benefits are cardinal obligations of any research ethics committee.[82]

People participate in trials for personal benefit but also for potential social benefit. Trial registration, by virtue of declaring the presence of a trial and declaring details of the trial protocol, can form the basis for further research. This indelible public record of a trial's existence is necessary as researchers or trial sponsors may seek to circumvent the ICMJE's requirement by publishing their results in journals not endorsing the ICMJE position; or not publishing any results. Registration can also inform future research subjects or patients, enlighten those who plan or fund new proposals; [82] and reduce duplication of effort and duplicate publication.

Access to a complete list of ongoing and planned trials is also important for those who search for all trials that are conducted (irrespective of publication status) on a particular topic to include in systematic reviews and meta-analyses.

These potential benefits of any trial are reasons for institutional ethics committees to balance against risks to trial participants, or lack of direct benefit from participation.[76]

However, endorsing prospective trials registration, though important in the context of this report, is not the only area that ethics committees and Institutional Review Boards in India require to be active in. They, as gatekeepers of the scientific and ethical aspects of all research under their purview, need to ensure that the protocols of all research that they evaluate have sufficient details in them to produce valid results, since attending to such details at the time of publication is likely to be insufficient.[75]

The Institutional Review Board of the Christian Medical College at Vellore has attempted to achieve these aims by revising the templates for protocol submission as design-specific protocols incorporating elements of reporting standards such as CONSORT for interventional studies, the STROBE document for observational studies, STAR-D and QUADASS for diagnostic test accuracy

protocols etc. The template for interventional studies also incorporates all the elements required by the CTRI for trials registration so that researchers need only cut and paste these elements during the registration process. The IRB of CMC also requires submission of the registration document in CTRI for recruitment to commence in any trial approved by it and ensures that this occurs.[75, 76]

To extend this to other ethics committees in India, a series of activities need to be planned to a) ascertain a complete or near complete list of ethics committees and Institutional Review Boards and Independent ethics committees in India, and b) include them in endeavors to improve the scientific merit of the trials they approve and their ethical conduct; and also endorse clinical trials registration as an activity within their remit.

A. Creating a complete list of ethics committees, Institutional Review Boards and Independent Ethics Committees in India

The ICMR's Bioethics initiative (http://icmr.nic.in/bioethics.htm) conducted a survey in conjunction with the WHO to evaluate the functioning of ethics committees in India. A list of ethics committees that were identified during this survey is available with the ICMR though this is not in the public domain. The ICMR also works closely with the Forum for Ethical Review Committees in the Asia Pacific (FERCAP) (http://www.fercapsidcer.org). Working with members of

the ICMR bioethics initiative and the WHO- India country office, a complete up to list of ethics committees that they had gathered can be ascertained.

This list can be supplemented and updated by contacting the Heads of Medical Colleges and independent research institutions gathered from the list maintained by the MCI and by searching the CTRI for addresses of institutional and other ethics committees from registered protocols and by searching the internet.

Option 7

Compile a complete list of Institutional Review Boards, Independent Ethics Committees and local research and ethics review committees with the help of the ICMR bioethics initiative.

Likelihood of success: High

Likelihood of increasing the number of trials recruiting children that are registered in the CTRI: High (if coupled with endeavors to work with ethics committees)

Importance to the endeavor to increase registration of pediatric trials: Important

B. Working with institutional review boards, independent ethics committees and local research and ethics review boards to improve their capacity for oversight and to endorse prospective trials registration

A yearly meeting of representatives from the above committees needs to be organized, in conjunction with the ICMR bioethics initiative and FERCAP, the CTRI, and the WHO-ICTRP to work towards facilitating improvement of their capacity to provide effective oversight of the research studies they approve and to endorse clinical trials registration.

As a first step, we plan to invite as many of them as can attend to the 8th Winter Symposium of the Christian Medical College (CMC), Vellore and the 3rd South Asian Regional Symposium on Evidence-Informed Healthcare organized by the Prof. BV Moses & ICMR Centre for Advanced research and Training in Evidence-Informed Healthcare to be held at CMC Vellore from January 11 to 14, 2009. On the 11th January, the plenary sessions will have presentations by the Secretary, Department of Health Research (who is also the Director General of the ICMR), the Drug Controller General of India, David Tovey, Editor in chief of the Cochrane Collaboration, by Members of the Equator Network and representatives of the WHO ICTRP. An afternoon workshop will have presentations and discussions by Dr. David Moher and Dr. Doug Altman on the role of CONSORT and other reporting guidelines in improving the reporting of trials and by An-Wen Chan on the Spirit initiative to improve the quality of protocols for clinical trials. The importance of prospective trials registration will also be stressed.

Representatives from FERCAP and the WHO ICTRP will also contribute to and lead the discussion that will hopefully see a plan of action to improve the protocol review process and a plan to ensure that clinical trials approved by them are registered in the CTRI before enrolment of the first participant.

Option 8

Hold an annual meeting of representatives from all identified ethics committees and review boards, starting with a workshop on January 11, 2009 at the 8th Winter symposium of the Christian Medical College, Vellore with representatives of the CONSORT working group, the Equator network, the Spirit initiative, the WHO-ICTRP and the CTRI to increase their oversight capacity for research approved by them, incorporate elements of good reporting standards in study protocols and to endorse prospective trials registration as a condition of ethics committee approval.

Likelihood of success: Very high

Likelihood of increasing the number of trials recruiting children that are registered in the CTRI: High

Importance to the endeavor to increase registration of pediatric trials: Important

Strategy 4: Work with editors of Indian Medical Journals to increase the proportion of journals that endorse prospective trials registration and enhance capacity to ensure use of the CONSORT and other reporting guidelines in manuscript submissions

As part of the strategies associated with the launch of the CTRI in July 2007, a meeting was held at the ICMR headquarters at New Delhi in October 2007 with the editors of biomedical journals of India to garner their support and commitment to the CTRI and make trial registration a prerequisite for considering a trial for publication in Indian journal. The results of the survey of editorial policy were presented and they were reminded of their editorial responsibilities that include safeguarding the rights of participants, establishing policies of submission, review and acceptance of manuscripts, and working towards improving the quality of the conduct and publication of research. This was followed by a meeting with medical journal editors at the All India Institute of Medical Sciences, New Delhi, organized by the editors of the National Medical Journal of India, and a workshop for editors during the 2nd South Asian Regional Symposium on Evidence-Informed Health Care organized by the South Asian Cochrane Network at the Christian Medical College, Vellore. [74]

In February, 2008, the first of a series of editorials appeared endorsing trials registration and signed by the editors of 12 leading Indian medical journals.[83] These editorials concluded with the statement that, "From January 2010 onwards, we will consider publication of a trial only if it has been registered prospectively if started in or after June 2008; trials undertaken before June 2008 need to be registered retrospectively."

The 11 participating journals are:

- Indian Journal of Medical Research
- Indian Journal of Cancer
- Indian Journal of Chest Diseases and Allied Sciences
- Indian Journal of Medical Sciences
- Indian Journal of Ophthalmology
- Indian Journal of Pediatrics
- Journal of Obstetrics and Gynecology of India
- Journal of Parasitic Diseases
- Journal of Postgraduate Medicine
- Journal of Vector Borne Diseases
- National Medical Journal of India

The 8th Winter symposium to be held at CMC Vellore in January 2009 provides an opportunity to invite the editors of Indian Medical Journals that publish trials to attend the workshop along with representatives of ethics committees and encourage other journal editors to endorse trials registration.

Option 9

Hold an annual meeting of editors of Indian Medical Journals that publish clinical trials, starting with a workshop on January 11, 2009 at the 8th Winter Symposium at the Christian Medical College, Vellore with representatives of the CONSORT working group, the Equator network, the Spirit initiative, the WHO-ICTRP and the CTRI, to shape editorial policies regarding submission of manuscripts to incorporate elements of good reporting standards in study reports, particularly CONSORT for reports of randomized controlled trials, to improve the peer review process, and to endorse prospective trials registration as a condition of submission of manuscripts for publication.

Likelihood of success: Very high

Likelihood of increasing the number of trials recruiting children that are registered in the CTRI: High

Importance to the endeavor to increase registration of pediatric trials: Important

In addition to this, to specifically increase prospective registration in the CTRI of the number of clinical trials recruiting children in India, a series of editorials or articles co-authored by leading paediatricians on the issues delineated herein regarding clinical trials in children could also influence the process of prospective registration in the CTRI of trials recruiting children in India. While the *Indian Journal of Pediatrics* is one of the 11 journals that have officially endorsed prospective trials registration as an editorial policy, the official journal of the Indian Academy of Paediatrics is the journal *Indian Pediatrics* that is yet to follow suit

Option 10

Author or co-authors editorials and other articles in Indian pediatric journals, particularly the official journal of the Indian Academy of Paediatrics, *Indian Pediatrics,* on the ethical and other issues pertaining to clinical trials in children and the need to prospectively register in the CTRI details of clinical trials recruiting children in India.

Likelihood of success: High

Likelihood of increasing the number of trials recruiting children that are registered in the CTRI: High

Importance to the endeavor to increase registration of pediatric trials: Important

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Strategy 5: Work with the Indian Pediatrics Association

The Indian Pediatrics Association has over 16,000 members and an active academic programme including the annual conference of paediatrics. Pedicon 2010 is due to be held at Hyderabad from January 7th to the 10th (http://www.pedicon2010.org/). Around 5000 delegates are expected to attend this event and a pre-conference workshop slot has been reserved by the organisers for the South Asian Cochrane Network on January 6th for a session on Evidence-based paediatrics that will be also used to endorse prospective trials registration. This opportunity could also be used to inset brochures/flyers in the conference bags of all delegates on the importance of prospective trials registration in the CTRI of all clinical trials recruiting children in India.

Option 11

Hold workshops annually targeted at pediatricians, starting with the 47th National Conference of the Indian Academy of Pediatrics, PEDICON 2010, to be held at

Hyderabad in January 2010, to raise awareness of the importance of prospectively registering clinical trials recruiting children in India in the CTRI.

Likelihood of success: High

Likelihood of increasing the number of trials recruiting children that are registered in the CTRI: Moderate to High

Importance to the endeavor to increase registration of pediatric trials: Important

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Strategy 6: With through the South Asian Cochrane Network

The South Asian Cochrane Network has 6 network sites in India. Apart from the co-ordinating site at CMC Vellore, one other site at the Tata Memorial Hospital, Mumbai, has a policy of requiring prospective clinical trials registration as a condition of approval by their Institutional Review Board. As part of the strategy to increase the number of trials recruiting children in India that are registered in the CTRI, a specific goal of the strategic plan of the South Asian Cochrane Network shall be the adoption of prospective trials registration as a policy by all the network sites in the country and a plan to influence other institutions and organizations in their sphere of influence to follow suit. This will be discussed at

the next steering group meeting of the South Asian Cochrane Network that will be held in Chennai on December 6, 2009.

Option 12

Incorporate prospective clinical trials registration as a specific strategy in the strategic plan of the South Asian Cochrane Network for 2009 to 2012 for all six network sites in India to implement in their own institutions and in other institutions and organizations in their spheres of influence.

Likelihood of success: High

Likelihood of increasing the number of trials recruiting children that are registered in the CTRI: Moderate to High

Importance to the endeavor to increase registration of pediatric trials: Important

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Strategy 7: Work with the media to highlight the importance of prospective clinical trials registration

A number of articles have appeared in the media already on clinical trials registration and the launch of the CTRI. Links need to be further established with the media to ensure that more people are aware of the importance of this initiative, particularly in connection with trials concerning children. A workshop for media in conjunction with the Winter Symposium to be held in January 2010

at CMC Vellore will continue with these efforts and also highlight the issues that arise when clinical trials recruit children.

Option 13

Organize workshops for media, starting with the 8th Winter symposium to be held at CMC Vellore in January 2010 to raise awareness of the importance of prospective clinical trials registration, particularly when trials recruit children.

Likelihood of success: Moderate

Likelihood of increasing the number of trials recruiting children that are registered in the CTRI: Uncertain

Importance to the endeavor to increase registration of pediatric trials: Moderate

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Strategy 8: Work with consumer groups

A useful strategy around the world to influence healthcare and shape health policy has been a strong consumer presence. However, there is a lack of influential consumer groups in India though this slowly changing. One strategy could be to identify and engage with consumer groups to help influence participants of clinical trials

Option 14

Organize workshops for media, starting with the 8th Winter symposium to be held at CMC Vellore in January 2010 to raise awareness of the importance of prospective clinical trials registration, particularly when trials recruit children.

Likelihood of success: Uncertain

Likelihood of increasing the number of trials recruiting children that are registered in the CTRI: Uncertain

Importance to the endeavor to increase registration of pediatric trials: Moderate

8. References

1. Concato J, Shah N, Horwitz R. Randomized controlled trial, observational studies and the hierarchy of research designs. *N Engl J Med* 2000;342:1887- 92.

2. Evans D. Hierarchy of evidence: a framework for ranking evidence evaluating healthcare interventions. *J Clin Nurs* 2003;12:77–84.

3. Schulz KF, Chalmers I, Hayes RJ, Altman D. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled clinical trials. *JAMA* 1995; 273:408-12.

4. Altman DG, Bland JM. How to randomise. *BMJ* 1999;319:703–4.

5. Hahné SJM, Charlett A, Purcell B, Samuelsson S, Camaroni I, Ehrhard I, et al. Effectiveness of antibiotics given before admission in reducing mortality from meningococcal disease: systematic review. *BMJ* 2006;332:1299-1303.

6. Harnden A, Ninis N, Thompson M, Perera R, Levin M, Mant D, Mayon-White R. Parenteral penicillin for children with meningococcal disease before hospital admission: case-control study. *BMJ* 2006;332:1295-8.

7. McCulloch P, Taylor I, Sasako M, Lovett B, Griffin D. Randomised trials in surgery: problems and possible solutions. *BMJ* 2002;324:1448–51.

8. Glasziou P, Chalmers I, Rawlins M, McCulloch P. When are randomised trials unnecessary? Picking signal from noise. *BMJ* 2007;334;349-51.

9. Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts. Treatments for myocardial infarction. J*AMA* 1992; 268:240-8.

10. Young C, Horton R. Putting clinical trials into context. *Lancet* 2005;366: 107-8.

11. Sackett DL, Strauss SE, Richardson WS, et al. *Evidence-based medicine: how to practice and teach EBM*. London: Churchill-Livingstone, 2000.

12. Begg CB, Cho MK, Eastwood S, Horton R, Moher D, Olkin I, Rennie D, et al. Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA* 1996;276:637-9.

13. Altman DG, Schulz KF, Moher D for the CONSORT Group. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001;134:663-94.

14. International Committee of Medical Journal Editors (ICMJE). *Uniform Requirements for Manuscripts Submitted to Biomedical Journals.* Available at *http://www.icmje.org* (accessed 28 December 2006).

15. Gulmezoglu A, Pang T, Horton R, Dickersin K. WHO facilitates international collaboration in setting standards for clinical trial registration. *Lancet* 2005; 365: 1829–31.

16. Tharyan P. The WHO International Clinical Trials Registry Platform and the Indian Clinical Trials Register. *Nat Med J India* 2006; 19: 161-4.

17. Tharyan P. Placebo controlled trials in psychiatry on trial. *Indian J Med Ethics* 2006; 1: 13-17.

18. World Health Organization. WHO-TDR. *Operational guidelines for ethic committees that review biomedical research.* Geneva: World Health Organization, 2000.

19. World Medical Association. Declaration of Helsinki. *Ethical Principles for Medical Research Involving Human Subjects.* Last revised October, 2008 Oct. Available at: http://www.wma.net/e/policy/b3.htm [accessed December 14, 2008].

20. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. *ICH Harmonised Tripartite Guidelines and Guidelines For Good Clinical Practice. E6(R1).* ICH Expert Working Group, 1996.

21. Indian Council of Medical Research. Ethical Guidelines for Biomedical Research on Human Participants. Indian Council of Medical Research. 2006. New Delhi. Available at: http://icmr.nic.in/ethical_guidelines.pdf. [Accessed August 13, 2008].

22. Ministry of Health and Family Welfare. *Good clinical practices for clinical research in India.* Schedule Y. New Delhi: Drug Technical Advisory Board, Ministry of Health and Family Welfare, 2005.

23. Mann H. The ASSERT statement: *A Standard for the Scientific and Ethical Review of Trials*. Available from www.assert-statement.org (accessed Feb 27, 2007).

24. Jüni P, Altman DG, Egger M. Assessing the quality of controlled clinical trials. *BMJ* 2001;323:42–6.

25. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.5 [updated May 2005]. In: The Cochrane Library, Issue 3, Chichester, UK: John Wiley & Sons, Ltd., 2005.

26. Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in metaanalyses? *Lancet* 1998;352:609-13.

27. Jadad AR. *Randomised Controlled Trials: A User's Guide.* London: BMJ Books, 1998.

28. Devereaux PJ, Manns BJ, GhaliWA, Quan H, Lacchetti C, Mouton VM, et al. Physician interpretations and textbook definitions of blinding terminology in randomized controlled trials. *JAMA* 2001;285:2000-3.

29. Montori, VM, Devereaux PJ, Adhikari NKJ, Burns KEA, Eggert CH, Briel M et al. Randomized trials stopped early for benefit. A systematic review. *JAMA* 2005;294:2203-9.

30. Divine GW, Brown JT, Frazer LM. The unit analysis error in studies about physicians' patient care behavior. *J Gen Int Med* 1992;7:623-9.

31. Bland JM, Kerry SM. Trials randomised in clusters. *BMJ* 1997;315:600.

32. Montgomery AA, Peters TJ, Little P. Design, analysis and presentation of factorial randomized controlled trials. *BMC Med Res Methodology* 2003; 3:26 (available from http://www.biomedcentral.com/1471-2288/3/26).

33. Gøtzsche PC. Lessons from and cautions about non-inferiority and equivalence randomized trials. *JAMA* 2006;295:1172-1174.

34. Campbell MJ. Extending CONSORT to include cluster trials. *BMJ* 2004;328:654–5

35. Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJW. CONSORT Group, Reporting of non-inferiority and equivalence randomized trials: an extension of the CONSORT statement. *JAMA* 2006; 295:1152-1160.

36. Godwin M, Ruhland L, Casson I, MacDonald S, Delva D, Birtwhistle R, et al. Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity. *BMC Med Res Methodology* 2003;3:28. Available from: http://www.biomedcentral.com/1471-2288/3/28. (Accessed January 1, 2007).

37. Mulrow CD. Systematic reviews: rationale for systematic reviews. *BMJ* 1994;309:597–9.

38. Pai M, McCulloch M, Gorman JD, Pai N, Enanoria W, Kennedy G, Tharyan P, Colford JM. Systematic Reviews and meta-analysis: an illustrated step-by step guide. *Natl Med J India* 2004; 17: 86-95.

39. Sackett DL, Strauss SE, Richardson WS, et al. *Evidence-based medicine: how to practice and teach EBM.* London: Churchill-Livingstone, 2000.

40. Ofori-Adjei D, Antes G, Tharyan P, Slade E, Tamber PS. Have online international medical journals made local journals obsolete? *PLoS Med* 2006; 3(8): e359. DOI: 10.1371/journal.pmed.0030359.

41. Committee on Bioethics. Ethics and the care of critically ill infants and children. *Pediatrics* 1996; *98*: 149-52.

42. Morales-Olivas FJ, Morales-Carpi C. Clinical trials in children. *Rev Recent Clin Trials* 2006; 1:251-8.

43. Ernest TB, Elder DP, Martini LG, Roberts M, Ford JL. Developing pediatric medicines: identifying the needs and recognizing the challenges. *J Pharm Pharmacol*. 2007; 59:1043-55.

44. Sammons HM. Ethical considerations for clinical trials on medicinal products conducted in the pediatric population. Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use. http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10/ethical_considerations.pdf (accessed 14 October 2009).

45. Osborne JP, O'Callaghan FJ. Running an international pediatric non-commercial trial. *Arch Dis Child* 2009; 94:729-33

46. Burman WJ, Cotton MF, Gibb DM, Walker AS, Vernon AA, Donald PR. Ensuring the involvement of children in the evaluation of new tuberculosis treatment regimens. *PLoS Med* 2008; 5(8):e176.

47. Sammons H. Ethical issues of clinical trials in children: a European perspective. *Arch Dis Child* 2009; 94:474-77.

48. Flynn JT, Nahata MC, Mahan JD Jnr, et al. Population pharmacokinetics of amlodipine in hypertensive children and adolescents. *J Clin Pharmacol* 2006; 46:905–16.

49. van der Lee JH, Wesseling J, Tanck MW, Offringa M. Efficient ways exist to obtain the optimal sample size in clinical trials in rare diseases. *J Clin Epidemiol* 2008; 61:324-30.

50. Malhotra S, Subodh BN. Informed consent & ethical issues in pediatric psychopharmacology. *Indian J Med Res* 2009; 129: 19-32.

51. Shah S, Whittle A, Wilfond B, Gensler G, Wendler D. How do institutional review boards apply the federal risk and benefit standards for pediatric research? *JAMA* 2004; 291:476–82.

52. Wendler D, Jenkins T. Children's and their parents' views on facing research risks for the benefit of others. *Arch Pediatr Adolesc Med* 2008; 162:9–14.

53. Ondrusek N, Aramovitch R, Pencharz P, Koren G. Empirical examination of the ability of children to consent to clinical research. *J Med Ethics* 1998; 24:158–65.

54. Leiken S. Minors assent, consent, or dissent to medical research. *IRB Rev Hum Subj Res* 1993; *15* : 1-7.

55. Gross CP, Krumholz HM, Van Wye G, Emanuel EJ, and Wendler D, Does random treatment assignment cause harm to research participants? *PLoS Med* 2006;3(3):6.

56. Smith PB, Li JS, Murphy MD, Califf RM, Benjamin DK Jr. Safety of placebo controls in pediatric hypertension trials. *Hypertension* 2008; 51:829-33.

57. Bhat R. Regulating the private health care sector: the case of the Indian Consumer Protection Act. *Health Policy Plan* 1996; 11:265-79.

58. Government of India. Ministry of Health and Family Welfare. Drugs and Cosmetic Act and Rules. 1945. Available at: http://cdsco.nic.in/html/Drugs&CosmeticAct.pdf. [Accessed Jan 24, 2008].

59. Central Drugs Standards Control Organization. *The Drugs and Cosmetics (Amendment) Bill, 2007: Bill No. LVII of 2007. A Bill further to amend the Drugs*

and Cosmetics Act, 1940. New Delhi: Central Drugs Standards Control Organization, 2007.

60. World Health Organization. International Clinical Trial Registry Platform (ICTRP). World Health Organization, Geneva. Available at http://www.who.int/ictrp/en/ [Accessed 10 January 2009].

61. DeAngelis CD, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, *et al.* Clinical trial registration: A statement from the International Committee of Medical Journal Editors. *N Engl J Med* 2004; 351:1250–1.

62. De Angelis CD, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, *et al*. Is this clinical trial fully registered? A statement from the International Committee of Medical Journal Editors. *Lancet* 2005; 365:1827–9.

63. Laine C, Horton R, DeAngelis CD, Drazen JM, Frizelle FA, Godlee F, *et al.* Clinical trial registration: Looking back and moving ahead. *Lancet* 2007; 369:1909–11.

64. Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database of Systematic Reviews* 2009, Issue 1. Art. No.: MR000006. DOI: 10.1002/14651858.MR000006.pub3.

65. Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med* 2008; 358:252-60.

66. Al-Marzouki S, Roberts I, Marshall T, Evans S. The effect of scientific misconduct on the results of clinical trials: A Delphi survey. *Contemp Clin Trials* 2005; 26:331–7.

67. Chan AW, Hrobjartsson A, Haahr MT, Gotzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: Comparison of protocols to published articles. *JAMA* 2004;291:2457–65.

68. Krleza-Jeric K, Chan AW, Dickersin K, Sim I, Grimshaw J, Gluud C. Principles for international registration of protocol information and results from human trials of health related interventions: Ottawa statement (Part 1). *BMJ* 2005;330:956–8.

69. World Health Organization. International Clinical Trial Registry Platform (ICTRP). About Registries. WHO ICTRP Trial Registration Data Set. World Health Organization, Geneva. Available at: http://www.who.int/ictrp/network/trds/en/index.html. [Accessed 10 January 2009].

70. Tharyan P, Ghersi D. Registering clinical trials in India: a scientific and ethical imperative. *Natl Med J India* 2008; 21(1):31-4.

71. Grobler L, Siegfried N, Askie L, Hooft L, Tharyan P, Antes G. Are national and multinational prospective trial registers necessary? *The Lancet* 2008; 372: 1201–02.

72. Normile D. Clinical trial guidelines at odds with US policy. *Science* 2008 Oct 24; (322): 516. [cited 2008 Dec 14]. Available from www.sciencemag.org

73. Macklin R. The Declaration of Helsinki: another revision. *Indian J Med Ethics* 2009;6: 2-4.

74. Tharyan P. Prospective Registration of Clinical Trials in India: Strategies, Achievements & Challenges. *J Evid Based Med* 2009; 1: 19-28.

75. Tharyan P, Premkumar TS, Mathew V, Barnabas JP, Manuelraj. Editorial policy and the reporting of randomized controlled trials: survey of instructions to authors and assessment of quality of randomised controlled trials in Indian Medical Journals (2004-2005). *Natl Med J India* 2008; 21:62-68.

76. Tharyan P. Ethics committees and clinical trials registration in India: opportunities, obligations, challenges and solutions. *Indian J Med Ethics* 2007; 4: 168-69.

77. Grobler L, Siegfried N, Askie L, Hooft L, Tharyan P, Antes G. Are national and multinational prospective trial registers necessary? *The Lancet* 2008; 372: 1201-02.

78. Tharyan P. Clinical Trial Registration in India: no longer a dream. *Trop Gasteroenterol* 2008; 29: 1-3.

79. Pandey A, Aggarwal AR, Seth SD, Maulik M, Bano R, Juneja A. Clinical Trials Registry – India: Redefining the conduct of clinical trials. *Indian J Cancer* 2008; 45: 79-82.

80. Directorate General of Health Services. Office of Drugs Controller General (India). (New Drug Division). *Registration of Clinical Trial in ICMR Clinical Trial Registry (www.ctri.in)- Regarding.* F.No. 12-01/09-DC-(Pt-32). Available at: http://cdsco.nic.in/ [accessed September 12, 2009].

81. Wong J, Ghersi D. Accessing the evidence: a search portal and reference site for clinical trials in children. WHO ICTRP poster. Available from http://www.who.int/ictrp/child/en/ [accessed September 12, 2009].

82. Levin LA, Palmer JG. Institutional review boards should require clinical trial registration. *Arch Intern Med* 2007; 167:1576-80.

83. Satyanarayana K, Sharma A, Parikh P, Vijayan VK, Sahu DK, Nayak BK, Gulati RK, Parikh MN, Singh PP, Bavdekar SB, Sreehari U, Sahni P. Statement on publishing clinical trials in Indian biomedical journals. *Indian J Med Res* 2008; 127:104-5.

9. Appendix 1: Terms of Reference

These are the terms of reference for a sub-contract with the South Asian Cochrane Centre, India to increase the prospective registration of clinical trials in children conducted in India.

Principal Investigator: Professor Prathap Tharyan

Aim: To develop a strategy to increase the number of clinical trials that are recruiting children in India registered on the Clinical Trials Registry India (CTRI).

Deliverables:

- A documented 3 year strategy for increasing the number of clinical trials that are recruiting children in India that are registered:
    - On CTRI
    - On other WHO Primary Registries (i.e. on the ICTRP Search Portal)

The strategy will:

- Describe the oversight challenges related to the conduct of clinical trials in children in India

- Establish a baseline in terms of number of registered trials recruiting children in India, and information on the intention to collect pharmacokinetic data in those trials (where it is relevant)
- Include a plan for consulting the relevant stakeholders (including CTRI, the Indian Pediatric Society and the Drug Controller General)
- Include a plan for raising awareness among those responsible for the conduct of clinical trials in children in India of the scientific, ethical and moral responsibility to register clinical trials
- Include a design for a survey of those responsible for the conduct of clinical trials in children in India
- Include a plan for raising awareness among research ethics committees in India of the scientific, ethical and moral responsibility to register clinical trials
- Include a design for a survey of those responsible for the oversight of clinical trials in children: specifically research ethics committees
- A plan for implementation of the strategy over a 3 year period
- Following consultation with the ICTRP Secretariat, commence implementation of 1 or more of the activities suggested in the strategy.

10. Appendix 2

[AMENDMENT TO THE ICMR ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH ON HUMAN PARTICIPANTS]

[This a draft of the proposed amendment and subject to ratification and input from other members of the CTR-I steering group and the ICMR]

Prospective Registration of Clinical Trials

Prospective registration of clinical trials and disclosure of a 20-item dataset in a publically accessible database before enrolling the first participant is endorsed by the World Health Organization's International Clinical Trials Registry Platform (WHO-ICTRP; http://www.who.int/ictrp/en/) as a scientific and ethical imperative. The International Committee of Medical Journal Editors (ICMJE) has also endorsed this position as a pre-requisite to submission of manuscripts for publication, as have the editors of many Indian Journals. Clause 19 of the World Medical Association's (WMA) 2008 revision of the *Declaration of Helsinki* (adopted by the 59th WMA General Assembly, Seoul, on October 18, 2008) reads, "Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject".

Prospective registration of clinical trials will, by providing a public record of the existence of a trial, it's essential elements and key personnel, prevent selective reporting (for example failure to report all adverse events) of the results of a trial. It will also prevent publication bias and discrepancies in reporting outcomes between trial protocols and published reports. Trial registers are also used by patients and healthcare providers to identify clinical trials they may wish to

participate in. They have other potential uses for policy makers and funding agencies, in research priority setting, resource utilization and capacity building for research, as well as for everyone involved in the evidence-informed healthcare decision making process as they provide a summary of necessary evidence that would be missing if one were only to rely on published trial reports, since many trials are never published or only report selected outcomes.

Clinical Trials Registry-India

On 20 July 2007, the Clinical Trials Registry–India (CTRI; http://www.ctri.in) was launched at the National Institute of Medical Statistics, New Delhi. The CTRI is a Primary Register of the WHO-ICTRP set up to prospectively register all clinical interventional trials involving human participants conducted in India. Trials that are currently ongoing are also being temporarily registered in the CTRI (but this is likely to change in the future). All trials that are fully registered in the CTRI will also meet the registration requirements of the ICMJE.

Observational studies such as epidemiological studies, case series and case reports (unless involving a prospective intervention with ethics committee

approval), cross-sectional, case-control and cohort studies do not require registration in the CTRI.

In addition to the WHO and ICMJE's 20-item dataset, the CTRI will require additional items to be disclosed. These items have been selected in order to:

1. *Improve transparency and accountability*: By disclosing all required details of the protocol of trials, public confidence in clinical trials is likely to be enhanced.
2. *Improve the internal validity of trials:* Empirical research has shown that some aspect of the methods of the trial are particularly important to produce reliable results by minimizing biases, confounders and the effects of chance or coincidence. These include the method of random sequence generation, adequate concealment of allocation of participants to interventions, adequate blinding of participants, investigators and outcome assessors, and inclusion of all participants' results. The CTRI hopes that these items will be disclosed by all registrants, as incorporating such elements at the protocol stage is likely to increase the internal validity of the trial and also increase the chances of publication in a high impact journal that endorses the ICMJE requirement of reporting trials in accordance with the CONSORT statement.

3. *Conform to accepted ethical standards:* The ICMR ethical guidelines for the conduct of trials mandates that clearance by local ethics committees is mandatory for all clinical trials and the CTRI hopes that by making disclosure of ethical clearance a mandatory field for registration, it will lead to better links with the ICMR's and other international bio-ethics initiatives.
4. *Lead to reporting of all relevant results of all clinical trials in India:* The WHO-ICTRP is also working towards full reporting of all relevant results from clinical trials and the CTRI will work with the WHO-ICTRP to facilitate reporting of results of all trials registered with the CTRI.

The following additional requirements are thus made to the ICMR Ethical Guidelines for Biomedical Research on Human Participants, 2006 for all clinical trials on human participants conducted in India with immediate effect:

1. All interventional clinical trials conducted in India and involving Indian participants must be registered in the Clinical Trials Registry- India (www.ctri.in)
2. An interventional clinical trial is any research study that prospectively assigns people to one or more health-related interventions (e.g., preventive care, drugs, surgical procedures, behavioural treatments, etc.) to evaluate their effects on health-related outcomes. Thus, early and late trials (Phase I to IV), trials of

marketed or non-marketed products, uncontrolled or those with a control comparison, randomized or non-randomized trials -- all should be registered.

3. Trials should be registered before the enrolment of the first patient.
4. The "Responsible Registrant" for a trial is either the principal investigator (PI) or the primary sponsor, to be decided by an agreement between the parties. The primary sponsor is ultimately accountable for ensuring that the trial is properly registered. For multi-centre and multi-sponsor trials, it is the lead PI or lead sponsor who should take responsibility for registration.
5. All multi-country trials with Indian sites also need to be registered in the CTRI. However, in case of multi-country trials, the Indian PI (or sponsor) should also quote any other Registration number (e.g.: the clinicaltrials.gov registration number) as its Secondary ID in the CTRI.
6. Ethics committees should ensure that all trials approved by them are fully registered in the CTRI and permit recruitment of participants to commence only after receiving the CTRI registration document. The committee should ensure that there are no discrepancies in the approved protocol and the registration document.
7. Registrants are also required to regularly update information on each trial (including patient accrual, trial and publication status).

8. The items that are required to be disclosed by the WHO and the ICMJE are:

1) Registration Number;
2) Trial Registration Date
3) Public title of study
4) Scientific Title of Study (Give Trial Acronym, if any)
5) Secondary IDs, if any
6) Contact Person (Scientific Query)
7) Contact Person (Public Query)
8) Funding Source/s
9) Primary Sponsor
10) Secondary Sponsor
11) Date of first enrolment
12) Target sample size
13) Health Condition/Problem studied
14) Intervention and Comparator agent
15) Key inclusion/Exclusion Criteria
16) Primary Outcome/s
17) Secondary Outcome/s

18)Countries of Recruitment

19)Status of Trial

20) Study Type

9. In addition, the CTRI requires the following items to be disclosed:

1) Principal Investigator's Name and Address
2) Name of Ethics Committee and approval status (with a copy of the ethics approval)
3) Regulatory Clearance obtained from DCGI (if required)
4) Estimated duration of trial
5) Site/s of study
6) Phase of Trial
7) Method of generating randomization sequence
8) Method of allocation concealment
9) Blinding and masking
10) Brief Summary

10. Registration is free and all records in the CTRI are searchable free of charge. Explanations for all CTRI items are provided in a downloadable form for registrants to use and all entries in the registration form should provide sufficient and accurate details of the trial to ensure transparency and clarity.

11. After registration in the CTRI, all amendments to the protocol that alter disclosed items in the CTRI will also need to be amended by the responsible registrant after ethics committee approval of the protocol amendment. The CTRI will maintain a record of all amendments and the original entries (an audit trail).
12. Registrants are also expected to publish the results of their trial within a reasonable period after completion of the trial (2 years), and provide a link to the publication in the CTRI registration from for the trial. In the future, the CTRI will work with the WHO-ICTRP to facilitate reporting of results of all trials registered with the CTRI and provide space for the reporting of results, if this becomes a requirement of the WHO-ICTRP.

Bibliography:

1. Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, et al. The revised CONSORT statement for reporting randomized trials: Explanation and elaboration. Ann Intern Med 2001;134:663–94.
2. Chan AW, Hrobjartsson A, Haahr MT, Gotzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: Comparison ofprotocols to published articles. JAMA 2004;291:2457–65.

3. DeAngelis CD, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: A statement from the International Committee of Medical Journal Editors. N Engl J Med 2004;351:1250–1.
4. De Angelis CD, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Is this clinical trial fully registered? A statement from the International Committee of Medical Journal Editors. Lancet 2005;365:1827–9.
5. Evans T, Gulmezoglu M, Pang T. Registering clinical trials: An essential role for WHO. Lancet 2004;363:1413–14.
6. International Committee of Medical Journal Editors (ICMJE). Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Available at http://www.icmje.org/
7. Laine C, Horton R, DeAngelis CD, Drazen JM, Frizelle FA, Godlee F, et al. Clinical trial registration: Looking back and moving ahead. Lancet 2007;369:1909–11.
8. Satyanarayana K, Sharma A, Parikh P, Vijayan VK, Sahu DK, Nayak BK, Gulati RK, Parikh MN, Singh PP, Bavdekar SB, Sreehari U, Sahni P. Statement on publishing clinical trials in Indian biomedical journals. Indian J Med Res. 2008;127:104-5.

9. Tharyan P. Ethics committees and clinical trials registration in India: Opportunities, obligations, challenges and solutions. Indian J Med Ethics 2007;4:168–9.
10. Tharyan P, Ghersi D. Registering clinical trials in India: a scientific and ethical imperative. Natl Med J India. 2008 Jan-Feb;21(1):31-4.
11. World Health Organization. International Clinical Trials Registry Platform (ICTRP).List of Registers. Available from http://www.who.int/ictrp/network/list_registers/en/index.html
12. World Medical Association. Declaration of Helsinki. Ethical principles for medical research involving human subjects. Adopted by the WMA in 1964 and last amended on October 18, 2008. Available from: http://www.wma.net/e/policy/b3.htm

11. Appendix 3: Draft performa for surveying ethics committees regarding approval for trials recruiting children

In conjunction with the ICMR's bioethics initiative, a survey of ethics committees could be undertaken to ascertain the procedures they have in place for clinical trials that recruit children. This survey will complement the earlier ICMR-WHO survey of Institutional Ethics Committees.

ICMR-WHO Survey of ethics committees 2010

We request your participation in this survey sponsored by the Indian Council of Medical Research, the WHO project on Better Medicines for Children, The WHO International Clinical Trials Registry Platform, The Clinical trials-Registry- India, and the South Asian Cochrane Network & Centre to evaluate the functioning of ethics committees in India. We shall ensure that the results of this survey do not identify individuals or ethics committees by name.

Serial Number:

Name of ethics committee:

Address:

Chairperson name and contact address:

Name of person filling questionnaire:

Type of ethics committee: (select one)

1. Medical college
2. Research Institution
3. Independent ethics committee
4. Non-governmental organization
5. Other (specify)

Please answer each of the following questions by circling the response number that is applicable to the functioning of your ethics committee.

A. Prospective registration of clinical trials

1. Does your ethics committee require that all clinical trials approved by it be registered in a public clinical trials registry before enrolling the first participant? A) Yes; B) No (if no, go to question 6)
2. If yes to the above, does this apply to all clinical trials or only industry funded clinical trials? A) All trials, irrespective of funding source; B) only industry funded trials that require the approval of the Drug Controller General of India; C) All industry funded trials; D) Unsure

3. Do you require that the trial registration document be submitted to the ethics committee before the trial can commence? A) Yes; B) No; C) Unsure
4. Do you insist that trials be registered in the Clinical Trials Registry-India (CTRI) or can this be done in any publically accessible trials registry? A) In the CTRI; B) Any public trials registry C) Unsure
5. Do you know if all trials approved by your ethics committee are prospectively registered in the CTRI? A) Unsure; B) yes, all are; C) Most are (what proportion?);
6. Do you know if the Drug Controller General of India has made any statement regarding prospective registration of clinical trials? A) Unsure; B) No statement has been issued; C) Yes (please elaborate)

B. Study design

7. Is the form for submission of research proposals a generic one for all types of study designs or do you have specific formats for different types of study designs appropriate to the research question being asked? A) generic format for all submissions; B) Study specific formats; C) Unsure

8. Do you require all applicable elements of standard reporting guidelines such as the CONSORT statement are covered in the protocols for interventional studies? A) Yes; B) No; C) Unsure

C. Clinical trials in Children

9. What proportion of clinical trials that are approved annually recruit children (individuals below 18 years of age)? A) less than 5%; B) 5-10%; C) 10-20%; D) 20-50%; E) more than 50%; F) unsure

10. Are there specific provisions concerning consent from parents for trials recruiting children? A) Yes; B) No; C) Unsure

11. Are you aware of any ethical or legal requirements regarding obtaining consent in trials recruiting children? A) No; B) Yes (please describe which guidelines or laws your committee follows)

12. Is consent required from one parent or both parents? A) Either; B) Both; C) Other (please describe)

13. In case of disagreement between parents, do you have any provision to deal with this situation? A) No; B) Unsure; C) Yes (Please describe)

14. Is assent to participate required from the child? A) Yes, B) No; C) Unsure; D) Depends on the age of the child

15. If assent is sought, from what age of the child is this required? A) Not routinely sought; B) _____ Years; C) Unsure

16. Do you require written assent from the child? A) No; B) unsure; C) Yes (from what age?)_____Years
17. Do you have any special provisions for neonates? A) No; B) Unsure; C) Yes (Please describe)
18. Do you have any special provisions for obtaining assent or consent from adolescents (12 to 18 years)? A) No; B) Unsure; C) Yes (please describe
19. Do you have provisions for adolescents to participate in trials in spite of parental objections? A) No; B) Unsure; C)Yes (please describe)
20. If a child or adolescent does not assent to the trial but parental approval is obtained, are there guidelines that you follow to address this? A) Parental wishes are paramount; B) Child's wishes are respected; C) Unsure; D) Depends on the situation (please elaborate)
21. Do you require separate information sheets during the consent process for children and for parents, suitably translated into local languages? A) Unsure; B) separate sheets for parents and children; C) No separate information sheets for parents and children; D) Other (please describe)
22. Do you have any guidelines for consent in emergency pediatric trials? A) Unsure; B) No; C) Yes (Please describe)

23. Do you have a policy regarding recruiting healthy children in clinical trials? A) Unsure; B) No specific policy other than the merits of the trial; C) Yes (please describe)

D. Pharmacokinetic studies

24. Do you have any guidelines or policies regarding sample collection (number, timing, total amount; alternatives to blood samples) from children recruited to trials or research studies? A) Unsure; B) No; C) yes (please describe)

E. Genetic studies and biological samples

25. Do you have any guidelines or policies that you follow for genetic studies or use of biological samples beyond the immediate study in children? A) Unsure; B) No; C) Yes (Please describe)

F. Data safety

26. Do you routinely insist on a Data Safety and Monitoring board for all pediatric trials? A) Unsure; B) Yes; C) Not for all pediatric trials but for some (please describe)

G. Publication of results

27. Do you have policies regarding submission of final reports of all trials approved by your ethics committee? A) Unsure; B) Yes; C) Not for all trials but for some (Please elaborate)

28. Do you have any mechanism to encourage publication of all results of all trials? A) Unsure; B) No: C) Yes (Please elaborate)

H. General

29. Does your ethics committee insist that all pediatric clinical trials be reviewed by a pediatrics specialist or person with knowledge of pediatric trials? A) Unsure; B) Not specifically; C) Yes, for all pediatric trials (please describe)

30. Do you have any specific policies to ensure post trial access to interventions, if appropriate? A) Unsure; B) No: C) Yes (Please describe)

Thank you for your participation.

Would you like to receive a copy of the results of this survey? A) Yes; B) No

Signature of respondent:

Date:

12. Appendix 4: Draft performa for surveying researchers conducting clinical trials recruiting children

A survey of all contact persons of trials registered in the CTRI that are recruiting children will provide valuable additional information. This survey could also be used to ascertain the views of researchers recruiting children in clinical trials who are yet to register their trials in the CTRI.

ICMR- WHO Survey of clinical trials recruiting children

We request your participation in this survey sponsored by the Indian Council of Medical Research, the WHO project on Better Medicines for Children, The WHO International Clinical Trials Registry Platform, The Clinical trials-Registry- India, and the South Asian Cochrane Network & Centre to evaluate the design and conduct of clinical trials recruiting children in India. We shall ensure that the results of this survey do not identify individuals, sponsors or trial identification details.

Serial Number:

Name of Trial:

Name and address of Principal Investigator:

Trial registration number in the Clinical Trials Registry-India (CTRI):

Trial registration number in other clinical trial registries (if applicable):

Other identification numbers or details (if not registered in a public trials registry)

Name of person filling questionnaire:

Funding source: Please describe:

Please also select one (or more) from the choices below:

1) Industry; 2) funding agency; 3) institution; 4) other

Please answer each of the following questions by circling the response number that is applicable to the functioning of your ethics committee.

A. Prospective registration of clinical trials

1. Was this trial registered in a public clinical trials registry before enrolling the first participant? A) Yes; B) No (if no, go to question 4)
2. For trials registered on the Clinical Trials Registry- India (CTRI), were there any difficulties that you encountered in the registration process?

   A) Not applicable; B) No; C) Yes (please describe)

3. Was trials registration a condition for ethics approval by the ethics committee that approved this trial?

A) No; B) Yes (please name the ethics committee)

4. Do you know if the Drug Controller General of India has made any statement regarding prospective registration of clinical trials? A) Unsure; B) No statement has been issued; C) Yes (please elaborate)

B. Study design

5. Does your trial protocol incorporate all applicable elements of standard reporting guidelines such as the CONSORT statement? A) Yes; B) No; C) Unsure

C. Clinical trials in Children

6. What age group of children does your trial plan to recruit?

A) Neonates; B) Children only (up to 12 years of age); C) Children and adolescents (up to 18 years of age); D) Adolescents only (12 to 18 years); E) Adults and children; F) Other (please describe)

7. Are there specific provisions in the protocol concerning consent from parents for trials recruiting children? A) Yes; B) No;

8. Are you aware of any ethical or legal requirements regarding obtaining consent in trials recruiting children? A) No; B) Yes (please describe)

9. Is consent required from one parent or both parents? A) Either; B) Both; C) Other (please describe)

10. In case of disagreement between parents, do you have any provision to deal with this situation? A) No; B) Unsure; C) Yes (Please describe)

11. Is assent to participate required from the child? A) Yes, B) No; C) Unsure; D) Depends on the age of the child

12. If assent is sought, from what age of the child is this required? A) Not routinely sought; B) _____ Years; C) Unsure

13. Do you require written assent from the child? A) No; B) unsure; C) Yes (from what age?)_____Years

14. Do you have any special provisions for neonates? A) Not applicable; B) No; C) Yes (Please describe)

15. Do you have any special provisions for obtaining assent or consent from adolescents (12 to 18 years)? A) Not applicable; B) No; C) Yes (please describe

16. Do you have provisions for adolescents to participate in the trial in spite of parental objections? A) Not applicable; B) No; C)Yes (please describe)

17. If a child or adolescent does not assent to the trial but parental approval is obtained, does the protocol have guidelines that you will follow to address this? A) Not applicable; B) Parental wishes are paramount; C) Child's wishes are respected; D) Unsure; D) Depends on the situation (please elaborate)
18. Does the protocol provide for separate information sheets during the consent process for children and for parents, suitably translated into local languages? A) Not applicable (state why); B) separate sheets for parents and children; C) No separate information sheets for parents and children; D) Other (please describe)
19. Does the protocol recruit emergency pediatric participants? If yes, do you have any guidelines for consent in emergency pediatric trials? A) Not applicable B) No; C) Yes (Please describe)
20. Does the protocol plan to recruit healthy children? A) No; C) Yes (please describe)

D. Pharmacokinetic studies

21. Does the protocol have any guidelines or policies regarding sample collection (number, timing, total amount; alternatives to blood samples)

from children recruited to trials or research studies? A) Not applicable; B) No; C) yes (please describe)

E. Genetic studies and biological samples

22. Does the study protocol have any guidelines or policies that you follow for genetic studies or use of biological samples beyond the immediate study in children? A) Not applicable; B) No; C) Yes (Please describe)

F. Data safety

23. Does the protocol provide details of a Data Safety and Monitoring board? A) Yes; C) No

G. Publication of results

24. Is there a written plan in the protocol regarding publication of results and authorship issues A)No; B) Yes (Please elaborate)

H. General

25. Do you have any specific policies to ensure post trial access to interventions, if appropriate? A) No; B) Yes (Please describe)

Thank you for your participation.

Would you like to receive a copy of the results of this survey? A) Yes; B) No

Signature of respondent:

Date:

13. Appendix 5: Contact details of stakeholders

A. Members of the Advisory Board of project to increase prospective trials registration in the CTRI of trials recruiting children in India

1. Professor Harshpal S. Sachdev

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2. Professor Meenu Singh

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Advanced Pediatric Centre

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   Assistant Professor in Pulmonary pediatrics

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   Postgraduate Institute for Medical Education and Research

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   India

   Email: jlmathew@rediffmail.com

Indian Academy of Pediatrics

Central Secretariat

Indian Academy of Pediatrics

Kailas Darshan

Kennedy Bridge

Mumbai

Maharashtra

India

400 007

Email: centraloffice@iapindia.org

Tel: 022-23889565; 022-23887922; 022-23887906

To locate all Indian Medical Journals reporting clinical trials

The South Asian Database of Controlled Clinical Trials (www.cochrane-sadcct.org)

To locate all Medical Institutions in India
Website of the Medical Council of India
(http://www.mciindia.org/)

Contact person at the Indian Council of Medical Research

Dr. Lalit Kant,
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Epidemiology and Communicable Diseases, Basic Medical Sciences,
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14. Appendix 6: Summary of proposed strategies

Strategy 1: Establishing a baseline number of clinical trials conducted in the country and the proportion recruiting children

A. Estimating the baseline number of all trials being conducted in India

For industry funded trials

Option 1

To ensure that all trials approved by the Drug Controller General of India are registered on the CTRI, employ a person to follow up actively the DCGI approved trials to see if they are registered, and that what is registered is what was approved since the DCGI's office currently does not have the staff to do this.

Likelihood of success: Moderate (needs to be negotiated with the DCGI)

Likelihood of providing required information: Very High

Importance to the endeavor to increase registration of pediatric trials: Important

For non-industry funded trials

Option 2:

Through the ICMR, a survey of medical colleges could be undertaken to ascertain the number of institutions undertaking trials in children.

Likelihood of success: Low (response rate likely to be low)

Likelihood of providing required information: Moderate (will not identify other types of institutions conducting trials with health related outcomes)

Importance to the endeavor to increase registration of pediatric trials: Important

B. Identifying the proportion of trials in India recruiting children registered on the CTRI

Option 3

The limitations of the CTRI and the WHO ICTRP Search Portal's filter for clinical trials in children suggest that:

A) The filter in the WHO ICTRP Search Portal to identify clinical trials in children needs to be modified to search for trials where recruitment is below 18 years by modifying the search terms to avoid the number 18 as this is possibly the reason why trials that specify 18 years and above in the CTRI free text field are identified and misclassified as trials in children.

B) Coupled with this, the CTRI also needs to be modified to add fields for age of participants as an extension of the WHO 20-item dataset for inclusion and exclusion criteria and provide a drop down list of age bands that will enable

better identification of trials recruiting children. The CTRI is currently planning to revise its software programme for the registry and in November / December will appoint a vendor to provide solutions to the lacunae in the current registry process and this child-specific modification could easily be included in the revision process.

Likelihood of success: High

Likelihood of providing required information: Very High

Importance to the endeavor to increase registration of pediatric trials: Important

D. Identify ongoing clinical trials in India that are recruiting children through members of the Indian Academy of Pediatrics

Option 4: Conduct a survey among members of the Indian Academy of Pediatrics to ascertain the number of ongoing trials recruiting children in India

Likelihood of success: Low (response rate likely to be low)

Likelihood of providing required information: Moderate

Importance to the endeavor to increase registration of pediatric trials: Important

Strategy 2: Legislative approaches to increasing the number of trials registered in the CTRI, especially ones recruiting children

A.New Legislative approaches:

Option 5

Lobby with parliamentarians to follow up on pending legislation (Drugs and Cosmetics (Amendment) Bill, 2007; Clinical Establishments (Registration and Regulation) Bill, 2007; Biomedical Research on Human Participants Bill, 2007**)**

Likelihood of success: Uncertain

Likelihood of increasing the number of trials recruiting children that are registered in the CTRI: High

Importance to the endeavor to increase registration of pediatric trials: Important

B.Work within existing legislative frameworks

Option 6

Pursue the amendment to the ICMR bioethics guidelines to specifically include endorsement of prospective trials registration for all trials recruiting participants in India in the CTRI.

Likelihood of success: Very high

Likelihood of increasing the number of trials recruiting children that are registered in the CTRI: High (if coupled with endeavors to work with ethics committees)

Importance to the endeavor to increase registration of pediatric trials: Important

Strategy 3: Work with ethics committees and Institutional Review Boards in India to endorse prospective trials registration in the CTRI of all clinical trials that they approve.

A.Creating a complete list of ethics committees, Institutional Review Boards and Independent Ethics Committees in India

Option 7

Compile a complete list of Institutional Review Boards, Independent Ethics Committees and local research and ethics review committees with the help of the ICMR bioethics initiative.

Likelihood of success: High

Likelihood of increasing the number of trials recruiting children that are registered in the CTRI: High (if coupled with endeavors to work with ethics committees)

Importance to the endeavor to increase registration of pediatric trials: Important

B.Working with institutional review boards, independent ethics committees and local research and ethics review boards to improve their capacity for oversight and to endorse prospective trials registration

Option 8

Hold an annual meeting of representatives from all identified ethics committees and review boards, starting with a workshop on January 11, 2009 at the 8th Winter symposium of the Christian Medical College, Vellore with representatives of the CONSORT working group, the Equator network, the Spirit initiative, the WHO-ICTRP and the CTRI to increase their oversight capacity for research approved by them, incorporate elements of good reporting standards in study protocols and to endorse prospective trials registration as a condition of ethics committee approval.

Likelihood of success: Very high

Likelihood of increasing the number of trials recruiting children that are registered in the CTRI: High

Importance to the endeavor to increase registration of pediatric trials: Important

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Strategy 4: Work with editors of Indian Medical Journals to increase the proportion of journals that endorse prospective trials registration and

enhance capacity to ensure use of the CONSORT and other reporting guidelines in manuscript submissions

Option 9

Hold an annual meeting of editors of Indian Medical Journals that publish clinical trials, starting with a workshop on January 11, 2009 at the 8th Winter Symposium at the Christian Medical College, Vellore with representatives of the CONSORT working group, the Equator network, the Spirit initiative, the WHO-ICTRP and the CTRI, to shape editorial policies regarding submission of manuscripts to incorporate elements of good reporting standards in study reports, particularly CONSORT for reports of randomized controlled trials, to improve the peer review process, and to endorse prospective trials registration as a condition of submission of manuscripts for publication.

Likelihood of success: Very high

Likelihood of increasing the number of trials recruiting children that are registered in the CTRI: High

Importance to the endeavor to increase registration of pediatric trials: Important

Option 10

Author or co-authors editorials and other articles in Indian pediatric journals, particularly the official journal of the Indian Academy of Paediatrics, *Indian Pediatrics,* on the ethical and other issues pertaining to clinical trials in children and the need to prospectively register in the CTRI details of clinical trials recruiting children in India.

Likelihood of success: High

Likelihood of increasing the number of trials recruiting children that are registered in the CTRI: High

Importance to the endeavor to increase registration of pediatric trials: Important

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Strategy 5: Work with the Indian Pediatrics Association

Option 11

Hold workshops annually targeted at pediatricians, starting with the 47th National Conference of the Indian Academy of Pediatrics, PEDICON 2010, to be held at Hyderabad in January 2010, to raise awareness of the importance of prospectively registering clinical trials recruiting children in India in the CTRI.

Likelihood of success: High

Likelihood of increasing the number of trials recruiting children that are registered in the CTRI: Moderate to High

Importance to the endeavor to increase registration of pediatric trials: Important

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Strategy 6: With through the South Asian Cochrane Network

Option 12

Incorporate prospective clinical trials registration as a specific strategy in the strategic plan of the South Asian Cochrane Network for 2009 to 2012 for all six network sites in India to implement in their own institutions and in other institutions and organizations in their spheres of influence.

Likelihood of success: High

Likelihood of increasing the number of trials recruiting children that are registered in the CTRI: Moderate to High

Importance to the endeavor to increase registration of pediatric trials: Important

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Strategy 7: Work with the media to highlight the importance of prospective clinical trials registration

Option 13

Organize workshops for media, starting with the 8th Winter symposium to be held at CMC Vellore in January 2010 to raise awareness of the importance of prospective clinical trials registration, particularly when trials recruit children.

Likelihood of success: Moderate

Likelihood of increasing the number of trials recruiting children that are registered in the CTRI: Uncertain

Importance to the endeavor to increase registration of pediatric trials: Moderate

Strategy 8: Work with consumer groups

Option 14

Organize workshops for media, starting with the 8th Winter symposium to be held at CMC Vellore in January 2010 to raise awareness of the importance of prospective clinical trials registration, particularly when trials recruit children.

Likelihood of success: Uncertain

Likelihood of increasing the number of trials recruiting children that are registered in the CTRI: Uncertain

Importance to the endeavor to increase registration of pediatric trials: Moderate