ETHICS IN PSYCHIATRIC RESEARCH

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1. INTRODUCTION

Psychiatric disorders are widely prevalent worldwide. Surveys conducted in developed as well as developing countries have shown that, during their entire lifetime, more than 25% of individuals develop one or more mental or behavioural disorders (WHO World Mental Health Survey Consortium, 2004). About 450 million people are estimated to be suffering from neuropsychiatric conditions (WHO World Mental Health Report, 2001). These conditions included unipolar depressive disorders, bipolar affective disorder, schizophrenia, epilepsy, alcohol and selected drug use disorders, Alzheimer's and other dementias, post traumatic stress disorder, obsessive and compulsive disorder, panic disorder, and primary insomnia. The most common diagnoses in primary care settings are depression, anxiety and substance abuse disorders. These disorders are present either alone or in addition to one or more physical disorders.

Psychiatric Disorders are widely prevalent globally; one in four families is affected by mental illness.

Apart from being widely prevalent, they are also universal and there are no consistent differences in prevalence between developed and developing countries. While no group is immune to mental disorders, the risk is higher among the poor, homeless, the unemployed, persons with low education, victims of violence, immigrants and refugees, indigenous populations, children and adolescents, abused women and the neglected elderly (Saraceno & Barbui, 1997; Patel et al, 1999; Patel 2001; WHO 2003). These factors also influence the prognosis of the disorders through inequities in case detection, access to care and to affordable treatments that make the already wide treatment gap in developed countries, even wider in low and middle income countries (WHO World Mental Health Survey Consortium, 2004).

Psychiatric disorders also cause considerable distress and social and economic costs to individuals and families as well as to societies and nations through years of productive lives lost through disability, absenteeism, lowered productivity, and exclusion from the workforce; there is also increased mortality from life style and medication related medical conditions, and increased suicides (WHO World Mental Health Report, 2001). Five of the world's 10 leading causes of disability are psychiatric: depression, alcohol abuse, bipolar mood disorder, schizophrenia, and obsessive compulsive disorder (WHO, 1997).

However, over the past half a century, research in epidemiology, improved diagnostic reliability due to operationalised diagnostic criteria and structured interview techniques, better techniques of drug discovery and in basic laboratory sciences, and clinical research in pharmacological and non-

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pharmacological interventions have led to better outcomes for people with mental health problems (Michels & Marzuk, 1993; WHO World Mental Health Report, 2001). This demonstrates the ethical and scientific imperative to conduct research in people with mental illness in order that the results may inform health policy and practice and improve the quality of life of millions of people with mental health problems and their families.

2. MENTAL ILLNESS AND VULNERABILITY

People with mental illness are vulnerable on several counts. The symptoms of psychiatric disorders include those that affect one's ability to interact socially, fulfil one's responsibilities, appraise one's situation rationally, impact decision making, and even one's contact with reality. Also fundamental to some psychiatric conditions are a decline in cognitive abilities and thereby the capacity to comprehend and appreciate one's situation sufficiently to fulfil legal definitions of competence (Roberts, 2002).

Reference has been made herein to the higher risk for mental disorders in economically and socially disadvantaged populations. These studies indicate that the risk of mental disorders is higher among the poor, homeless, the unemployed, persons with low education, victims of violence, immigrants and refugees, indigenous populations, children and adolescents, abused women and the neglected elderly (Saraceno & Barbui, 1997; Patel et al, 1999; Patel 2001; WHO 2003). Added to this is the stigma and social disfranchisement that accompanies the diagnosis of mental illness that leads to a relational disadvantage arising from feelings of powerlessness. However, the personal suffering and public health consequences of mental illness create a societal and ethical imperative to perform scientific studies on etiology, treatment, and prevention in these vulnerable groups in order to find effective interventions that cannot be extrapolated by research in other groups without these vulnerabilities (Michels, 1999; Miller & Finns, 1999; Dunn et al, 2006).

3. ETHICAL ISSUES IN RESEARCH IN PEOPLE WITH MENTAL DISORDERS

While the benefits accruing to people with mental illness from research over the past decades are laudable, they have also been accompanied by considerable concerns about the ethics of advancing scientific knowledge at the expense of the individual safety and interests of people with mental health (Applebaum, 1997; Srinivasan et al, 2006; Mudur 2006).

Many of these concerns pertain to research in humans in general, but particular concerns relate to the inexactness of psychiatric diagnoses and therefore the validity of research findings (Quitkin, 1999); the political abuses of psychiatric research beginning with the excesses of the Nazi era (Birley, 2000; Strous, 2007), and continuing even today as exemplified by the use of coercive techniques of unproven efficacy such as narco-analysis (Jessani, 2006; Jagadeesh, 2007; Kala, 2007); vulnerability (assumed and actual) of people with psychiatric conditions (Roberts, 2001), and the use of research designs that include medication-free intervals and placebo controls (Carpenter et al, 2003; Moser et al, 2005), interventional and observational research in prodromal or early onset conditions (Haroun et al, 2006), and genetic research (Jones et al, 2002; Yeh et al, 2004).

Issues regarding the validity of and capacity to consent in psychiatric populations have also been widely debated (Dunn et al, 2006). These concerns have been specifically aroused by the global outsourcing of clinical trials to the developing world and highlight global alarm at the relative lack of capacity to provide proper ethical oversight compared to the ability to provide inexpensive budgets, facilities, trained research personnel and un-empowered, largely drug-naive patient populations for lucrative multinational drug trials. Concerns have also been expressed of the ethics of research in

developing countries, particularly when done solely for regulatory approval elsewhere, and the standards of care to be adopted in such studies (Angell, 1997).

Should research be done in people with impaired decisional capacity?

Traditionally, people with mental illness are presumed to have poor decisional ability (Benson et al, 1985) and this is borne out by empirical evidence (Kim, 2006). However, systematic evaluation, even in non-psychiatric populations and in high-income countries, has shown that participants in randomised trials recall information poorly, are not often aware that placebos form one arm of treatment, demonstrate inadequate comprehension of the process of chance in treatment allocation, understand and use only a proportion of what is presented in consent forms, do not really understand the issue of equipoise, and participate not for altruistic reasons but because they expect some improvement by participation (Edwards et al, 1998). Cognitive dysfunction and the symptoms shown to be associated with impaired decisional capacity are not unique to schizophrenia and may occur with many other forms of illness (Moser et al, 2002). Furthermore, studies have also shown that many people with schizophrenia are able to give informed consent and retain related information across time. There is also evidence that individuals who have schizophrenia and lack adequate decision-making capacity may improve significantly with educational remediation (Wirshing et al, 1998; Carpenter et al, 2000; Moser et al, 2006).

Nevertheless, measures to protect vulnerable participants are needed to ensure that the methods of scientific research do not infringe on the rights of the mentally ill. This is all the more likely when research is combined with clinical care, as is usual in many centres where research is conducted in India. Many participants of undisputed capacity to consent are still unable to differentiate between treatments that increase research validity such as using placebos to mask treatments and those that are therapeutic, and this *'therapeutic misconception'* is all the more likely when research trials are conducted in treatment centres and by their usual treatment teams. This misconception leads to an unrealistic or inappropriate expectation of personal benefit or individualized care (Applebaum et al, 1982). This phenomenon has since been described in many non-psychiatric research populations. Older age, lower education, and worse health placed people at higher risk for holding a therapeutic misconception (Lidz et al, 2004; Dunn et al, 2006).

The cardinal principles that govern and shape ethical research practices hinge on the upholding of *respect for the autonomy of the individual*, exemplified in adherence to maintaining confidentiality, truth telling , informed consent, and protection of vulnerable people; a belief in *beneficence and non-malfeasance*, where the benefits and safety of the individual take precedence over scientific, financial or monetary advantage. The cornerstone of this belief is the careful risk-benefit assessment that precedes and continues after ethical review. The principle of *justice* is manifest in a fair selection of subjects so that all people who might benefit from the fruits of research are included. This principle is also evident in the order of preference in the selection of classes of subjects, where adults are selected before children, non-pregnant women before pregnant women and people with reduced capacity to consent or prisoners may be involved as research subjects, if at all, only on certain conditions.

These principles have gradually eroded over the years in all cultures due to the fragmentation of healthcare and the pressures of academia and industry. In developing countries, cultural issues have compounded these challenges of traditional ethical principles, where collectivism has trumped individual autonomy due the structure of paternalistic families and health care systems; vestiges of the Guru-sishya (chela) model of interaction permeating the doctor patient relationship and precluding the contractual model envisaged by the informed consent process. Further subverting the process are the low bargaining power the average individual has in the average health encounter;

inadequate advocacy support; inequities in access to care of any quality, the costs and distances involved in accessing healthcare, etc., so that what may seem reasonable compensation for participation in research may be powerful inducements to participate (Tharyan 2006). Other cultural influences are widespread utilization of alternative health care systems. These range from the ancient Ayurvedha, Siddha and Unnani traditions to the utilization of indigenous healers early in the pathway to care, that have traditionally eschewed empiricism and have fostered a holistic tradition where symptom removal is not necessarily the overt goal of treatment and diagnoses based on contemporary disease categories not the norm. This model of healthcare mirrors the faith-based approach widespread use of religious rituals and supplications as an initial and sustained "co-intervention" through all phases of healthcare (and presumably health-research).

Meanwhile the predominant privatization of health care in India has led to the rapid growth of a model of care that uses profit as the bottom line to determine health care components and participation in research, rather than the need to generate reliable evidence or advance the interests of research participants. Lack of formal clinical ethics training in most academic and treatment centres is now balanced by ever increasing research ethics courses; however, it is unclear whether this leads to observance of the spirit or the just the letter of ethical principles and practices. This has led to eroding public confidence in research in a country where healthcare already comes under the ambit of the Consumer Protection Act (COPRA).

4. REGULATION AND OVERSIGHT OF RESEARCH IN PEOPLE WITH PSYCHIATRIC DISORDERS

The ethical principles that guide research in human participants stem from guidance from various organizations through the years. These principles, though nascent for long in the writings of different people from different parts of the world, were codified and revised over the years in response to a series of research abuses separated in time and space by a common thread of upholding the primacy of scientific enquiry and advancement over protection of participants/subjects.

The Nuremberg Code

The earliest such attempt was the ***Nuremberg Code*** formulated in 1947 in the wake of Nazi atrocities of experiments with prisoners during World War II (Annas & Grodin, 1992). The tragedy of this dark period in the history of research and psychiatry was the central role of psychiatrists, many senior academics of the time, in devising and executing the plans to sterilize and also euthanize many hundreds of thousands of mentally ill people in their Neo-Darwinian quest of racial cleansing (Strous, 2007). This period demonstrated the worst of what can be done in the name of research: when philosophical constructs lead to clinical action without empirical evidence, conflicts of interest arose due to political ideology and influence, resulting in the unacceptably blurred roles of clinicians and researchers on a misconceived, preventive, pseudoscientific mission without external, independent oversight.

Key Elements of the Nuremberg Code

? The voluntary consent of the human subject is absolutely essential
? The results of the research must be useful and unobtainable by other means.
? The study must be rationally based on knowledge of the disease or condition to be studied.

The Nuremberg Code clearly delineated the need for, and parameters of, informed consent in

research; the need for a favourable risk benefit ratio and the need for qualified research staff and appropriate research designs (see box) and was meant to prevent future abuses in the name of research. This was backed by the *Universal Declaration of Human Rights* (adopted by the General Assembly of the United Nations) in 1948.

The Declaration of Helsinki

The Declaration of Helsinki of the World Medical Association (WMA) has been revised several times since it was first adopted by the 18th General Assembly of the WMA in Helsinki, Finland in 1964. The most recent revision was adopted by the 56th General Assembly of the WMA in Seoul in October 2008 (WMA 2008). It contains 35 clauses organised in three sections that outline the principles that ought to be followed in all medical research involving human participants. The first section provides an introduction with 10 clauses that defines human research, delineates why it is necessary and stresses the obligation of the physician to prioritize participant health so that "the well-being of the individual research subject must take precedence over all other interests". This section also reminds physicians that special populations involved in research must be closely monitored and their rights protected, particularly those "who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence". The second section contains 19 clauses that lay down the general principles of medical research. These include endorsement of the notion that all research should be scientifically valid as well as ethically underpinned; the need for a scientifically justified research protocol that is transparent about all elements of the design, potential conflicts of interest, incentives, compensation and issues of post-trial access to beneficial interventions identified by the study, where applicable. The roles of research ethics committees in approving and monitoring research as well as the roles of researchers in connection with ethics committees are also mentioned, as are the requirements of their competence to conduct research and the need to appraise carefully the risks and benefits of the proposed research. Issues pertaining to informed consent and confidentiality are elaborated upon as are processes to be followed when the capacity to consent is compromised or refused but research in such people is still though necessary. Finally, issues bearing on transparency, making results available and publication ethics are also expounded in the remaining clauses in this section. The third section contains five clauses that outline the principles to be followed when research is combined with care; these address situations when the use of placebos may be justified, and the need to delineate what constitutes research from medical care so that care is never compromised for the sake of research. The Declaration acknowledges the need for research and the attendant risks but stresses that all research ought to benefit local communities as well as the research participant directly.

Other important ethical documents that have influenced research ethics

An important contribution to shaping the direction of contemporary research ethics was the 1966 paper by Henry Beecher, Professor of Anaesthesia at Massachusetts General Hospital, in the *New England Journal of Medicine* that exposed published research practices in the US where scant regard was paid to the welfare of human subjects in the interests of promoting science (Beecher, 1966). This seminal paper placed the onus of not publishing unethical research on medical journal editors, a view that was later endorsed by the International Committee of Medical Journal Editors (ICMJE), also known as the Vancouver Group, in their *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* that in its many revisions not only addressed publication issues but also provided leadership and guidance on many ethical issues pertaining to human and animal research (ICMJE 2004).

In 1979, the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research created by the U.S. Department of Health, Education, and Welfare (DHEW)

published the *Belmont Report* (National Commission, 1979) that laid down details of how the principles of respect for autonomy, beneficence and justice may be protected in research by proper attention to informed consent, risk benefit analysis and fair selection of research participants. In 1991, the *Common Rule* combined all regulations of the DHEW into a set of regulations (46 CFR 45) to guide all federal research in the US (DHHS, 2001) and this also applies to all pharmaceutical research under the Food and Drug Administration. The Council for International Organizations of Medical Sciences (CIOMS), a non-governmental organization founded in 1949, published the CIOMS manual, *Proposed International Ethical Guidelines for Biomedical Research Involving Human Subjects,* in 1982 to translate the Declaration of Helsinki for use in member countries of the WHO, particularly in the developing world; its revisions have specifically debated issues such as the standards of care to be followed in resource poor countries when research is funded by industrialized nations and also issues such as research in vulnerable populations and the conditions where research using placebos may be justified (CIOMS, 2002).

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use held at Brussels in 1990 was the result of a combined attempt by regulatory agencies and pharmaceutical industries in Europe, the US and Japan to arrive at a harmonized policy on key areas concerning the manner in which the efficacy, safety and quality of new drugs are approved and the *ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice (E6)* was released in 1996 (ICH-GCP, 1996) to reflect the good clinical practices of the European Union, the US, Japan, Australia, Canada, the Nordic countries and the WHO. Relevant sections of the ICH-GCP (E6) contain a glossary of definitions, notably that of 'vulnerable subjects' that does not include psychiatric patients *per se* at all but only if they are "individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate." The specific vulnerable groups mentioned are health profession trainees, health industry employees, the military, prisoners, the chronically ill, the terminally ill, residents of nursing homes, the impoverished, emergency patients, ethnic minority groups, minors, and "those incapable of giving consent", though psychiatric patients could fall into any one of these groups. The definitions also differentiate Independent Ethics Committees (IECs) that may be institutional, regional, national or international from Institutional Review Boards (IRBs) that are, by definition, institutional and form one type of IEC. ICH-GCP (E6) also delineates the composition and specific duties of an IEC/IRB. A major part of the ICH-GCP is devoted to enumerating good clinical practices in relation to the design and conduct of clinical trials with due attention paid to pre-clinical evidence and the risk-benefit ratio justifying the trial, methods of collecting, identifying, storing, verifying, interpreting and protecting data and using products made according to good manufacturing practices (GMP).

The National Bioethics Advisory Commission (NBAC), created by President Clinton released in 1998 and 1999 its report titled *"Research Involving Persons with Mental Disorders That May Affect Decision making Capacity"* (NBAC, 1998). This voluminous report carried 21 recommendations covering diverse areas such as categories of research-related risk, research design, informed consent and capacity, surrogate decision making, education, research and support, and the role of IRBs. While welcomed by many for its goal of protecting decisionally impaired psychiatric research participants, the report was also critiqued for suggesting in its recommendations that all psychiatrically ill participants in studies with more than increased risk should undergo evaluations for the capacity to consent, implying an automatic incapacity to consent unless proved otherwise (Oldham et al, 1999).

These important documents and guidelines contain many common elements but also some differences that are relevant to research in people with mental illness, notably the elements required in the informed consent documents and the use of placebos in psychosis; for the later, the Declaration of Helsinki and the CIOMS guidelines are the most restrictive, while the Belmont report, the common rule and the ICH-GCP (E6) are more permissive (Fischer, 2006).

5. ETHICAL GUIDELINES AND REGULATIONS GOVERNING RESEARCH IN INDIA

The 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'* (ICMR, 2006). 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.

The Drugs and Cosmetic Act & Rules

The Drugs and Cosmetics Act 1940 (Act 23 of 1940 as amended up to 30th June 2005) and the Drugs and Cosmetic Rules 1945 (as amended up to 30th 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 (Government of India, 2005). 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. Schedule Y requires that all applications for clinical trials should conform to the requirements of the Declaration of Helsinki, the Ethical Guidelines for Biomedical Research on Human Participants of the ICMR and the Good Clinical Practice Guidelines issued by Central Drugs Standard Control Organization (http://cdsco.nic.in/html/GCP1.html). 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 but does not include psychiatric patients as deserving special consideration as a vulnerable group per se nor does it provide guidance on dealing with non-consenting or decisionally impaired psychiatric participants.

Good Clinical Practices for Clinical Research in India

Good Clinical Practice (GCP) guidelines for biomedical studies in India 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. All internationally funded research needs approval by the Health Minister's Screening Committee (HMSC); this is to screen such research for potential violations of national security and intellectual property rights.

Study Design
The scientific validity of research is an ethical prerequisite. Research that does not yield reliable results is a waste of resources and is unethical. One major contributor to such outcomes is the poor design of research studies. Each type of research question is best answered by specific types of study designs. Hence, research questions pertaining to the incidence of a particular condition are best answered by a cohort design while cross-sectional studies could evaluate prevalence; those that deal with etiology are best studied using a case control or a cohort design; those that evaluate diagnostic accuracy are best answered using cross sectional or cohort design, or a randomized controlled trial (RCT) if outcomes are also to be measured; the efficacy of interventions are best studied using RCTs though safety may require longer term cohorts to capture outcomes that develop later or case control designs for rare outcomes.

All research designs, however appropriate, are prone to bias, confounding and the effects of chance. Hence, the design should incorporate procedures specifically meant to eliminate bias, confounding and the effects of random error (chance) and fluctuations in the course of the disease or condition.

The optimal standards for reporting studies vary according to the study design. The consolidated standards for reporting the results of randomized controlled trials (*CONSORT statement*) and its many extensions (www.consortstatement.org) are universally accepted as providing evidence-based elements in relation to minimizing bias and improving transparency in reporting the results of trials. However, the reporting of important elements that minimize bias in randomized controlled trials (Tharyan & Adhikari, 2007) is suboptimal in Indian medical journals, raising doubts about the validity of these trials (Tharyan et al, 2008). Similarly, the *Strobe Document* (von Elm et al, 2007) provides recommendations on reporting observational studies (case-control, cross-sectional and cohort studies) that are widely accepted, while studies of diagnostic test accuracy are expected to be reported in accordance with the *STARD initiative* (Bossuyt et al, 2003) Qualitative research too requires methods to reduce bias and increase transparency.

The Declaration of Helsinki states that “The design and performance of each research study involving human subjects must be clearly described in a research protocol” (WMA 2008). The ICMR guidelines, Schedule Y of the Drugs and Cosmetic Act & Rules and the Indian GCP guidelines are more detailed in the requirements of the contents of study protocols. The ICMR guidelines are also refer to the CONSORT statement and its extensions (www.consortstatement.org) in relation to reporting the results of trials. However, poor reporting may be due to poor design and incorporating elements from the CONSORT Statement, the STARD initiative and the STROBE document in the *design* of research protocols, rather than referring to their requirements only when reporting results will ensure more reliable results (Tharyan et al, 2008).

6. ETHICAL REVIEW

All research proposals involving human participants should be cleared by an appropriately constituted and authorised Institutional Ethics Committee (IEC) also referred to as Institutional Review Board (IRB), or an independent ethics committees (IEC) functioning outside institutions for those researchers who have no institutional attachments or work in institutions with no ethics

committee. The IRB/IEC should be properly constituted as per the requirements of the ICMR guidelines and that of Schedule Y and should have and follow Standard Operating Procedures (SOP) as per the guidelines of the WHO (available at www.who.int).

The responsibilities of an IEC/IRB can be defined as follows (ICMR 2006)
1. To protect the dignity, rights and well being of the potential research participants.
2. To ensure that universal ethical values and international scientific standards are expressed in terms of local community values and customs.
3. To assist in the development and the education of a research community responsive to local health care requirements.

All research should not only be scientifically valid but also socially relevant: relevant to the population being tested as well as to society at large. It must improve understanding or care and must not cause undesirable social repercussions. Research with no or little social value include: "Me too" studies done to fulfill publication requirements, non-generalizable research, research with questionable outcome measures and poor design, fraudulent research and research that is not disseminated. Other ethical requirements of research include fair subject selection, minimization of risks and measures to protect vulnerable participants.

The IEC/IRB should facilitate and guide researchers on ensuring the welfare and safety of the research participants as well as ensuring the scientific validity of the proposed research. It is advisable that the scientific review precedes ethical review and that these be undertaken by separate committees, a Scientific Review Committee and an Ethical Review Committee (ICMR 2006), though in institutions where this is lacking, the IEC/IRB may undertake review of the scientific and ethical aspects of the proposal. IRBs are entrusted not only with the initial review of the proposed research protocols but also with regular monitoring of research to ensure compliance with the protocol and safety of participants.

The composition of IRBs/IEC should be multidisciplinary and should comprise of the following (ICMR 2006):
1. A Chairperson (independent of the host institution)
2. One to two persons from basic medical science area
3. One to two clinicians from various Institutes
4. One legal expert or retired judge
5. One social scientist/ representative of non-governmental voluntary agency
6. One philosopher/ ethicist/ theologian
7. One lay person from the community
8. Member Secretary

According to Schedule Y the minimum number of IRB members that need to be present for each research proposal is 5 and should comprise the following:
1. One basic medical scientist (preferably one pharmacologist)
2. One clinician
3. One legal expert or retired judge
4. One social scientist/ representative of non-governmental organization/philosopher/ ethicist/ theologian or a similar person
5. One lay person from the community

The Terms of References of the IRB/IEC should be specified in the SOP which should be made available to each member. These should include Terms of Appointment with reference to the duration

of the term, responsibilities; policies for removal, replacement and resignation; frequency of meetings, and payment of processing fee to the IEC for review, honorarium/ consultancy to the members/ invited experts *etc.* (ICMR 2006). All proposals will be scrutinised to decide under which of the following three categories it will be considered: *exemption from review*, *expedited review* and *full review.* Those proposals that represent less than minor risk (such as chart review with no identifying data collection) are exempt from review though this decision has to be made by the IRB and not the individual researcher. Research activities that present no more than minimal risk to human participants can go though the expedited review process, while all other proposals require full review (ICMR 2006).

Fair Subject Selection
In assessing whether selection criteria of research studies serve all the cardinal ethical principles, IEC/IRB members should assess whether inclusion and exclusion are based on scientific objectives and not on perceived advantage or disadvantage (mental illness; poor, marginalized). They should keep in mind that excluding too many people results in poor generalizability of results while increasing measures to protect and facilitate the inclusion of vulnerable participants can increase generalizability. Risk-benefit ratio important to evaluate; higher risk over benefit is a valid reason to exclude (see below). As far as possible the selection of subjects must be consistent with clinical practice standards.

Assessing The Risk-benefit Ratio
An important duty of researchers and members of IRBs/IECs is careful evaluation of the potential risk-benefit ratio of research protocols.

Assessment of Benefit includes:
Physical: Improvement, control, recovery, cure; **Psychological:** Improvement, recovery, wellbeing; **Social:** advantages; restitution of functioning; **Economic:** gain, to all or most study participants, not only benefit in clinical care

This assessment also includes: the likelihood of occurrence of benefit, the magnitude of benefit from the study interventions (not just by being a participant and due to other aspects of care or research design), the duration of benefit, and the methods of increasing likelihood/magnitude/duration of benefit.

Assessment of Risk includes:

Physical: Adverse events, complications, disease relapse, recurrence, progression; disability, death; **Psychological:** distress, disorder; **Social:** Embarrassment, stigma, discrimination; **Economic:** loss, unfair payments.

This assessment also includes: the likelihood of occurrence, the magnitude of harm, the duration of effects, and the methods that will be used to minimize the occurrence, magnitude and duration of unwanted effects.

Clauses 21 and 21 of the Declaration of Helsinki state, “Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects

(WMA 2008).

If risk exceeds benefit by a small amount, the IEC/IRB should evaluate the value of knowledge gained and benefit to society; in the first instance, attempts must be made to exclude those who stand to gain very little from the study. If risk to individual is high and social benefit is high, though individual benefit is uncertain, competence to consent and independent verification of validity of consent should form an essential part of design, if approval is sought or provided.

The review committee members must keep in mind that an essential requirement of the current versions of the Declaration of Helsinki is that opportunities for direct benefit should exist for the individual, not just benefit to society.

Apart from detailed scientific information, the protocol should include information regarding funding, sponsors, institutional affiliations, and other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits (WMA, 2008). All changes to approved protocols should be approved by the IRB/IEC.

The ethical review should be done in formal meetings and EC should not take decisions through circulation of proposals (ICMR 2008).

Further details on the functioning of IRBs can be accessed from the ICMR Guidelines, Schedule Y and the Indian ICH-GCP guidelines.

7. INFORMED CONSENT

Informed consent is "consent given voluntarily by a competent individual who has received the necessary information, has adequately understood the information and after considering the information, has arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation" (ICMR, 2006). Informed consent is based on the principle that competent individuals are entitled to choose freely whether to participate in research or not and protects the individual's freedom of choice and respect for the individual's autonomy. It also protects the subjects' rights. Taking informed consent is a "process" and does not merely consist of a signature on the consent form. Informed consent is a communication process between the researcher and the participant and starts before the research is initiated and continues throughout the duration of the study. The investigator or his delegate must discuss all pertinent aspects of the study, answer any queries / doubts, request consent and then if freely given, documented. The ultimate responsibility is the investigator's.

Informed consent includes a verbal description and discussion of the details of the study including the process of randomization, the components of the study, and other details mentioned in the checklist below (from Schedule Y 2005) as well as a written *information sheet* containing all relevant information in simple, non-technical language in the participant's vernacular and given to the participant to keep. Adequate time must be provided for the participant to decide on participation. A separate i*nformed consent form* must be used to document consent. Sample information sheets and consent forms are available in Schedule Y.

In case of illiterate participants, a witness is crucial and thumb impressions are allowed. All signatures should be dated and in case a date is forgotten on the day the consent is taken, it must be retaken on the next visit and dated, with a clear explanation documented in the source document. The

investigator MUST NOT date the consent at any point in time; this must be done by the witness in the case of illiterate participants. In the case of minors, proxy consent from a parent/responsible guardian is permitted and only the parent/responsible guardian may sign the informed consent form. However, it is mandatory that the minor provides assent (permission) to participate and, if possible, this should be recorded in a separate assent form. If the participant is incompetent to provide valid informed consent and it is deemed ethically justified to include this person in research, then the proxy consent of a responsible family member/legal guardian and a witness must be taken.

Each subject (or their representative) must be given a copy of the signed consent form. The original consent form should be filed in such a manner as to insure immediate retrieval when required by auditing entities, IRB, or sponsor monitors. Written documentation of informed consent is required. Therefore, obtaining consent from an authorized third party via the telephone is not acceptable.

Obtaining informed consent from participants must be accomplished prior to performing the research activity and using only an IRB approved consent form. Written requests for amendments to an existing consent form must be approved by the IRB prior to implementation. Upon receipt of an IRB approved consent form, all old versions should be discarded to prevent inadvertent use of an outdated consent form. Copies of the most recently approved consent form may be made and should be used until superseded by an amended consent form. The consent form must be reviewed at least annually as part of the continuing review process

The essential elements of an informed consent document are (Schedule Y)

1. "Statement that the study involves research and explanation of the purpose of the research
2. Expected duration of the Subject's participation
3. Description of the procedures to be followed, including all invasive procedures and
4. Description of any reasonably foreseeable risks or discomforts to the Subject
5. Description of any benefits to the Subject or others reasonably expected from research. If no benefit is expected Subject should be made aware of this.
6. Disclosure of specific appropriate alternative procedures or therapies available to the Subject.
7. Statement describing the extent to which confidentiality of records identifying the Subject will be maintained and who will have access to Subject's medical records
8. Trial treatment schedule(s) and the probability for random assignment to each treatment (for randomized trials)
9. Compensation and/or treatment(s) available to the Subject in the event of a trial-related injury
10. An explanation about whom to contact for trial related queries, rights of Subjects and in the event of any injury
11. The anticipated prorated payment, if any, to the Subject for participating in the trial
12. Subject's responsibilities on participation in the trial
13. Statement that participation is voluntary, that the subject can withdraw from the study at any time and that refusal to participate will not involve any penalty or loss of benefits to which the Subject is otherwise entitled
14. Any other pertinent information

Additional elements, which may be required:

a. Statement of foreseeable circumstances under which the Subject's participation may be terminated by the Investigator without the Subject's consent.
b. Additional costs to the Subject that may result from participation in the study.
c. The consequences of a Subject's decision to withdraw from the research and procedures for orderly termination of participation by Subject.
d. Statement that the Subject or Subject's representative will be notified in a timely manner if

significant new findings develop during the course of the research which may affect the Subject's willingness to continue participation will be provided.

e. A statement that the particular treatment or procedure may involve risks to the Subject (or to the embryo or fetus, if the Subject is or may become pregnant), which are currently unforeseeable.

f. Approximate number of Subjects enrolled in the study".

The guidelines of the ICMR also include as requirements of informed consent (ICMR 2006):

1. If test for genetics and HIV is to be done, counseling for consent for testing must be given as per national guidelines
2. Storage period of biological sample and related data with choice offered to participant regarding future use of sample, refusal for storage and receipt of its results.

Fresh or re-consent is taken in the following situations (ICMR 2006; ScheduleY):

1. Availability of new information that would result in changes in the protocol or change the balance of risks and benefits;
2. When a research participant who did not originally consent, and whose participation was under proxy consent from a legally responsible person, regains consciousness from an unconscious state or regains capacity to consent;
3. When long term follow-up or study extension is planned later;
4. When there is change in treatment modality, procedures, site visits.

Waiver of consent (ICMR 2006)

Voluntary informed consent can be waived if it is justified that the research involves not more than minimal risk or when the participant and the researcher do not come into contact or when it is necessitated in emergency situations. If such studies have protections in place for both privacy and confidentiality, and do not violate the rights of the participants then IRBs/IECs may waive the requirement for informed consent.

When capacity to consent is lacking (WMA 2008)

The Declaration of Helsinki is clear that "No competent individual may be enrolled in a research study unless he or she freely agrees". The Declaration, however, provides for participation of persons with psychiatric disorder lacking capacity in research under two separate clauses.

1. "For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden" (WMA 2008; clause 27).
2. "Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative" (WMA 2008; clause 29).

An additional caveat in clause 28 reads, “When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected”.

This clause may seem at variance with the permission to proceed with proxy consent of a legally authorized representative (usually a family member in India) contained in the previous clauses, but emphasizes the need to justify recruiting mentally incapacitated participants in research without their consent.

Individuals who have severe mental disorder and lack adequate decision-making capacity may improve significantly with educational remediation (Wirshing et al, 1998; Carpenter et al, 2000; Moser et al, 2006). Patients can be given information through conversation, lectures, pamphlets, articles, medication groups, instruction sheets, books and videotapes, consent forms, and interactive videodiscs. Only one's inclination, resources and imagination limit methods of providing adequate information in a manner and language that patients would understand. But they are not substitutes for discussion with patients and careful documentation of valid informed consent.

Assessing competence to consent in research

It has long been recognized that assessing competence to consent to participation is complex and often done arbitrarily. There have, therefore been calls for more formal assessments of the competence to consent to research among vulnerable subjects, particularly when research involves more than minimal risk (National Bioethics Advisory Commission, 1998).

Assessment of competence includes evaluation of the person's ability to (Applebaum & Roth 1982):

1. *Communicate choices.* This is an ability to maintain and communicate stable choices, long enough for them to be implemented;
2. *Understand relevant information*. Persons who cannot understand what they have been told about a treatment are not competent to decide whether to accept or reject it;
3. *Appreciate one's situation and the consequences*: Patients may comprehend certain information, but fail to grasp what it means for them.
4. *Manipulate information rationally.* This is the ability to use logical processes to compare the benefits and risks of various treatment options.

The MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) (Appelbaum and Grisso, 2001) is generally recognized as the best of currently available scales for formal assessment of competence to provide valid informed consent to participate in research (Dunn et al, 2007); it is also the most widely used in empirical research on consent capacity and adequate performance on the MacCAT-CR was used in the CATIE trial (a large-scale clinical trial) as part of the criteria for independent consent (Stroup et al, 2003). It assesses competence on four subscales: *Understanding information, appreciation of the significance of the information, reasoning with the information,* and *expressing a choice*. Decisional capacity depends on the context and there is no particular level of ability to determine adequate capacity in all circumstances (Appelbaum and Grisso, 2001). Studies vary in level of risk and in the risk/benefit ratio. General consensus exists that as the degree of risk increases, a higher level of capacity is desirable. The MacCAT-CR has no established cut-score or algorithm for categorical determinations of capacity or incapacity. Scores on capacity assessment instruments, though helpful, should generally be supplemented with other

important information, such as mental status and decision-making context (Appelbaum and Grisso, 2001). This scale has not been adequately validated in the Indian context.

When research is combined with care

The Declaration of Helsinki states (clause 26), "When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship" (WMA 2008). This situation is particularly likely to occur in the typical doctor-patient encounter that prevails in India and hence this is particularly relevant to consent to participate in research.

The Declaration states (clause 31), "The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects".

The Declaration also states (clause 34), "The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship (WMA 2008).

Thus, if consent is obtained by the treating team, then it would be ideal that the adequacy of the comprehension of the participant (and their families) and lack of compulsion to participate be assessed by an independent person.

8. CONFIDENTIALITY

The Declaration of Helsinki states (Clause 11) that "It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects". It also states (Clause 23) that "Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity (WMA 2008).

Since mental illness is stigmatizing, the need for confidentiality is most important. This is especially important in (and difficult) in community surveys; it is also difficult when using proxy consent. There is a need for special caution in evaluating family dynamics and not using participants with stormy family relationships. Maintaining confidentiality is also important in case presentations and research reports.

The ICMR guidelines (ICMR 2006) states :

"The investigator must safeguard the confidentiality of research data, which might lead to the identification of the individual participants. Data of individual participants can be disclosed under the following circumstances :

1. only in a court of law under the orders of the presiding judge or
2. there is threat to a person's life or
3. in cases of severe adverse reaction may be required to communicate to drug registration authority or

4. if there is risk to public health it takes precedence over personal right to privacy and may have to be communicated to health authority.

Therefore, the limitations in maintaining the confidentiality of data should be anticipated and assessed and communicated to appropriate individuals or authorities as the case may be".

9. SPECIAL ISSUES WITH REGARD TO INTERVENTIONAL RESEARCH

The rapid increase in the outsourcing of clinical trials to India and the recent ethical controversies that have risen as a consequence (Srinivasan et al, 2006; Mudur 2006, Tharyan 2006) have led to concerns that have translated into a call for accountability, scientific rigour and transparency in the design, conduct and reporting of clinical trials. The main issues to be kept in mind are the following (Tharyan & Adhikai, 2007):

1. The need for a 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 (Antman et al, 1992).

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 (Young & Horton, 2005). 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 generalisable across populations, settings, and treatment variations, or whether findings vary significantly by particular subgroups. Moreover, the explicit methods used in systematic reviews limit bias and, hopefully, improve reliability and accuracy of conclusions (Pai et al, 2004).

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 4700 regularly-updated systematic reviews and protocols of reviews in preparation (Issue 4 2008); The Cochrane Controlled Trials Register (CENTRAL) currently contains references, mostly with abstracts, of more than 4,90,000 controlled clinical trials- easily the largest collection of such trials in the world (Allen et al, 2008).

All residents in India now have complimentary access to the full contents of *The Cochrane Library,* thanks to sponsorship provided by the Indian Council of Medical Research (ICMR) that recently signed a three-year contract for a national subscription with the publishers, John Wiley & Sons. Among the systematic reviews in *The Cochrane Library* are those produced by five review groups devoted to evaluating the effects of interventions used in mental health; in addition are available abstracts and citations to published systematic reviews and health technology assessment from other sources.

All research should also have a social value and should benefit the participants and communities they live in. The questions researched should be of relevance to healthcare in the region and not only

serve the interests of researchers or sponsors. The standards of care used to chose comparators and all aspects of multi-country trials should conform to the best available national standards of care in India (ICMR 2006).

2. Scientific Validity

Relevant issues in this regard are (Tharyan & Adhikari, 2007): Does the protocol contain a well constructed research question with details of participants, interventions, comparisons (including routes and doses) and outcomes, (primary and secondary) (PICO)? Are all relevant outcomes included in the protocol as well as the ways they will be collected and when? Does the protocol describe adequately the methods to generate the randomization sequence, conceal allocation, blind participants and outcome assessors and evaluate blinding (if appropriate), and methods to deal with trial attrition? Does the protocol describe in sufficient detail the estimated sample size for the primary outcome(s) and its justification? Does the protocol describe adequately the responsibilities of investigators and methods to ensure integrity of data collected and rules for interim analysis? Does the protocol ensure that all elements that are required to be reported by the CONSORT and ICMJE guidelines will be collected and recorded? Are ethical issues addressed adequately in accordance with international and local regulations and requirements? Has ethics committee approval been obtained? Adherence to these issues at the inception of the trial will ensure that the results are valid and reliable and the conduct of the trial ethical (Tharyan et al, 2008).

In reporting results, the relevant issues are: Have deviations from the protocol been reported? Is there a description or diagram of participant flow though the various stages of the trial? Have absolute values been reported in addition to proportions for binary outcomes? Have means as well as standard deviations (or standard errors) and numbers of participants for each intervention been reported for continuous outcomes? Have effect measures and confidence intervals been reported in addition to (or instead of) p values? Have drop-outs and withdrawals been described? Was an intention to treat analysis used? Have post-hoc analyses and sub-group analyses been kept to a minimum? Have all important outcomes been reported? Have funding sources and conflicts of interest been declared?

When interpreting results and reporting conclusions, the relevant issues are: Does the direction and strength of the effect as well as precision of the results for primary outcomes indicate the efficacy of the intervention? Are adverse effects likely to outweigh the potential benefits of the intervention? What are the results and what is the magnitude of effect? How precise are the estimates of effect? Are the results likely to be clinically significant? Is evidence of 'no effect being confused' for 'evidence of no effect'? Are the results of this study generalizable? How do these results compare with results generated elsewhere? How do they affect the pooled estimates from other trials? Is there sufficient evidence of effect? Is there significant variability in results? Are there any ethical concerns or conflicts of interest that would affect interpretation? Have the individual contributions of the authors been stated? Have funding sources and conflicts of interest been declared?

3. Prospective trials registration

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 (Evans et al, 2004). The International Committee of Medical Journal Editors (ICMJE) has also endorsed this position as a pre-requisite to submission of manuscripts for publication (DeAngelis et al, 2004; DeAngelis et al, 2005; Laine et al, 2007), as have the editors of

many Indian Journals (Satyanarayana et al, 2008). 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" (WMA 2008).

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 utilisation 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 (Chan et al, 2004; Tharyan & Ghersi, 2008; Grobler et al, 2008).

Clinical Trials Registry-India

On 20 July 2007, the Clinical Trials RegistryIndia (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 (Tharyan & Ghersi, 2008).

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. This includes early and late trials (Phase I to IV), trials of marketed or non-marketed products, uncontrolled or those with a control comparison, and randomized or non-randomized trials.

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 normal fluctuations in the course of an illness. 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 (Tharyan & Ghersi, 2007).

5. *Help prevent wasteful duplication of research*: as researchers, funders and ethics committees are more able to assess whether similar studies have already been conducted, or are ongoing.

Requiring prospective registration can be considered an ethical imperative for IRBs/IECs/*ethics committees* (apart from trial sponsors and investigators) since safeguarding the rights of trial participants and weighing risks and benefits are cardinal obligations of any research ethics committee. People participate in trials for personal benefit but also for potential social benefit. Trials 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 trials existence is necessary, as researchers or trial sponsors may seek to circumvent the ICMJE requirement of prospective registration, as a pre-requisite to publication in member journals, by publication of results in journals not endorsing the ICMJE position; or not publishing any results. Registration can also inform those who might be future research subjects or patients; can enlighten those who plan or fund new proposals; and can serve to reduce unnecessary (and sometimes risky) future duplication of effort, and duplicate publication of the results of a single trial masquerading as several trials (Tharyan, 2007).

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

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

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. 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). 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 (Tharyan & Ghersi, 2008).

There are a number of compelling reasons why registering trials in the CTRI is important. The CTRI is ideally placed to promote, identify and track clinical trials being conducted in India; this is currently not possible. There is an urgent need to improve the ability of researchers to conduct high quality clinical trials; through the CTRI, the needs of these researchers may be identified and met. The CTRI can be an important tool to strengthen the regulatory and ethical framework capacity within India by liaising closely with national regulatory bodies such as the Drug Controller General of India, the ICMR and local ethics committees. The CTRI has been developed within a specific political framework and policy-makers and agencies such as the Department of Science and Technology, the WHO India Country Office and the ICMR have "invested" in it as a source of national pride, hence adding to its legitimacy and resulting in its status as a primary register of the WHO stable of registers so that all trials in the CTRI will be identifiable though the WHO ICTRP search portal.

4. The use of placebos

An industry-funded placebo-controlled clinical trial of Risperidone, a newer antipsychotic drug in the treatment of acute mania conducted across eight centres in India, invited considerable criticism and debate regarding the ethics of using placebos in clinical research when effective treatments exist; the methods of evaluating the effects of interventions in health care research; the validity of informed consent, particularly in supposedly vulnerable populations and societies; the interpretation of ethical guidelines; and the role of ethics committees, regulatory agencies, sponsors and medical journal editors in international collaborative clinical research (Mudur 2006; Tharyan 2006).

The Declaration of Helsinki (clause 32) states, "The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

1. The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
2. Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme

care must be taken to avoid abuse of this option.

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 acknowledges (clause 7) 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 (Gross et al, 2006).

Another compelling reason to use placebos comparators for new interventions is because even though effective interventions exist for many psychiatric conditions, evidence suggests that given the high placebo response rates in many psychiatric conditions, including acute mania, it may be misleading to make reliable conclusions of efficacy in the absence of a placebo comparator, even when supposedly effective treatments exist (Tharyan, 2006). In fact, The National Depressive and Manic-Depressive Association Consensus Statement from the US on the use of placebo in clinical trials of mood disorders concluded that the placebo has a definite scientific role in mood disorder studies and that findings of equivalence between a new drug and standard treatment are not evidence of efficacy unless the new drug is also significantly more effective than placebo (Charney et al, 2002).

Reconciling the differences between the needs of clinicians, whose primary aim is to protect that interests of patients, and the needs of clinician-researchers, whose aims include advancing scientific knowledge resulting in seemingly ethically dubious practices such as random allocation and the use of placebos, requires attention being paid to critical issues. These are particularly important when a new drug is being evaluated and or a marketed drug is being tested for a new indication. These studies must 1) have the potential to yield scientifically valid and clinically useful information, and the magnitude of these benefits must be reasonable and proportional to the risks that subjects are running, including those associated with the deferral of some components of standard therapy. 2) The consent obtained should be valid (competent), informed, and voluntary (if possible) and independently monitored. 3) Participants should understand these deviations from usual clinical care. 4) The period on placebo or on no treatment should be as short as possible. 5) Participants should be closely monitored and should be withdrawn from the trial if symptoms do not improve in a reasonable time frame, if they worsen, or if the participant so desires. 6) Symptomatic treatment must be offered to all and effective interventions offered to non-responders. 7) All participants must be followed up to assess harms associated with participation and their views also ascertained regarding participation (Tharyan, 2006).

5. Monitoring and reporting adverse events

Adverse events or adverse drug reactions (AE/ ADR) arising in a trial may be expected or unexpected. All anticipated events should specified in the protocol. They may be mild, moderate or severe/ serious and for each one, the causality relationship should be examined. An AE or unexpected ADR requires expedited review by the ethics committee. Unexpected AE/ ADRs and all SAE (serious adverse event) should be reported to the sponsor by the investigator within 24 hours and to the ethics committee that accorded approval to the study protocol within seven days. In the event of death the IRB/IEC should also be informed within 24 hours. Any unexpected SAE occurring during a clinical trial should be communicated promptly within 14 calendar days by the Sponsor to the

Licensing Authority and to the Investigator(s) of other trial sites participating in the study. The reporting of the SAE to the regulatory authority immediately is to enable it to stop the clinical trials of unapproved drugs or withdraw from market approved drugs based on report of Phase IV studies. All other serious unexpected reactions (ADRs) that are not fatal or life threatening must be filed as soon as possible but not later than 14 calendar days. At the end of the trial, all adverse events whether related to trial or not are to be listed, evaluated and discussed in detail in the final report (ICMR, 2006).

For studies that involve more than minor risk, an independent Data Safety Management Board (DSMB) should be formed that should review all adverse events and any pre-agreed interim analyses to determine whether pre-agreed conditions for termination of the study due to a clear benefit due to the experimental intervention or clear evidence of harm.

The IRB/IEC reviewing the protocol must review these aspects as well before giving approval.

6. Compensation for participation and for research-related injury

Participants may be compensated for participation in research in two sets of circumstances. Reasonable re-imbursement for out-of pocket expenses incurred during travel and loss of earnings due to participation may be compensated (this includes the guardian in cases of minors or those with diminished capacity), as may free medical care for all conditions arising as a pre-requisite for inclusion into the study or during the period of the study. It is unethical to expect participants to pay for research-related investigations or treatments, unless this would form part of usual care, and not only for research and all participants are equally charged for such expenses. All such re-imbursements must be pre-approved by the IRB/IEC, so that they may not serve as inducements to participate. All expenses that participants will have to bear should also be sanctioned by the IRB/IEC; Examples of additional research costs include: Prolongation of treatment or hospitalization; Extra diagnostic tests necessary for the research; Extra clinical or laboratory assessments to evaluate research treatment outcome; A research treatment (whether randomly assigned or not) which may be more costly that a standard treatment; Other substantial costs associated with extra visits. All such payments should also be mentioned in the information sheet provided to participants during the consent process. If participants are withdrawn from the study due to medical reasons, the ICMR guidelines require that they receive the full benefits of participation, while if they withdraw consent, they should receive compensation proportionate to their participation (ICMR 2006).

Undue inducement through compensation for individual participants, families and populations should be avoided. This prohibition, however, does not include agreements with individuals, families, groups, communities or populations that foresee technology transfer, local training, joint ventures, provision of health care reimbursement, costs of travel and loss of wages and the possible use of a percentage of any royalties for humanitarian purposes (ICMR, 2006).

The second instance where participants are entitled for compensation concerns injury occurring as a consequence of participation in the trial, including death. It is the obligation of the sponsor, be it a commercial organization, institution or individual, to undertake this responsibility, either through insurance cover, or other means, to ensure that this is in place before the conduct of the trial and all such matters are stated clearly in the consent document. If the trial is covered by insurance in a multi-centred trial, then legal opinion form the participating centres lawyers should be obtained and an Indian insurance agency's agreement also sought, so that participants will have recourse to justice should any mishap occur. If compensation is not planned, this should also be stated in the informed consent document and cleared by the IRB/IEC beforehand.

All financial transactions, including the budget for the study and the amounts that investigators would get paid by sponsors for all stages of recruitment and study completion should be stated in the protocol and should be approved by the IRB/IEC along with any agreements signed between all parties concerned (ICMR 2006).

7. Post trial access

The Declaration of Helsinki (WMA 2008) in clause 14 states, "The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits;" a view that is also endorsed by the ICMR guidelines (ICMR 2006). This is a controversial issue considering that many participants in multi-country trials would not have access to drugs in phase I, II and III trials until they have been approved by regulatory agencies in their country, even if they were affordable; and considering that superiority demonstrated during the trial over placebo or other comparator need not necessarily translate into the intervention being the most suitable for them in the overall scheme of management.

The post-trial benefits could also include better services accruing to the community such as establishment of clinics, health services, educational programmes or other methods that improve healthcare of the participants and the communities they live in; though this should not serve as inducements for people to participate in research against their better judgement.

However, this recommendation serves to remind researchers that they have obligations to the welfare of participants beyond the period of research and hence, such agreements for continuation of the most appropriate care beyond the trial should also be stated in the informed consent document, including the duration of such post-trial access to the investigational drug, or other appropriate care, the duration of such access and who will pay for this. Such arrangements should also be approved by the IRB/IEC.

10. PUBLICATION ISSUES

Publishing research is an ethical imperative. The Declaration of Helsinki states in clause 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" (WMA 2008).

Conflicts of interest

Conflicts of interest are those that might compromise the integrity of the results through conscious or unconscious attempts to present them in a way that would be favourable to the researcher's investigation. These may arise due to financial, academic, political or personal reasons. They are rarely disclosed in publications of trial reports in Indian medical journals (Tharyan et al, 2008).

Financial conflicts arise when the investigator has significant financial dealings with the sponsors in the form of salary or other payments for services like consulting fees or honorarium per participant; research grants; equity interests in stocks, stock options or other ownership interests; and intellectual property rights from patents, copyrights and royalties from such rights. All such potential conflicts

should be declared in the trial protocol and report so that IRB/IEC members and readers may be aware of them in granting approval and interpreting the results

Authorship issues

Decision regarding authorship should commence at the design stage of each study. The International Committee of Medical Journal Editors (http://www.icmje.org/#author) has recommended the following criteria for authorship; these criteria are still appropriate for those journals that distinguish authors from other contributors.

1 "Authorship credit should be based on
   a. substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;
   b. drafting the article or revising it critically for important intellectual content; and
   c. final approval of the version to be published.
   d. Authors should meet conditions a, b and c.
2 When a large, multi-center group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship/contributorship defined above and editors will ask these individuals to complete journal-specific author and conflict of interest disclosure forms. When submitting a group author manuscript, the corresponding author should clearly indicate the preferred citation and should clearly identify all individual authors as well as the group name. Journals will generally list other members of the group in the acknowledgements.
3 The National Library of Medicine indexes the group name and the names of individuals the group has identified as being directly responsible for the manuscript.
4 Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
5 All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
6 Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.
7 Some journals now also request that one or more authors, referred to as "guarantors," be identified as the persons who take responsibility for the integrity of the work as a whole, from inception to published article, and publish that information.
8 Increasingly, authorship of multi-center trials is attributed to a group. All members of the group who are named as authors should fully meet the above criteria for authorship/contributorship.
9 The group should jointly make decisions about contributors/authors before submitting the manuscript for publication. The corresponding author/guarantor should be prepared to explain the presence and order of these individuals. It is not the role of editors to make authorship/contributorship decisions or to arbitrate conflicts related to authorship".

11. SCIENTIFIC MISCONDUCT

Research misconduct means fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.

(a) **Fabrication** is the wilful making up data or results and recording or reporting them.

(b) **Falsification** is the wilful manipulation of research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research report.

(c) **Plagiarism** is the appropriation of another person's ideas, processes, results, or words without

giving appropriate credit.
Research misconduct does not include honest error or differences of opinion.
Disputes about authorship do not normally come under the scope of research misconduct. In some instances, failure to include a researcher, who contributed significantly to the research, as an author or to acknowledge his/her contribution could amount to plagiarism.

Each institution engaging in research should develop policies to prevent research misconduct. The reasons that contribute to misconduct include:

a. Pressure to get results to obtain funding or tenure
b. Publications are linked to promotions
c. Increasing complexity of research environment: interdisciplinary, collaborative research; industry funding, which can create conflicts of interest; responsibilities & new skills required to manage research; now many PIs being asked to manage their own research budgets; more graduate students to supervise, larger labs/projects, hence less time for thorough oversight
d. Inadequate training in proper conduct

Institutions should foster trust and integrity in research rather than emphasise the need to churn out large numbers of papers.

The methods to prevent misconduct include:

a. Educating students about research ethics and conducting research ethics and GCP workshops to certify all researchers;
b. Developing and disseminating policies that all investigators are aware of;
c. Senior researchers setting standards, verifying data and serving as mentors;
d. Reviewing and revising protocol submission forms in a proper manner so that researchers are facilitated in producing good work as well as deterred from sloppy research;
e. Ensuring prospective registration of trials and reporting results so that fabrication, falsification and plagiarism can be detected, as well as publication bias and selective reporting can be avoided;
f. Educating researchers of the need to maintain fidelity to protocols and respect for the integrity of data;
g. Setting clear rules for data collection and analysis; data monitoring and detecting sloppy research by conducting audits;
h. Teaching researchers about avoiding plagiarism by acknowledging others work or ideas appropriately and seeking permission to reproduce others work, when appropriate;
i. Investigating allegations promptly and taking necessary action at an administrative level.

12. SUMMARY OF GUIDELINES FOR RESEARCH IN PEOPLE WITH MENTAL DISORDERS

Purpose

The purpose of these guidelines is to provide a set of guidelines specific to research in people with Mental Disorders in India. They should be used along with the elaborations presented in earlier chapters of this document.

1. General Principles

1.1 All research on people with psychiatric disorders and normal human volunteers should be conducted in accordance with the ethical norms laid down by the latest revisions of the

? ***Ethical Guidelines for Biomedical Research on Human Subjects of the Indian Council for Medical Research (ICMR)***,

- ? ***Drugs and Cosmetics Act and Rules,* in particular *Schedule Y,***
- ? ***Declaration of Helsinki of the World Medical Association***, and the
- ? ***Indian Good Clinical Practice Guidelines*** *and the* ***ICH-GCP guidelines***.
- ? In addition all research will also conform to applicable central, state and local laws and regulations.

1.2. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. However, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

1.3 Psychiatric patients, like all other patients, must be able to benefit from the fruits of research and, hence, they must have the opportunity to participate freely in sound research and should not be excluded from this opportunity only because they are psychiatric patients.

1.4 All research on people with psychiatric disorders should be preceded by the submission of a research protocol that is submitted and approved by a properly constituted Ethics committee (Institutional Review Board) that reviews and approves the scientific and ethical aspects of the proposal before the research is conducted.

1.6 All research involving people with psychiatric disorders should have a social value that is of relevance to the population being studied and should include community and cultural concerns.

1.7 All research proposals should follow sound scientific methods as deemed appropriate by the research question and the appropriate study design. These design elements should be incorporated into the design of the research protocol in order to improve the scientific validity of the proposal.

1.8 All research proposals should provide sufficient information as laid down by the ICMR guidelines to ensure that ethical issues have been adequately dealt with.

1.9 All research done on people with psychiatric disorders and normal volunteers should follow the principles of respect for the autonomy, beneficence, non-malfeasance, and justice and concern for vulnerable participants.

1.10 All such research should assess the anticipated risks to the participant or to others compared to the anticipated benefits and should not be done if the risks significantly outweigh the anticipated benefits.

1.11 All such research should take place only with the documented informed consent of the individual, if the capacity to consent is present. It is strongly recommended that the voluntariness, understanding of the risks and benefits, and the validity of the consent be verified by an independent person other than the investigator obtaining the consent.

1.12 In people with impaired capacity to consent, the informed consent of a responsible family member may be obtained. If during the course of research, the capacity to consent is restored to the participant, attempts should be made to obtain and document informed consent.

1.13 All research involving human participants should be undertaken only by competent researchers who have sufficient training and facilities and the time to safely undertake the research. The responsibility of the safety of participants and the integrity of the research rests with the investigators even if consent has been freely given.

1.14 All attempts should be made to preserve the confidentiality of participants and the information arising from participation in research.

2 Institutional Review Boards (Independent Ethics Committees)

2.1 All research proposals should be submitted for approval by an ethics committee with a proper mandate, written policies and standard operating procedures and composition, terms of appointment and responsibilities as laid down by the ICMR bioethics guidelines and Schedule Y of the Drugs and Cosmetics Act.

2.2 The mandate of the IRB is to review and approve the scientific merit of the proposal and the ethical safeguards, including the risk benefit ratio, distribution of burden and benefit and provisions for appropriate compensations, wherever required.

2.3 The scientific merit may be determined by a separate Research Committee, if possible or by the IRB/IEC if this is not possible, provided all such members have the required expertise in scientific matters, particularly in relation to research in mental illness.

2.4 The IRB/IEC has the mandate to suggest strategies to improve research proposals that fall short of the expected scientific and ethical standards and to refuse approval of research proposals that do not meet the expected scientific and ethical standards.

2.5 The IRB also has the mandate to:

a. provide ongoing monitoring of all research that it approves, including site visits and audits of procedures and documentation
b. Require periodic reports of progress and adverse effects and final reports of all research that it approves
c. Require that the results be made publically available in the form of research publications
d. Ensure that universal ethical values and international scientific standards are expressed in terms of local community values and customs.

2.6 The composition of the EC shall reflect that recommended by the ICMR's guidelines and Schedule Y of the Drugs and Cosmetics Act and include a social scientist, an ethicist/theologian/representative of an non-governmental organization, a legal expert, a lay person from the community, a basic medical scientist (preferably a pharmacologist) and a clinician.

2.7 A minimum of 6 persons (listed above) should be present at the review of each proposal

2.8 The Chairperson of the EC should be a person of stature with a scientific background and adequate familiarity with the principles of ethics and related issues. He/she will be from outside the Institution to maintain the independence of the Committee. The deputy chairperson may be from within the institution and the member secretary will be from within the institution to ensure the efficient functioning of the IRB/IEC.

2.9 The IRB may call upon independent consultants who may provide special expertise to the IRB on proposed research protocols. These consultants may be specialists in ethical or legal aspects, specific diseases or methodologies, or they may be representatives of communities, patients, or special interest groups. They are required to give their specialized views and may be required to attend convened IRB meetings but do not take part in the decision making process, which is conducted by members of the IRB.

2.10 All members reviewing the scientific aspects must be conversant with relevant guidelines for the design, conduct and reporting of various types of research designs.

2.11 All IRB/IEC members must be conversant with the latest versions of the ICH-GCP guidelines (as modified for India), and ICMR guidelines for research involving human subjects and Schedule Y of the Drugs and Cosmetics Act and the Declaration of Helsinki. Opportunities for continuing education of members must be provided.

2.12 IRBs are permitted by the ICMR guidelines to charge a *non-refundable processing fee* for research proposals that are funded by agencies or organizations with a commercial orientation (pharmaceutical companies, contract research organizations etc) for IRB approval. This fee

need not be applicable to proposals that are funded by non-commercial sponsors (governmental or non-governmental funding agency). This processing fee should be independent of the eventual decision to accept, revise or reject the proposal.

2.13 All research proposals should contain the elements of research design and proposed analysis and address ethical issues as stipulated by the ICMR guidelines, Schedule Y of the Drugs and Cosmetics Acts and Rules and the Indian ICH-GCP guidelines.

2.14 Depending on the risk involved, proposals may be categorised three types, namely, *exemption from review*, *expedited review* and *full review*. An investigator cannot decide that her/his protocol falls in the exempted category without approval from the IEC. All proposals will be scrutinised to decide under which of the following three categories it will be considered

3. Prospective registration of clinical trials

3.1 The Declaration of Helsinki requires that all trials should be prospectively registered in a publically accessible database before enrollment of the first participant. The ICMR and the WHO require prospective registration of all clinical trials before enrolment of the first participant in a Primary Register of the WHO International Clinical Trials Registry Platform. Further, prior registration is now a condition of publishing clinical trials for many journals.

- ? From 1st July 2005 the International Committee of Medical Journal Editors (ICMJE) has declared that their journals will not publish the results of any clinical trials not included on an authorized register at the trials inception.
- ? From Jan 2010, Editors of 12 Indian Medical Journals will not publish reports of trials that have not been prospectively registered.

3.2 The ICMR requires all trials conducted in India to be prospectively registered in the Clinical Trials Registry- India (CTRI; www.ctri.in). Schedule Y requires that the Declaration of Helsinki and all ICMR guidelines be followed for clinical trials. The CTRI is a Primary Register of the WHO International Clinical Trials Registry Platform and trials fully registered here will fulfill the ICMJE criteria of prospective trials registration.

3.3 All interventional clinical trials conducted in India and involving Indian participants need to be registered.

3.4 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, behavioral treatments, etc.) to evaluate their effects on health-related outcomes. Thus, early and late trials, trials of marketed or non-marketed products, randomized or non-randomized trials -- all should be registered.

3.5 The CTRI accepts registration of trials that have already commenced at the time of registration (for a limited period).

3.6 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.

3.7 For multi-center and multi-sponsor trials, it is the lead PI or lead sponsor who should take responsibility for registration. However, in case of multi-country trials, the Indian PI should also get the trial registered in CTRI quoting any other Registration number (e.g: clinicaltrials.gov registration number as its Secondary ID.

3.8 The CTRI requires, in addition to the entry of the WHO 20-item dataset, contact details of the ethics committee and a copy of EC approval (and DCGI approval, if applicable). Full details of all required items can be accessed from www.ctri.in

3.9 IRBs/IECs are recommended to only grant provisional approval for clinical trials in humans till the permanent CTRI registration number and a copy of the registration document is submitted to it, and the IRB/IEC should state this in the initial decision letter. Researchers may not commence

recruitment until the final clearance is received and this should await receipt of the permanent registration number and registration document. Once this is received, the EC should issue the final clearance letter.

3.10 Registrants are also required to regularly update information on each trial (including patient accrual, trial and publication status).

3.11 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.

3.12 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).

3.13 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.

4. Reporting adverse events

4.1 Researchers should report any adverse events, and amendments to the protocol to the IRBs . Reporting of adverse event should follow the format and timelines recommended in Schedule Y of the Drugs and Cosmetics Act.

4.2 Researchers and IRBs should consider the appointment of an independent Data and Safety Monitoring Board for studies that involve more than minimal risk to the participants or others.

4.3 All documents pertaining to the project should be archived for minimum period of 3 years after the study is completed. The list of essential documents to be stored is laid down in the ICMR guidelines.

5. Informed consent

5.1 Informed consent is "consent given voluntarily by a competent individual who has received the necessary information, has adequately understood the information and after considering the information, has arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation".

5.2 Informed consent is based on the principle that competent individuals are entitled to choose freely whether to participate in research or not and protects the individual's freedom of choice and respect for the individual's autonomy. It also protects the subjects' rights.

5.3 Taking informed consent is a "process" and does not merely consist of a signature on the consent form. Informed consent is a communication process between the researcher and the participant and starts before the research is initiated and continues throughout the duration of the study. The investigator or his delegate must discuss all pertinent aspects of the study, answer any queries / doubts, request consent and then if freely given, documented. The ultimate responsibility is the investigator's.

5.4 Informed consent includes a verbal description and discussion of the details of the study including the process of randomization, the components of the study, and other details mentioned in Schedule Y and the ICMR guidelines, as well as a written *information sheet* containing all relevant information in simple, non-technical language in the participant's vernacular and given to the participant to keep. Adequate time must be provided for the participant to decide on participation. A separate i*nformed consent form* must be used to

document consent.

5.5 In case of illiterate participants, a witness is crucial and thumb impressions are allowed. All signatures should be dated and in case a date is forgotten on the day the consent is taken, it must be retaken on the next visit and dated, with a clear explanation documented in the source document.

5.6 The investigator must not date the consent at any point in time; this must be done by the witness in the case of illiterate participants.

5.7 In the case of minors, proxy consent from a parent/responsible guardian is permitted and only the parent/responsible guardian may sign the informed consent form. However, it is mandatory that the minor provides assent (permission) to participate and, if possible, this should be recorded in a separate assent form.

5.8 If the participant is incompetent to provide valid informed consent and it is deemed ethically justified to include this person in research, then the proxy consent of a responsible family member/legal guardian and a witness must be taken. There should an independent verification of the validity of the consent given.

5.9 Each subject (or their representative) must be given a copy of the signed consent form. The original consent form should be filed in such a manner as to insure immediate retrieval when required by auditing entities, IRB, or sponsor monitors.

5.10 Written documentation of informed consent is required. Therefore, obtaining consent from an authorized third party via the telephone is not acceptable.

5.11 Obtaining informed consent from subjects must be accomplished prior to performing the research activity and using only an IRB/IEC approved consent form. Written requests for amendments to an existing consent form must be approved by the IRB/IEC prior to implementation.

6. Compensation

6.1 The protocol for the study should include permissible reimbursements to participants that compensates them for reasonable expenses associated with study participation but does not amount to inducement.

6.1 Arrangements should be made to provide compensation for study related injury or disability and medical care by arrangements with Indian insurance agencies for studies with potential for harm. All such arrangements should be clearly detailed and approved by the IRB/IEC.

7. Authorship and publication issues

7.1 The results of all research should be made publicly available within a reasonable period of time after completion of the study.

7.2 All substantial contributors should receive authorship credit which should be based on:

- ? substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;
- ? drafting the article or revising it critically for important intellectual content; and
- ? final approval of the version to be published.
- ? Authors should meet conditions a, b and c.

8. Research misconduct

8.1 **Research misconduct** means fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.

(a) **Fabrication** is the willful making up data or results and recording or reporting them.

(b) **Falsification** is the willful manipulation of research materials, equipment, or processes, or

changing or omitting data or results such that the research is not accurately represented in the research report.

(c) **Plagiarism** is the appropriation of another person's ideas, processes, results, or words without giving appropriate credit.

(d) Research misconduct does not include honest error or differences of opinion.

(e) Disputes about authorship do not normally come under the scope of research misconduct. In some instances, failure to include a researcher, who contributed significantly to the research, as an author or to acknowledge his/her contribution could amount to plagiarism.

8.2 Matters pertaining primarily to the scientific validity and ethical conduct of research will ordinarily fall under the purview of the Institutional Review Board (IRB), unless they pertain to research misconduct.

8.3 It is the responsibility of the IRB to liaise with appropriate authorities to investigate allegations of misconduct about any proposal approved by them.

8.4 Policies should be developed by IRBs on how to proceed when such allegations are made so as to ensure integrity of the study results and the safety of the participants (including pausing or stopping the study), and to provide a fair chance to the investigator to clear his/her reputation.

9. Conflicts of interest

9.1 All researchers should declare any potential conflicts of interest (financial, academic, institutional, personal) in the research protocol as well as in all publications related to the study.

9.2 All IRB members should also declare conflict of interest with the topic of the study or any researcher associated with the study and should not participate in reviews of proposals in which they might have a conflict of interest.

9.3 IRB members should evaluate each proposal to ascertain if there are undisclosed conflicts of interest as well as to ascertain if these interests outweigh the primary responsibility to the safety of the patient and integrity of the study.

10. Post-trial benefits

10.1 The study proposal and consent form should provide details of arrangements made, if any, regarding continued access to care of the study drug to participants , should it prove effective and safe, and this should form part of pre-trial agreements with sponsors and participants.

10.2 It is recommended that for new drugs yet to be marketed, sponsors agree to provide the drug till the drug is marketed, though this may not always be possible. Such arrangements should have the approval of the DCGI.

11. Competence to perform and approve research

11.1 All researchers should receive adequate training in research methodology and research ethics and should read a copy of the ICMRs bioethics guidelines, Schedule Y of the Drugs and Cosmetics Act and other relevant documents. In addition, they should read research methodology guidelines such as the CONSORT and other documents relevant to the design of the study they plan to conduct. They should also have the requisite time, facilities and personnel to safely conduct the proposed research. Similarly, all IRB/IEC members should be suitable knowledgeable about these guidelines and should have opportunities for ongoing training.

References

1. The WHO World Mental Health Survey Consortium. Prevalence, Severity, and Unmet Need for Treatment of Mental Disorders in the World Health Organization World Mental Health Surveys. *JAMA* 2004;291: *2581-2590*.
2. World Health Organization. *The World Health Report 2001. Mental Health: New Understanding, New Hope.* Geneva, World Health Organization, 2001. Available at: http://www.who.int/whr/2001/en/ (Accessed 12 Jan 2007).
3. World Health Organization, *Investing in Mental Health,* Geneva, World Health Organization, 2003. Available at: http://www.who.int/mental_health/en/investing_in_mnh_final.pdf (Accessed 1 March 2007).
4. Patel V. Poverty, inequality, and mental health in developing countries. In: D Leon and G Walt, (Eds) *Poverty, inequality and health: an international perspective,* Oxford, Oxford University Press. 2001. 247261.
5. Saraceno B, C Barbui. Poverty and mental illness. *Can J Psychiat* 1997; 42: 285290.
6. Patel V, Araya R, de Lima M, A Ludermir, C Todd. Women, poverty and common mental disorders in four restructuring societies. *Socl Sci Med* 1999;49:14611471.
7. World Health Organization. The global burden of disease. Cambridge, Mass.: Harvard University Press, 1997.
8. Michels R, Marzuk PM. Progress in psychiatry. *NEJM* 1993;329:552-560.
9. Appelbaum PS. Rethinking the conduct of psychiatric research. *Arch Gen Psychiat* 1997;54:117-120.
10. Roberts LW. Ethics and Mental Illness Research. *Psychiat Clin N Am* 2002; 25: 525-545.
11. Srinivasan SS, Pai A, Bhan A, Jesani A, Thomas G. Trial of risperidone in India concerns. *Br J Psychiat* 2006; 188:489.
12. Mudur G. Indian study sparks debate on the use of placebo in psychiatry trials. *BMJ* 2006; 332:566.
13. Strous RD. Psychiatry during the Nazi era: ethical lessons for the modern professional. *Ann Gen Psychiat* 2007, **6**:8 doi:10.1186/1744-859X-6-8.
14. Birley JLT. Political abuse of psychiatry. *Acta Psychiatrica Scand* 2000: 101:13-15.
15. Quitkin FM. Placebos, drug effects, and study design: a clinician's guide. *Am J Psychiat* 1999;156:829-836.
16. Moser D, Reese R, Schultz S, et al. Informed consent in medication-free schizophrenia research. *Am J Psychiat* 2005;162:12091211.
17. Jones I, Scourfield J, McCandless F, Craddock N. Attitudes towards future testing for bipolar disorder susceptibility genes: a preliminary investigation. *J Aff Dis* 2002;71:189193.
18. Yeh M, Morley KI, Hall WD. The policy and ethical implications of genetic research on attention deficit hyperactivity disorder. *Austr N Z J Psychiat.* 2004;38:1019.
19. Haroun N, Dunn L, Haroun A, Cadenhead KS. Risk and Protection in Prodromal Schizophrenia: Ethical Implications for Clinical Practice and Future Research. *Schizophrenia Bull* 2006 32: 166-178.

20. Carpenter WT, Applebaum PS, Levine RJ. The Declaration of Helsinki and clinical trials: A focus on placebo-controlled trials in schizophrenia. *Am J Psychiat* 2003;160:356362.
21. Dunn LB, Candilis PJ, Roberts LW. Emerging Empirical Evidence on the Ethics of Schizophrenia Research. *Schizophrenia Bull* 2006 32: 47-68.
22. Angell M. The ethics of clinical research in the third world. *New Engl J Med* 1997; 337:847-849.
23. Michels R. Are research ethics bad for our mental health? *New Engl J Med* 1999;340:14271430.
24. Miller FG, Fins JJ. Protecting vulnerable research subjects without unduly constraining neuropsychiatric research. *Arch Gen Psychiat*. 1999;56:701702.
25. Edwards SJ, Lilford RJ, Braunholtz DA, Jackson JC, Hewison J, Thornton J. Ethical issues in the design and conduct of randomised controlled trials. *Health Technol Assess*. 1998;2(15): 1-132.
26. Benson PR, Roth LH, Winslade WJ. Informed consent in psychiatric research: preliminary findings from an ongoing investigation. *Soc Sci Med* 1985;20:13311341.
27. Moser DJ, Schultz SK, Arndt S, Benjamin ML, Fleming FW, Brems CS, Paulsen JS, Appelbaum PS, Andreasen NC. Capacity to provide informed consent for participation in schizophrenia and HIV research. *Am J Psychiat* 2002;159:12011207.
28. Kim SYH. Does Decisional Impairment Become Decisional Incompetence? Ethical and Methodological Issues in Capacity Research in Schizophrenia. *Schizophrenia Bull* 2006 32: 92-97.
29. Wirshing DA, Wirshing WC, Marder SR, Liberman RP, Mintz J: Informed consent: assessment of comprehension. *Am J Psychiat* 1998; 155:15081511.
30. Carpenter WT, Gold JM, Lahti AC, Queern CA, Conley RR, Bartko JJ, Kovnick J, Appelbaum PS: Decisional capacity for informed consent in schizophrenia research. *Arch Gen Psychiat* 2000; 57:533538.
31. Moser DJ, Reese RL, Hey CT, Schultz SK, Arndt S, Beglinger LJ, Duff KM, Andreasen NC. Using a Brief Intervention to Improve Decisional Capacity in Schizophrenia Research. *Schizophrenia Bull* 2006 32: 116-120.
32. Appelbaum PS, Roth LH, Lidz C. The therapeutic misconception: informed consent in psychiatric research. *Int J Law Psychiat* 1982;5:319329.
33. Lidz CW, Appelbaum PS, Grisso T, Renaud M. Therapeutic misconception and the appreciation of risks in clinical trials. *Soc Sci Med* 2004;58:16891697.
34. Jesani A. Medical professional and interrogation: Lies about finding the truth. *Indian J Med Ethics* 2006; 3: 116-117.
35. Kala AK. Of ethically compromising positions and blatant lies about 'truth serum.' *Indian Journal of Psychiatry* 2007; 49: 6-9.
36. Jagadeesh N. Narco analysis leads to more questions than answers. *Indian J Med Ethics* 2007; 3: 9.
37. Annas GJ, Grodin MA. The Nazi Doctors and the Nuremberg Code. New York: Oxford University Press; 1992.
38. Beecher HK. Ethics and clinical research. New England Journal of Medicine 1966; 274(24):13541360.

39. International Committee of Medical Journal Editors (aka the Vancouver Group). Uniform Requirements for Writing Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. 2004. Available at www.icmje.org. (Accessed March 21, 2007).
40. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (aka the Belmont Report). 1979. Available at http://ohsr.od.nih.gov/guidelines/belmont.html. (Accessed November 1, 2007).
41. Department of Health and Human Services, National Institutes of Health, Office for Protection from Research Risks. *Title 45: Public Welfare, Part 46: Protection of Human Subjects* (aka the Common Rule). 2001. Available at www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm. (Accessed November 1, 2007).
42. Council for International Organizations of Medical Sciences. International Ethical Guidelines for Biomedical Research Involving Human Subjects. 2002. Available at www.cioms.ch. (Accessed November 1, 2007).
43. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Steering Committee. *ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice (E6).* 1996. Available at www.ich.org. (Accessed October 2, 2008).
44. National Bioethics Advisory Commission. *Research Involving Persons With Mental Disorders That May Affect Decision-making Capacity.* 1998. Available at www.georgetown.edu/research/nrcbl/nbac/capacity/TOC.htm. (Accessed July 20, 2006).
45. Oldham JM, Haimowitz S, Delano SJ. Protection of persons with mental disorders from research risk. *Arch Gen Psychiat* 1999;56(8):688693.
46. Fischer BA. A summary of important documents in the field of Research Ethics. *Schizophrenia Bull* 2006;32:69-80.
47. 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).
48. 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).
49. 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). *Nat Med J India* 2008; 21:62-68.
50. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies. *PLoS Med* 2007; 4(10):e296.
51. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, Lijmer JG, Moher D, Rennie D, de Vet HC. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *BMJ* 2003; 326(7379):41-44.
52. Tharyan P, Adhikari SD. Randomized controlled clinical trials: critical issues. *J Anaes Clin Pharm*

2007;23(3): 231-240.

53. Appelbaum PS, Grisso T. MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR). Sarasota, FL: Professional Resource Press; 2001.
54. Flory J, Emanuel E. Interventions to improve research participants' understanding in informed consent for research: a systematic review. JAMA. 2004;292(13):1593-601.
55. Tharyan P. Whose trial is it anyway? Reflections on morality, double standards, uncertainty and criticism in international collaborative health research. *Monash Bioethics Review*, 2006; 24:53-68.
56. Appelbaum PS, Roth LH. Competency to consent to research: a psychiatric overview. *Arch Gen Psychiat* 1982;39:951958.
57. Stroup TS, McEvoy JP, Swartz MS, et al. The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project: schizophrenia trial design and protocol development. *Schizophrenia Bull* 2003;29:1531.
58. Dunn LB, Palmer BW, Appelbaum PS, Saks ER, Aarons GA, Jeste DV. Prevalence and correlates of adequate performance on a measure of abilities related to decisional capacity: Differences among three standards for the MACCAT-CR in patients with schizophrenia. *Schizophrenia Res* 2007; 89: 110118.
59. 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. JAMA 1992; 268:240-8.
60. Young C, Horton R. Putting clinical trials into context. Lancet 2005;366: 107-8.
61. 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. National Medical Journal of India 2004;17: 86-95.
62. 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;291:245765.
63. 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;351:12501.
64. 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;365:18279.
65. Evans T, Gulmezoglu M, Pang T. Registering clinical trials: An essential role for WHO. *Lancet* 2004;363:141314.
66. International Committee of Medical Journal Editors (ICMJE). Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Available at http://www.icmje.org/ (accessed 21 November 2007).
67. Laine C, Horton R, DeAngelis CD, Drazen JM, Frizelle FA, Godlee F, et al. Clinical trial registration: Looking back and moving ahead. *Lancet* 2007;369:190911.
68. 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.

69. Tharyan P. Ethics committees and clinical trials registration in India: Opportunities, obligations, challenges and solutions. *Indian J Med Ethics* 2007;4:1689.
70. 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.
71. 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
72. Allen C, Clarke M, Tharyan P. International Activity in The Cochrane Collaboration with particular reference to India. *Nat Med J India* 2007; 20: 250-255.
73. Charney DS, Nemeroff CB, Lewis L, et al. National Depressive and Manic-Depressive Association Consensus Statement on the use of placebo in clinical trials of mood disorders. *Arch Gen Psychiat* 2002;59:262-70.
74. 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.
75. Grobler L, Siegfried N, Askie L, Hooft L, Tharyan P, Antes G. Are national and multinational prospective trial registers necessary? *The Lancet* 2008; 372: 1201-1202.