

Conducting CNS trials in Developing Countries

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Introduction

- The WHO report (*Dejarlais et al, 1995*) and the Global Burden of Disease Study (*Murray & Lopez, 1996*)
 - huge burden of illness and severe disability that accompanies mental illness in people living in low-income countries
- Results of psychiatric studies from the developing world less likely to be published in international journals (*Patel & Sumathipala, 2001*)



Introduction (Contd.)

Psychiatric studies from the developing world criticized on the following grounds:

- Several of these studies have not investigated major psychiatric problems, but have focused on non-significant problems
- Studies have been funding agency driven, usually catering to the priorities of external agencies, instead of national priorities
- The quality of research in many instances is lower
- The information generated from research has not been well documented, disseminated and put to use by policy and decision – makers at all levels and sectors of society



Challenges

Some substance to these assertions

But researchers in developing countries work in extremely difficult conditions (*Alem and Kebede; 2003*)

The challenges faced by researchers can be grouped into four main categories

The macro environment:

- Socio, economic and political environment
- Policy and decision makers do not demand and utilize research
- The public and politicians not aware of the utility of research
- Governments unwilling to allocate resources from public funds for health research in general and for psychiatric research in particular



Challenges (Contd.)

The work environment:

- Research infrastructure weak
 - Inadequate budgets and equipment
 - Scarcity of trained technicians commonplace
 - The epidemiological expertise available concentrate on infections disease
- “Brain drain”

Personal factors:

- Low salaries of researchers compel private practice instead of research
- Insufficient training of staff research methods and executions of studies



Challenges (Contd.)

Intrinsic Nature of Psychiatric Research:

- Validity of Data
 - Western Psychiatric instruments geared to western culture
 - Direct application or translation into local languages - questionable validity
 - No vital-event registration system, unreliable socio-demographic information

Problems with collaboration:

- Under pressure to conform to western models in exchange for
 - collaborative arrangements
 - acceptance by the international scientific community
 - participating in meeting
 - publications
 - financial support



Challenges (Contd.)

- Lack of resources and the threat of intellectual isolation
 - push bright young researchers into adopting values, conceptual frames of reference and research agendas that make their work acceptable to western colleagues
- Under representation of developing countries on international panels of experts who prioritize and find solution to problems in developing countries



Special issues related to research design in developing countries: A site perspective



Cultural Issues

- There are differences in the cultural sensitivity and values in different countries
- Some of the problems faced in India are:
 - Asking the unmarried females about their partners, sexual activity and asking them to take adequate contraceptive measures.
 - Patients unwilling to undergo blood investigations due to cultural beliefs (body takes 28 days to make a drop of blood)
 - Assessments like semen analysis are refused



Language Issues

- India has number of regional languages and dialects. Apart from “Hindi” and “English” there are 21 other official languages which are recognized by the Indian Constitution
- It is difficult to translate the documents into the regional languages as the verbatim translation often loses its true meaning
 - e.g. No word in “Hindi” for placebo
 - The inter rater reliability is questionable because all the raters are certified/trained in instruments in English but the actual interviews are conducted in a regional language
 - Should rater training be in the regional languages?



Medical Practices

- There is a difference in the medical practices in each country. In India the difficulty faced are:
 - Most of the physicians do not maintain adequate records of their patients except in Government Institutes
 - The diagnosis of the patient is often not documented on the prescription
 - It is not uncommon to find a patient receiving Clozapine for reasons other than having “treatment resistant schizophrenia”



Ethical Issues

- An informed consent may have been rightfully and genuinely obtained
 - but it may still be questioned where the patient population is illiterate, ignorant and poor
 - matters become worse for studies involving psychiatric patients
 - regulatory bodies and ethics committees limit themselves to giving approvals and they do not directly oversee/audit the clinical trials
 - recent developments of organizations coming under one umbrella having internal SOPs & QA procedures are welcome



Ethical Issues (Contd.)

- **Illiteracy:**
 - the doctor is often looked upon as a person of greater stature and the patient may leave the decision upon the doctor if he should participate in the study or not
 - taking informed consent thus becomes difficult
 - often have to use color markers on the blisters and seal the medication that is not to be taken, with tape
 - one possibility is to videotape the interview using a webcam and have it independently reviewed



Ethical Issues (Contd.)

- The patient may not be able to afford the treatment and may participate in the study due to limited availability of health care and treatment options
- There is inadequate community/cultural experience with or understanding of scientific research
 - On one hand there is a group of people who think the medication in research (*foreign medication*) is better and are enthusiastic to participate
 - On the other hand there are individuals who paint all the research black and label the participants as “guinea pigs”



Ethical Issues (Contd.)

- The training and selection of Ethics Committees is not standardized and there are wide variations. The problems faced at our sites are
 - The number of studies under one investigator was curtailed although it was noted itself by the authorities that there was no deficiency in the quality of the work
- This scenario may change and there is some news that the working of individual EC's in India shall be overseen by a central regulatory authority



Logistic Problems

- Electronic CRFs require a working broadband connection
 - our site commonly faces problems despite having connections from two internet service providers
- The international toll free phone numbers often do not work from some sites and the process of making phone calls and later getting the bill reimbursed is cumbersome



Logistic Problems (Contd.)

- The time zones of the centers are very different
 - at times it is difficult to contact the medical monitor, the central lab when required urgently
 - teleconferences have to be held at odd hours and the all staff cannot attend these meetings.



Logistic Problems (Contd.)

- The deadlines and recruitment periods are sometimes intimated at the last minute
 - Patients in the pre-screening or screening phase may have to be aggressively recruited because of lack of prior intimation resulting in inconvenience for the patients
 - For one study two patients were hospitalized as they volunteered to participate in the study but in the evening our site was informed that the recruitment period was over



Other Issues

- There are differences in the parameters such as lab values across the cultures and populations
 - even patients who are healthy otherwise may get abnormal lab values
 - anemia is more commonly detected in vegetarians
 - if the weight is chosen as an exclusion criteria, some healthy individuals may be excluded due to low weight but normal BMI



Other Issues (Contd.)

- Populations having endemic parasitic infections may have high eosinophil counts that are not significant
- Tobacco preparation (Gutka) pouches sometimes contains cannabis and is detected in urine although patient denies taking it
- These abnormalities cause a greater work load as each aberration has to be discussed with the medical monitor and a documented approval becomes necessary for a patient who other wise is clinically healthy



Conclusions

- Working in clinical trials have brought a growth in infrastructure and research methodologies to the centers involved. This exposure to working according international standard is beneficial
- There are issues which are specific to the developing countries, which may be a cause of concern for the sponsors
- We should work to strike a balance so that clinical trials promote a research culture and does not stifle the other areas of research



