

BIOETHICS IN PUBLIC HEALTH RESEARCH
SEVENTH GLOBAL FORUM FOR BIOETHICS IN RESEARCH

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BACKGROUND

Although Bioethics in its traditional form and existing guidelines have largely been concerned with issues of relevance to individual rights and protection, recent increase in public health and health systems research have brought additional issues and challenges into focus. There is an increasing interest in the conceptual ethical frameworks and regulation of research involving population and public health interventions. While some principles may be common, several issues pertaining to health systems (HSys) research, public health (PH) research and health services (HServ) research require different approaches. These issues may pertain to large scale social experiments undertaken within health systems or research that involves units of randomization that represent population groups rather than individuals. These challenges and ‘conceptually different approaches’ were the theme of Seventh Global Forum for Bioethics in Research (GFBR) which was held at the Aga Khan University in Karachi from February 17-19, 2006. As per the tradition of previous forum, the 7th forum was organized by the Aga Khan University with the financial and technical assistance of several organizations including the National Institutes of Health (USA), the Wellcome Trust, the Medical Research Council (UK), the European Union, the World Health Organization and the Steering Committee of the GFBR. The meeting was attended by over 150 national and international delegates representing all continents of the world.

Research in PH, HSys & HServ is based on the premise that the information will be used for protection and promotion of the health of communities through the generation and utilization of evidence based information. It is assumed that the information

generated by researchers, policy makers and managers at all level of health system lead to strengthen the health systems and services in a country or region. Researchers in these fields use a variety of tools such as epidemiology to collect data for surveillance, vital statistics, disease and injury reporting, and disease registries. These interventions may also include policy-making mechanisms at population level for creating or enforcing health-related regulations and legislations. Examples of such interventions may include mandatory screening, public health treatment protocols, mass vaccination campaigns, and rarely extreme steps such as quarantining of communities as was necessary during the recent SARS and Avian flu outbreaks. Since a variety of research protocols and projects now deal with approaches to these issues in public health settings, a number of ethical considerations emerge. Some of the fundamental research and implementation principles in PH and HSys research may appear to be in conflict with current guidelines and principles articulated in the context of clinical research and practice that caters to individuals.

In order to defend the 'common welfare and good', collective power is exercised in health systems to inspect, license, regulate, and impose charges. In other instances large scale interventions (e.g., water fluoridation and fortification of staple foods) are also undertaken, leaving most people without the possibility of opting out. Public health activities, including research, are generally understood in teleological terms; that is, measurement of 'success' is based on the improvement in the health of the public rather than in the advancement of individual rights and liberties, which are seen as subsidiary to the greater public good. As such, one challenge within public health is an examination of the choice of such means and when and in particular how research in such settings can be ethically regulated. The most commonly used lens for decision-making in clinical and research ethics is based on principles enunciated in the Belmont Report (respect for persons, beneficence, and justice). Yet clinical research differs from PH, HSys & HServ research in terms of context, mandate, and range of activities. Clinical research ethics are rooted in the responsibility of the researcher in his/her research contract with the patient that is legitimized by the 'informed consent' of the research subjects. PH, HSys & HServ-R assumes a population-focus whereby the contract is with society as whole and is either

legitimized by the policies and law of government or has its support. Indeed, while patients may accept or reject a request to participate in clinical research, the nature of research interventions in large population and health system settings may make such individual choice either impossible or redundant.

The 7th global forum meeting in Karachi Pakistan focused to create a better understanding of the ethical regulation of research in PH, HSys& HServ through presentations and discussion of real life case studies and dilemmas, a tool that has been successfully used in previous GFBR meetings.

PROCEEDINGS

The 7th global forum meeting lasted for three days and each day was divided into three major themes, the plenary sessions where the background issues and the specific case studies were presented with subsequent discussion in subgroups followed by report-back and open discussion in plenary. Representatives from more than 20 countries around the world participated actively in the discussion. There were over 150 registered participants for this meeting, of which 67 were overseas participants representing more than 20 countries.

INAUGURAL SESSION (FEB 17, 2006)

The Director General Health, Government of Pakistan, Dr. Abdul Majid Rajput was the chief guest at the inaugural session of the Forum. In his welcoming speech, he emphasized on the policy issues related to public health ethics at the government level and assured his full support for the promotion of research ethics training and capacity development. The Dean Aga Khan Medical College, Dr. Mohammad Khurshid in his welcome address reiterated full support from the Aga Khan University for the development of Bioethics at the Aga Khan University, Pakistan and the Aga Khan Development Network. Dr. Shamsh Kassim-Lakha, the President of the Aga Khan

University, shed light on the indigenous issues of Bioethics in his welcome address. He informed participants that AKU will start the masters in Bioethics in near future.

The key note speaker in the inaugural session was Dr. Farhat Moazam (Professor and Chairperson, Center of Biomedical Ethics and Culture, SIUT, Karachi, Pakistan) who spoke on “Making a Case for ‘Indigenizing’ Bioethics”. She presented an overview of the birth of Contemporary Bioethics in USA and the combination of circumstances that led to its defining characteristics –the “culture” of American Bioethics. Contemporary Bioethics get an initiation in 1970s in USA when there were wide spread violent protests against the Vietnam War. Civil rights movement was at its peak, and there was a push for recognition of the primacy of equal rights and self governance of individuals. Vocal feminist movements were becoming a major force. There was a rise on the instances of professional misconduct, and litigation against medical and scientific communities. She underscored that the founders of American Contemporary Bioethics were not American healthcare professionals but philosophers, theologians, sociologists, lawyers, feminists, and also members of the lay public.

In Pakistan, Contemporary Bioethics was imported in early 1980 by the physicians who were mostly trained in USA but has significantly evolved since. She stated that Western Bioethics was insensitive to the cultural norms of the developing nations and ignores the fact that a majority of people continue to follow and turn to religion for moral guidance. Pakistan is a traditional, collective society in which the family, and not the individual, forms the social unit, and religious values remain central in life for most people. Interdependencies and obligations to others are emphasized rather than individual rights. She stated that Islam offers a form of virtue ethics; its premise is that virtues can and should be inculcated to achieve moral excellence of character, and that an ethical individual will, perforce of habit, act ethically towards others. This idea is not restricted to Islam alone; the notion of virtue ethics and aspiration for a life of moral achievement is also found in Aristotle’s writings.

In another invited presentation, Dr. Khadija. T. Moalla from UNDP/HARPAS presented her thoughts on “Religious Leaders Initiative on HIV/AIDS in the Arab Region” and discussed the utilization of services of religious leaders in interacting with HIV/AIDS patients and associated ethical issues. She presented the UNDP/HARPAS Religious Leaders Initiative on HIV/AIDS in The Arab Region- *Theoretical Frameworks and Backgrounds to Ethical Dilemmas in Research*. HARPAS (HIV and AIDS regional program in Arab states) covered 20 Arab countries out of 22 that are included in the Arab league. Their initiative was action based because they wanted to make a difference in Arab world. They planned to work with religious leaders which hold a pivotal role in their culture. She presented the framework of analysis to understand underlying stigma of HIV in general, intention of commitment and change of behavior at individual level and cultural norms and values at collective level. Their initiative focused on dealing with model of legislation protecting the rights of people with HIV and the prime focus was on the stigmatization related to it. Question was raised that shall they should work with religious leaders as there was a fear of backfire while working with religious leaders, attitude of hopelessly reactionary, attitude of rigidness and it may actually hinder the process of democratization

Religious leaders were the key players in their culture and they have enormous impact on people’s attitude and values. It will not be useful avoiding the role of religious leaders as it will lead to isolating developmental efforts from the public. People living with HIV and AIDS need acceptance and support from their religious leaders. The most important factor under consideration was the reaction of people living with HIV infection and the acceptance of HIV people by religious leaders. The interest was not academic but to change the response. So for the Religious Leaders (RLs) Initiative, a major colloquium was held with 5 sub-regional trainings and 2 experts meetings. 700 major RLs were involved. A theoretical framework generated an action plan was developed. Stigma for RLs may be based on condemnation, a defensive tool to protect the "good majority" against unaccepted sexual behavior. RLs also emphasized on the distinction between stigma and discrimination.

Plan started working with 700 key religious leaders from 21 Arab States. An initiative was started with a Technical Meeting with religious leaders who are working on HIV people like in prisons in Lebanon and Sudan. After 5 months, they had major Cairo colloquium at Damascus, (28/6 – 1/7 2004) where 30 Religious leaders with some experience in HIV/AIDS participated. Initial Consensus was done and the draft of Religious Kits and Action Plan was discussed.

Another Cairo Colloquium was held inviting 500 key religious leaders from the 21 Arab States on 11-13 December 2004. 80 first rank Religious Leaders participated and this included all Muslim and Christian Denominations. 21 Arab countries were involved under Auspices of the League of Arab States and 2 final versions based on Qur'aan and Sunnah and Holy Bible for Christians were prepared and an action plan was chalked out. They formed 5 sub-regional workshops with RLs and there was an extraordinary Media Coverage done with 40 agencies including major news papers and regional TV stations. The initiative was led by the Steering Committee of 12 Religious Leaders. They prioritize the Action Plan Items, review the final version of the Religious Kits, decided for next step in the region, Networking and facilitating in nominating various activities for the participants.

The theme of 5 Sub-regional Workshops was sensitizing, motivating and training RLs, held at Rabat, Maghreb sub-region (July 2004); Damascus: Middle East sub-region (Muslim and Christian) (August 2004); Sanaa:Yemen & Horn of Africa sub-region (September.2005); and Kuwait: Gulf Countries sub-region (September 2004)

The national initiatives were mushrooming in almost every Arab country, creating a regional transformation. An Imam from an important Mosque in Cairo delivered a Friday sermon on HIV/AIDS in front of 6,000 worshipers. He also proposed a plan to the Minister of Awqaf (Religious Affairs) to share the training he received with hundreds of his peers. A senior Imam from Morocco started training ten Imams from each of the 14 governorates. His own leaders developed this into an ambitious plan to train all thirty thousands Moroccan Imams

The ethical issues raised were mainly the roots of stigmatization. Lessons learnt from these initiatives were; there was lack of information and misconceptions in Arab States. With the rise in awareness in the minds of RLs, the realization appeared that confronting HIV/AIDS requires avoiding labeling, condemnations, a call for love and compassion in action toward vulnerable groups and people living with HIV and AIDS was needed.

In this milieu, Cairo Declaration was made which stated, *“Patients are our brothers and sisters, and we stand by them seeking God’s healing for each one of them...”*
“People living with HIV/AIDS and their families deserve care, support, treatment, and education, whether or not they are responsible for their illness.”

It also stated, *“We reiterate that abstinence and faithfulness are the two cornerstones of our preventive strategies but we understand the medical call for the use of different preventive means to reduce the harm to oneself and others. We emphasize the importance of reaching out to vulnerable groups, including commercial sex workers and their clients, injecting drug users, men having sex with men, and those who are involved in harmful (traditional) practices.”*

The process of Change was the Religious Leaders interacting with people living with HIV and AIDS and the leadership development exercises go beyond statistics and intellectual arguments. It is essential to develop an empathetic understanding of the issues that surround HIV/AIDS. To allow exploration, Empathetic and Motivational approaches were needed which provides the platform for RLs to explore the issues in a safe and warm environment and trusting that they will find the right answers. A Pluralistic society was achievable. Sunni, Shiite, Orthodox, Catholics, and Protestants all convened together, some were conservatives, and others were more liberal. It was not doctrinal dialogue but was about facing developmental challenges and feeling unity against this

issue which can only be done by the network of RL and a continuous effort by RLs at national level. For this purpose, a literature review was done and the critical issues that raised that not to get infected were reviewed by an Imam from Sudan. For Empirical Research, questions were raised that was this research project possible without the initiative and how can it benefit the response and then of course the preparation for empirical research. To achieve this goal, its essential to review the relevant literature and document the relevant experiences, discussions and processes. In nutshell, focus was in putting research in Geopolitical Context and a scientific adventure is required into researching social phenomena, beliefs, sex, silence, denial, death and prejudice in a context of pressure from fundamentalists, terrorism, Global oppressive regimes and poverty.

PLENARY SESSION 1 (FEB 17, 2006)

The first plenary session focused on issues of ethical regulation of research in health system research and set the scene for subsequent discussions.

Dr. Jerome Singh (Centre for the AIDS Programme of Research in South Africa) made a background presentation on “Ethics and health systems research”. He underscored that the overall objective of health systems research is to contribute to the generation of evidence-based information for use by policy makers and managers at all levels of the health system for strengthening the health systems and services in a country or region. The functions and operational components of health research systems were; stewardship, financing, creating and sustaining resources, and producing and using research. Health systems include health research networks that contribute to research and technological innovation; production systems (e.g., agricultural and pharmaceutical systems), social and health delivery systems that influence and oversee nutrition and health; regulatory and court systems for decision-making, monitoring and control; and groups of end-users (e.g. citizens,) and other relevant stakeholders.

CASE STUDY-1

A CLUSTER-RANDOMIZED TRIAL OF HOME-BASED VERSUS, HEALTH FACILITY-BASED CARE FOR HIV/AIDS:

In order to test the effectiveness of models of care for HIV/AIDS that rely less on the expertise of professional staff, that minimizes the burden to existing health services, and that do not require patients to travel long distances, a trial was conducted through a partnership involving The AIDS Support Organization (TASO), Uganda Ministry of Health (MOH), Medical Research Council (MRC) Unit on AIDS in Uganda, and the US Centers for Disease Control and Prevention (CDC). The trial compared facility-based care with home-based care.

The facility-based care arm was a model that is broadly similar to that being used in urban centers across Africa where patients are treated in hospital settings. In this arm, patients are asked to come to the TASO Clinic in Jinja (Uganda's second largest town) to collect their drugs at 2 weeks after entry into the programme and every month thereafter. They are seen by a physician every three months, as well as monthly by a nurse who refers them to a doctor if necessary.

The home-based arm of the trial followed the mode used by TASO outside the Jinja clinic, with non-clinical field workers delivering drugs and monitoring patients in their homes at 2 weeks after ART-initiation and monthly thereafter. Patients are asked to come to the clinic for routine clinical review and counseling at 2 and 6 months and every 6 months thereafter.

Home-based care is popular with patients as it reduces the need to travel to clinics; it is also practical for the health services, which face a severe shortage of professional staff. However, its effectiveness was unproven; in particular, it was uncertain whether non-clinically qualified fieldworkers can monitor patients on anti-retroviral therapy (ART) adequately and make referral when needed. Also, regular home visits by fieldworkers may be unacceptable given the stigma associated with HIV, and may prove difficult to

sustain when patients return to better health and are reluctant to stay at home to receive the visits.

It is against this background that this trial was designed to determine the effectiveness of home-based compared with facility-based ART delivery and HIV/AIDS care. Forty-four areas were defined geographically and grouped into strata according to estimated number of HIV+ patients and distance from the Jinja clinic. The clusters were randomized within each stratum to receive either home- or facility-based care. Patients in both arms were told to come to the clinic at any time they feel unwell. In exceptional cases, when a patient was bed-ridden and unable to travel, home-care would be provided by a TASO team including a physician, as resources allow. The trial was designed with 1000 patients, each followed for at least 3 years, a sufficient number to show approximate equivalence between the two modes of ART delivery. The primary endpoint was the time for plasma viral-load to exceed 500 copies/ml; secondary endpoints included adherence, clinical treatment failure, cost, and development of resistance to antiretroviral drugs.

Patients were able to refuse entry to the trial or withdrew at any time, for whatever reason. Patients who refused or withdrew received all subsequent care (including ART) from TASO according to the standard facility-based regime, which has been shown to be effective and is established as the standard of care in Africa, whereas the evidence on the effectiveness of home-based ART care for HIV/AIDS in Africa was lacking and inadequate.

DISCUSSION

The discussion revolved around the issue of informed consent especially its process. It was suggested that for such researches investigators should follow a community participation approach right from the beginning i.e. right at the time of research proposal development. This approach is extremely important to control the issue of stigma and efforts should be made to discuss on these issues by involving community dialogue before approaching the individual research participant.

It was also discussed that for the research projects in which the designs are very difficult to implement and there are associated implicit or explicit stigma issues e.g. in HIV research, community information and the community consent or assent should be very carefully sought and deliberate attempts should be made to release only very necessary and limited information in order to avoid the risk of certain treatment arms being identified. In such research projects community information should be deliberately kept in very broad terms without project details. The relevant information in detail should then be provided at a household level or at an individual level this will decrease the risk of finger pointing at individuals because of some obvious characteristics. One group suggested that stigma could also be reduced by integration of research project into series of studies or with ongoing studies or with ongoing healthcare projects so that these become part of the routine follow-up. Another thought was that the developing countries have a cohesive culture and issues of stigmatization are always there in small communities and villages so much so that even going to hospital is stigmatizing to an extent sometime.

In the debate on preference of a particular study design over another, it was discussed that health systems research deals with groups not individual and in order to discuss preference of cluster randomized trial over other designs, researchers would feel easy for cluster randomized trial if the risk of intervention involved is low but if the risk of intervention is high then it's difficult to select the cluster randomized trial. As far the participants are concerned, it would be easier to convince them that the whole area will be randomized rather than individuals. Cluster randomized trials are powerful and stronger for intervention where issue of choice and different allocation are not problematic and there is general risk of contamination. However, the moment participants are offered choice in a particular cluster, there is immediate threat to cluster randomized trial design. Problem also arises when more and more participants request for changing the mode of treatment which will lead to selection bias. In situations where a researcher has to balance between an individual right in the cluster randomized setting there are constraint in terms of choices like issues related to traveling to health facility for the poor and the ill population and stigmatization issues.

Provision of post trial benefit was discussed and it was a unanimous voice that these benefits are now an established norm and especially for the trial participants it is now considered obligatory to make sure that at least some sort of post trial benefits are offered. It was also suggested that post-trial benefits should be negotiated with the research community at the time of pre-trial exploration.

Should autonomy of choice take precedence over issues of methodology or logistical issues in research design, this was debated at depth. Generally, one group had an opinion that given that the research is important for the participating community and there had been consultation with the communities regarding the risk involved (none to minimal risks only) methodological and logistical issues should take precedence over the autonomy as long as measures are taken to protect the participants. Another group argued that if the drop out rate from a trial is large or if it is too risky then there are serious issues with the study design and in such situations, autonomy should be given an edge over the holiness of methodology and logistical ease.

Pre-trial negotiations were also discussed and generally there was a consensus that the participating community should be involved in the discussion on the indigenous community health and research needs. Community should also be consulted on the scientifically sound and ethically justifiable research methodology that is acceptable to them. By doing so issues such as stigma could be reduced and community will be more enthusiastic to participate in this developmental process. These measures should be implemented by the researchers, research organizations, and research funding agencies.

PLENARY SESSION 2

The second plenary session further developed the theme of PH and HSys Research further

Professor Jimmy Whitworth (Wellcome Trust) presented on “Ethical considerations for Cluster Randomised Trials”. He mentioned that in cluster randomized trials clusters of people (in social units rather than as individuals) are randomized to intervention and control groups and outcome are measured on individuals within clusters. Intervention in cluster randomized trials can be broadly categorized into two categories, Intervention received by the whole cluster (e.g. fluoridation of water supply) and Intervention that individuals can decide to receive (e.g. video show on prevention of HIV). So far, best guidance in cluster randomized trials on methodological and ethical considerations is from MRC clinical trials series.

Cluster randomized trials are one of the very important tools used in PH, HSys, and HServ researches throughout the world these days. In cluster randomized trial, clusters of people (in social units rather than as individuals) are randomized to intervention and control groups and outcome are measured on individuals within clusters. Intervention in cluster randomized trials can be broadly categorized into two categories, 1) intervention received by the whole cluster (e.g. fluoridation of water supply) and 2) intervention that individuals can decide to receive (e.g. video show on prevention of HIV).

Fundamental considerations for cluster randomized trial are: participant’s interests must prevail; research must have potential to generate scientific understanding; favorable balance of risk and benefit; individual voluntary informed consent; independent ethical review; and peer review. The key ethical issues involved in cluster randomized trial are, recruitment bias, consent (community, individual ensuring informed consent), participants in control arm, and scientific research requirement. These key ethical issues

are difficult to address because the research is based on the larger community blocks rather than an individual based.

CASE STUDY-2

A CLUSTER-RANDOMIZED CONTROLLED TRIAL ON THE EFFECTIVENESS OF AN EDUCATIONAL INTERVENTION DELIVERED THROUGH THE HEALTH SERVICES TO IMPROVE NUTRITION IN YOUNG CHILDREN

The government of Peru operates several types of health facilities that serve the people living in its peri-urban shanty towns, which are characterized by poor housing, a general lack of one or more essential services (*e.g.*, piped water, reliable electrical supply, sewage disposal), and inhabitants with low and insecure income. Most families have access to various nutritious foods, so acute malnutrition (*i.e.*, low weight for height) is unusual in children, but anemia and growth-faltering (leading to stunted growth) are common.

To test means of improving the nutritional status of young children, the regional health authority in Trujillo (a city 400 km north of Lima with a population of 600,000) undertook a cluster-randomized trial. Three types of facilities serving Trujillo's peri-urban communities— community hospitals offering maternal and peri-natal specialist services; health centers with medical staff always in attendance; and health centers with more limited services—were included (facilities offering unique services were excluded from the study.)

The intervention began at the facility level; its implementation process and the effect of the intervention on child outcomes were studied by following cohorts of children from birth to age 18 months, with a final survey at the end of the experiment. The aim was to see whether, in the health facilities assigned to the intervention-arm of the study, the profile of nutrition was raised and nutrition services were integrated into existing child-oriented national programmes such as immunization, monitoring of growth and

development, and management of acute respiratory infections and diarrhea. The intervention consisted of:

- enhancing the quality of nutrition counseling through staff training and the provision of simple, standardized, age-appropriate messages to be used at all points of contact with young children in the facility. (These messages were: a thick puree satisfies and nourishes your baby, equivalent to three portions of soup; at each meal, give puree or thick-food preparation first; add a special food to your baby's serving, (chicken) liver, egg, or fish; and teach your child to eat with love, patience, and good humor.)
- Assisting facilities in developing their own protocols for use of the educational materials.
- Designing clinical history forms to help prompt physicians to include brief questions and advice on nutrition, and training to improve anthropometry skills in health-care workers.
- Demonstrating the preparation of complementary foods, so that facilities could run group sessions for caregivers of children of similar ages to enhance the coverage and nutritional content of the growth-and-development-monitoring programme in well-baby clinics.

It was hypothesized that the intervention would lead to improved feeding practices, dietary intakes, and growth of children in the catchment areas of the intervention health facilities. The primary outcome was growth measured by weight, length, and Z scores for weight-for-age and length-for-age at age 18 months, as assessed by fieldworkers. Secondary outcomes were the proportion of children receiving recommended feeding practices and the 24-h dietary intake of energy, iron, and zinc from complementary foods at ages 6, 9, 12, and 18 months. A cohort of newborns was randomly assigned after a census of each health facility's catchment population.

DISCUSSION

The first discussion point on this case study was on “equipoise” and whether there is any justification to conduct a cluster randomized trial on this topic because the premise that improving the knowledge would ultimately impact the outcome anyway. There was a lack of clarity among the participants regarding the hypothesis of the case study. The hypothesis of this research was to find the feasibility of health system’s approach to provide feasible nutrition education that could be skilled up to population level subsequently.

It was also discussed that whether individual informed consent is necessary in such situations, most discussants agreed that it is mandatory to take informed consent from the mothers and specifically communicate them that there will be two arms of trial however, discussants agreed that it is not necessary to tell the research participants which arm they are in because it would jeopardize the results. There was also a show of hand on whether researchers should mention in which arm the participant is falling. Vast majority of forum discussants maintained that this information should not be passed to the research participants because revealing will destroy the whole experiment. As far as obtaining informed consent from the community is concerned, most of the discussants thought that it’s an obligation of the researcher to take an assent for accessing these communities but full consent is not mandatory in such situations. An important concern was raised regarding the need of consent from health workers because they were also the target of intervention. It was clarified that consent was taken from the health services workers. Interestingly, in one situation a workers’ rejection was over ruled by the health authorities but this is the way most of the public health authorities works.

Similarly, an interesting finding shared was that even after best of explanation to research participants regarding the blinding and randomization and subsequent reassurance from the participants that they have understood it fully yet it is not infrequent to find out that the majority of the participant will ultimately say “I trust my doctor; he must have chosen

the best for me” however, with cluster randomization, at least, this communication challenge could be surpassed.

Opting-out as a deliberate attempt was not considered in this case study however; incidentally in the selected clusters, other health facilities were also available which could have been accessed if participants chose to opt-out from this trial. Opting-in was the main worry for the researchers because participants could feel that things were better in the intervention arm. Some of the discussant raised their concern over the fairness issue in cluster randomized trial which is further complicated by non availability of viable alternatives; however, discussion on this issue remained inconclusive. One group argued hypothetically that if there a situation in which the offered intervention is highly risky but there is also big benefit as well, under such notion, cluster randomized trial might be unacceptable if only community consent is sought. In such situation, individual consent is mandatory within each cluster. It was also suggested that the least acceptable standard for everybody should be the standard of care so that nobody is falling below the standard of care.

A concern was raised that the discussion on current case study is revolving around the randomization issue. However this is not the only study design available. We can compare this year with the last year, from this part of the country to another part of the same country or another country, the whole discussion is taking a shape that randomization is the only viable option, this is wrong and should be rejected and everything may not supposedly be put in that gold standard.

It was also mentioned that currently there is lack of clarity on many of these health-systems interventions. There lies a dilemma if these large scale interventions are implemented, without being tested through experimental designs, will ultimately end up by exposing population to much greater risk of harm from these half baked whimsical interventions. The solution for such large scale interventions is that these trials should be introduced either through a phased design or through an allocation whereby people have looked at the hard outcome and are convinced that this can be implemented.

Definition of 'research community' was also discussed and according to the experts, just defining a community on the basis of geographic area is certainly a mistake. There are several groups that could form research community including; sharing certain economic conditions, based on diseases etc.

There was consensus on the issue that alternate mode of treatment should be provided to families who decided not to participate in this research study and that the researcher has more responsibility to research participants. It was also recommended that at least minimal standard of care should be available for those people who decide to opt-out.

There was also a consensus on the point that the result of the trial should be shared by the participant communities because sharing is beneficial for them in either case.

It was thought that researchers should consult with the community at the time of developing research protocol in order to incorporate or modify the study design in line with community need. Similarly for setting up the research agenda for the community, we can think of many layers which include the researchers, government organization, NGOs and above all, the community itself.

Another important issue discussed was the capacity of Ethics Review Committee for reviewing the public health research proposals because these researches deal with large populations, not on the individual basis. So it was felt that Ethics Review Committee should be trained in dealing with public health research proposals.

PLENARY SESSION 3

This session focused on the ethical issues involved in vaccine research and was preceded by a summary presentation on the recommendations from the special WHO workshop on the use of vaccines in research.

Dr. John Clemens (Director General, International Vaccine Institute, South Korea) presented “Ethical Prerequisites for Research on Vi (typhoid vaccine) in Complex Emergencies”. He mentioned that currently, policy uncertainties impede the routine use of Vi polysaccharide in populations at risk of typhoid fever during relief efforts for complex emergencies. It is essential to resolve to these uncertainties by carrying-out operational research in the context of delivery of Vi vaccine in such settings. Randomized controlled trials are not a prerequisite for scientific credibility of research for future utilization of Vi vaccine for complex emergencies. However, operational research is an available option but this too requires independent ethical review because complex emergencies involve vulnerable population either by natural or man-made disasters.

This was then followed by the presentation of the case study.

CASE STUDY-3

RESEARCH ON VACCINATION IN EMERGENCY SITUATIONS

The recent cataclysmic earthquake in the North West Frontier Province (NWFP) of Pakistan dislodged nearly 2 million people from their homes. Most are now living in temporary camps where hygiene conditions are far from ideal; they are very likely to develop infectious diseases, especially typhoid and other water-borne illnesses. Various organizations are providing services to restore and protect the health of the earthquake victims, but financial and operational problems keep the basic health units within most of the compounds from working optimally.

The Government of Pakistan recognizes the potential for a typhoid outbreak, but it is unable to afford any preventive measures such as vaccination for those at risk. An NGO that is providing health care in the Mansehra district, one of the worst affected areas in the NWFP, proposes to give typhoid vaccinations to children living in the camps as well as in some high-risk hamlets. The NGO approached various donor agencies about providing the vaccine, and one agreed to provide 1 million doses if the vaccine were administered in a way that allowed formal evaluation of its effectiveness under such conditions. This study would be critical in generating evidence for the future use of this vaccine in similar situations. The Government and the NGO willingly agree.

As the million doses of the donated vaccine begin to arrive, critical decisions remain to be made about the vaccination campaign as well as how to integrate the required evaluation. Two suggestions are floated:

- to use a case-control design, matching people in camps and villages in the affected area with those in control villages from unaffected areas, or
- to allocate villages in the earthquake zone on a cluster-randomized basis either to have a vaccination campaign or no intervention.

Both designs have proponents and detractors. In the first alternative, the local governments in the unaffected areas are only willing to participate if assured that their residents will get the vaccine in due course; in the second, the manner in which the clusters are chosen is regarded as problematic. A final decision is urgently needed, given the limited vaccine supply and the pressure of time before an epidemic of typhoid strikes.

DISCUSSION

The discussion was generated on whether a cluster randomized trial is ethically justifiable in such situations; majority of the discussants agreed that this is not an ethically defensible design because it would mean that half of the population will not receive any vaccine or any benefit perhaps. Under emergency situations when standard of care is not available, conducting a cluster randomized trial will be difficult to stand the ethics

challenge. Similarly, if case control study design is chosen then perhaps control will be in disadvantageous group. If the controls are selected from different region then there is a chance that result of the research is not defensible on the scientific ground.

There was nearly a consensus that under the given circumstances investigators should not conduct research and carry on with the vaccination. If it is necessary to carry out research then perhaps a better approach could be to built-in evaluation strategy for the intervention. Similarly, providing choice to the research participants in the form of opting-in or opting-out of vaccine trial could also be a feasible alternative. Likewise, it was also discussed that the vaccine could be provided to both the disaster and non-disaster areas and then evaluation should be done for the effectiveness of the vaccine in both areas as a follow-up. In case if the cluster randomized trial is allowed then an established standard of care should be available to the both populations.

There was also discussion on the issue that this vaccine is already tested and has been found to be effective thus there is no reason to go for efficacy trial once again. This brought in the issue of resource prioritization because there were other equally competing issues such as provision of sanitation and emergency health care provision that needed the resource allocation on priority basis. By providing resources for sanitation, the incidence of typhoid could also have been controlled or impact could be improved many fold if both the sanitation and typhoid vaccine could have been provided rather than diverting resources to research in such situations. By doing research, resource prioritization was not considered appropriately. It was also discussed that perhaps a good monitoring and evaluation strategy will be useful exercise rather than conducting a separate research and thus wasting the potential resources.

Similarly, discussants criticized the stance of the donor agency to tie the vaccination supply grant with a 'research study'. Most of the participants hold the view that this is equivalent to using the vulnerable population who already victim of the natural disaster.

Participants discussed that there are scientific ways and means available for predicting the natural disasters (earthquake belts) and we should plan proactively to prevent and

control the harm of such disasters rather than waiting for such events to occur and then act. We should plan such research studies a head of time and in that way it could be carried out in a much organized way as compared to a research which is done in an emergency situation with involved deficiencies and difficult ethical issues to handle.

Another important discussion was generated on the concern that this research was planned on the vulnerable population. The NGO which was conducting research was also providing healthcare to the same population and this may lead to therapeutic misconception and participants could find it difficult to say 'no' to research because that organization (NGO) is the only source of health care.

CONCLUSION

Complex ethical issues involving the cultural & religious differences, standard of care, consent, post trial access to benefit and stigma are very difficult to be resolved in such short time duration meetings. However, the biggest success of such meetings is in the identification of involved ethical issues in such situations and then richness in discussion which reflect perception of issues and its analysis from participants of various cultures and background; to this extend meeting has been very successful by generating in-depth discussion on ethical issues in PH, HSys, and HServ research. These issues will keep on coming and in future and this iteration is necessary for maturity of thought processes and in coming to some direction while handling the ethical issues.

The meeting was adjourned successfully on February, 19, 2006.