# **Review Article**

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# Vulnerable population and methods for their safeguard

## **INTRODUCTION**

The inherited skepticism of disregard and contempt for human rights from the past has left powerful influences, making autonomy, justice and safety the citadels for current ethical research practices. Civil rights violations from the infamous Nazi and Tuskegee to radiation human experimentations have promoted sustained maturation and augmentation of clinical bioethical research environments. The lack of informed consent (IC), or coercive, guileful, forceful influences and methods that were used to obtain consent from potential participants; this associated with impaired risk-benefit scales, unjustified research population selections have prompted international regulations to stand firm on principles advocating conscientious clinical and ethical research systems. Following marketing approvals, medicinal products are conventionally utilized by pharmaceutical organizations, medical practitioners and allied bodies across a wide range of age groups, genders, special populations, nationalities and races, who unfortunately had not been satisfactorily represented in pertinent clinical studies resulting in deficient evidence-based health care.

### **Vulnerable population**

There are several definitions available for the term "vulnerable population", the words simply imply the disadvantaged sub-segment of the community<sup>[1]</sup> requiring utmost care, specific ancillary considerations and augmented protections in research. The vulnerable individuals' freedom and capability to protect one-self from

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intended or inherent risks is variably abbreviated, from decreased freewill to inability to make informed choices. Vulnerable communities need assiduous attention during designing studies with unique recruitment considerations and quality scrutiny measurements of overall safety and efficacy strategies ensuing research. Ethical dilemmas are widely prevalent in research involving these populations with regard to communications, data privacy and therapeutic deliberations. Non-therapeutic research participation is granted if the envisaged risks are minimal<sup>[2]</sup> and well-being of this community is not compromised. Research with this sub-segment of population is validated if reasonable direct benefits are foreseen, in compliance with local legal regulations.<sup>[1,3]</sup> The vulnerable populations refers to but not limited to children, minors, pregnant women, fetuses, human in vitro fertilization, prisoners, employees, military persons and students in hierarchical organizations, terminally ill, comatose, physically and intellectually challenged individuals, institutionalized, elderly individuals, visual or hearing impaired, ethnic minorities, refugees, international research, economically and educationally disabled and healthy volunteers.<sup>[1,4]</sup> Due to their circumstances, the communities may be inclined to participate in a clinical study or be unjustifiably influenced by the expectations of predicted benefits associated with participation.[3]

There is an aggrandized awareness with pressing needs to include potential participants from heterogeneous demographics and variegated vulnerable backgrounds, both from the regulatory and patient groups.<sup>[5]</sup>

The cornerstones of vulnerable participant safeguard ubiquitously comprises of comprehensive IC process, authorized substitute decision makers, addressing privacy and confidentiality concerns, justified benefit versus risk assessments, equitable justice and methods of subject selection.<sup>[2,6]</sup>

#### **Discussion on methods for safeguard**

Changes in benefit to risk ratios, either aggravated risks than those assumed and or a decrease in direct benefits presaged to the vulnerable participant should deter fresh enrolment and stagger or discontinue further participation up till the issue is appropriately corrected. The interim analyses of research may be made available in public domain to apprise the scientific community of the integrity of the study and initiate public trust.

Development of comprehensive safety monitoring plans with Data Safety Monitoring Committee (DSMC) supervision and wherever applicable with Observational Study Monitoring Boards are crucial. Their role may be optimized by involving them in both, early and late trial phases<sup>[7]</sup> soliciting vulnerable subjects, to contribute recommendations to the scientific caliber, integrity, safety, lucidity, timeliness, and quality of data and documentation. Compliance to advocated norms and sustained monitoring by ethical review boards (ERBs),<sup>[8]</sup> governmental agencies and independent DSMC is obligatory.

Any form of willful violations to Good Clinical Practices (GCP) with connotations to autonomy, voluntariness, distributive justice, other parameters of safeguards are to be imperatively scrutinized and those involved to be appropriately penalized by applicable authorities.

Protection of rights, well-being, safety with measurements of risk-benefit scales, privacy and confidentiality of vulnerable subjects and ascertaining appended safeguards<sup>[4]</sup> are prerogatives of ERBs. Infringement of methodologies in data collection and dissemination could bring individuals into disrepute, especially in research involving socially sensitive issues associated with stigma, as with HIV, mental illnesses, genetic<sup>[4]</sup> or of epidemiological natures. Confidentiality transgressions with unethical usage of personal data may occur endangering the social fabric of this already disadvantaged community. Therefore, establishment of updated security mechanisms of human research data protections is of paramount priority to industry, ERBs and supervising committees.

The trial documents require meeting the expectations of ERBs, especially with reference to vulnerable subjects' protection.<sup>[9]</sup> Competent and trained ERBs overseeing sensitive studies should observe full-scheduled reviews<sup>[4]</sup> and may have representatives from specific populations during deliberations. The concerned ERBs prior to decision making may establish site research conditions, example a prison site<sup>[10]</sup> with relevance to participant rights, safety and well-being. The ERBs' standard practices should include continued review for compliance whilst monitoring these trials.

Presently due to disparate factors, there is neither uniformity nor equitable standards in the understanding and grading of risks globally for these populations with relevance to extent of acceptability and evaluation of quantum of risks to establish consistent safeguards in biomedical research aiding stakeholders.

Role of regulatory in biomedical and behavioral research is maximal in providing scientific direction to industry and unambiguous thought-through instructions.<sup>[11]</sup> Regulatory governance is critical, more so in socially sensitive trials and also contributes to evolving a responsible media. International collaborations of regulatory organizations can establish scientific and regulatory policies to positively impact global safeguards for vulnerable populations.

Stringent reporting guidelines should be followed by industry in maintaining validated databases for safety data dissemination highlighted for this community, with risks being regularly interpreted by expert clinical evaluators, steering committees and timely recommendations shared between stakeholders. There is a continual need to federate and be vigilant to develop strategies for establishing appropriate advancements in monitoring plans according to trends scrutinized from research.

The quality of IC Process has an impressive influence on the tenets of research with direct implications to comprehension of proposed study particularly in vulnerable subjects.<sup>[3]</sup> The salient facets, procedures and risks need to be repeated consistently during the IC process, and where possible usage of audiovisual and illustrative tools to enhance quality of consent process.<sup>[12]</sup> The presence of independent consent and ERB monitors<sup>[13]</sup> supervising procedures in assessing decisional capacities, re-consent and follow up during the study promotes additional safeguards. The principles and spirit of GCP of respect for persons devoid of prejudice and therapeutic misconception is assured through an effective consent process. The informed consent document (ICD) should also comply with all applicable elements deliberated in the local regulatory norms.<sup>[9]</sup> Language and literacy capabilities of the potential vulnerable participants are to be assessed by the research site personnel.<sup>[12]</sup> The acceptable language in ICDs may be equivalent to that of local middle school level of education and essentially non-technical<sup>[3]</sup> to suit the solicited community. The font of the written documentation should be easy on the eve, accepting pediatric and geriatric patients<sup>[14]</sup> notably. The ICDs should not be lengthy<sup>[15]</sup> and at the tail end a frequently asked questionnaire with a simple summary of goals for the study maybe enumerated empowering the comprehension, in achieving a superior caliber of consent.<sup>[16]</sup>

The philosophy involved in including pregnant women is based on the principle that information gleaned from good research leads to augmented standards of maternal and fetal healthcare.<sup>[5]</sup> This population may *inadvertently* be exposed to high risks of unintentional detrimental effects as a result of their conditions as noted in post marketing research practices.<sup>[17]</sup> The apprehensions in including lactating, pregnant and women of child bearing potential, originates from scientific and social concerns of anticipated potential risks to the embryo, fetus and neonate.<sup>[16]</sup> However, exclusion of this population could lead to unjustified deprivation of vital diagnostic, preventative and therapeutic information. Should the exclusion of this sub-segment be planned, a viable justification needs to be elucidated in the relevant research documents.<sup>[16]</sup> In medical practice, pregnant women commonly suffer from co-morbid conditions, for which standard treatment options maybe nonexistent consequent to non-availability of exposure data, leading to serious health implications. If the data following exposure to medicinal or pharmaceutical products suggests significant maternal, fetal or neonatal harm, justifies desuetude of this population.<sup>[2]</sup> The channels to mitigate risks through responsible approaches following product exposure in the appropriate preterm trimester<sup>[16]</sup> is based on various scientific principles and requires to be anticipated by industry and concerned stakeholders.

Assimilation of safety and efficacy profiles of the intervention from available preclinical, clinical and post marketing experiences is the natural evolution ensuring detailed evaluation of foreknown risks versus benefits preceding inclusion of this population.<sup>[1]</sup>

It would be of immense importance where feasible, for the product to have undergone non-clinical female reproductive and developmental toxicity studies to achieve aforementioned interpretations in the investigator brochure to be reflected in protocol and patient information forms (PIF).<sup>[4]</sup> Data from studies conducted on non-pregnant females maybe extrapolated to determine susceptibility and predict unexpected dangers following pregnancy. Studies involving physically invasive examinations or interventions or in high risk maternal and fetal complications mandates special review by ERBs,<sup>[4]</sup> and DSMCs assuring unbiased analyses of retrospective data. Programs and registries for follow up evaluations subsequent to pregnancy research for fetus and child are prerequisites.<sup>[2,17]</sup>

Consent documents should clearly communicate all available information regarding anticipated potential harm to fetal development and parent.<sup>[3]</sup> In the circumstances where no pertinent investigational product information is available regarding unknown or probable fetotoxic or materno-toxic effects, the same is unambiguously declared in the ICD.<sup>[18]</sup> Research in intellectually challenged individuals is an arduous, daunting task for investigators as cognition of the subject forms a major determinant in establishing adequate comprehension justifying communication to secure transfer of information. Psychiatric patients, who are behaviorally or emotionally challenged and assessed to be *incompetent* to provide independent IC warrant surrogate consents.<sup>[3]</sup> The decisional capacity of prospective vulnerable subjects is a direct determinant to their enrolment eligibility. Further, the experienced investigator must rise to the challenge of enhanced responsibility in social justification of selection of these participants<sup>[6]</sup> and in assessing the ability of subjects' intellectual judgments and skills. In these circumstances, the protocol should discuss the conditions to seek surrogate consent from a legally authorized/acceptable representative<sup>[3]</sup> (LAR) or waiver of consent as appropriate. Patients with certain medical conditions may in the future regain reasoning capability to *independently re-consent* or resist further participation during the study, to be respected by the investigator and similar anticipatory conditions reflected in ERB reviewed documents.

Medicinal preparations in the market are regularly prescribed to children as off-label use as pediatric labeling information is unavailable, thereby associated with perils of unproven efficacy and unknown safety. Parents are required to make the decision on their behalf<sup>[3]</sup> as *children* are believed to have *limited cognitive and emotional capabilities* from ethical and legal perspectives. Dedicated pediatric trials maybe essential where the disease predominantly affects this age group, uniquely in the scenario of being predisposed to certain medical conditions.<sup>[4]</sup>

By legal definition, pediatric subjects aged less than 18 years (equivalent to age of majority) are considered minors and worldwide are not permitted to provide consent. The child assent or agreement is obtained considering the ambit of the child's understanding; generally a minimum age for which is characterized in the protocol. *Age-appropriate assent forms* across pediatric to adolescent age groups may be developed which need to be simple, user-friendly, with pictures and illustrations<sup>[14]</sup> wherever possible.

Assent being intrinsically insufficient necessitates supplementation with consents from legal guardian/parents; although assent maybe waived by concerned ERBs under specific conditions.<sup>[19]</sup> In special circumstances, should the child refuse to provide assent, this decision may not be nullified by the consent provided by legal parents/guardians.<sup>[19]</sup> If the anticipated discomforts for the proposed research are higher than minimal with no foreseen direct benefits to the subject, nonetheless, research is authenticated if sufficient targeted scientific information may be garnered.<sup>[19]</sup>

During the study if the subject attains legal maturity, necessitates an adult consent to be sought for. Pediatric studies are prone to sensitive issues and risks, needing periodic reassessments by the concerned ethics, scientific review boards with public concurrence. In non-therapeutic research, declination to participate by the child requires to be abided by the investigator.<sup>[2]</sup>

Prisoners by nature of their circumstances possess abbreviated freedom to consent or decline consent and hence necessarily are treated equitably as regular subjects. The ICDs and PIF undergo legal and ERB screens.<sup>[10]</sup> Mostly, research conducted on prisoners pertains to health and social issues with potential direct benefits, confined to their environmental conditions.<sup>[10]</sup> Should a trial subject become a prisoner during participation, that individual should be assigned the requisite precautions and safeguards.

An impartial witness provides consent for an illiterate, legally blind or a physically challenged subject who may be unable to write, by participating in the entire consent process, in the absence of a literate LAR.<sup>[3]</sup> The discerning witness *without* conflicts of interest comprehends the information and conveys to the probable subject, establishing a robustuous consent process and transfers knowledge and responsibilities involved in proposed research.

Research in the terminally ill and in conditions of emergency medicine,<sup>[3]</sup> in these circumstances subjects are potentially very vulnerable as *waiver* from consent may be inevitable despite several social, legal and ethical debates.<sup>[20]</sup> The conditions for waiver need to be characterized in the protocol in accord with concerned ERBs.<sup>[3]</sup> Unlicensed interventions maybe dispensed with no alternative standard therapies being available, with *inadequate* clinical safety and efficacy data.<sup>[1]</sup> Nevertheless, the requisites for subject consent/LAR later in the study are to be implemented. Considering the acuteness of the underlying clinical pathology, participants may reach the study endpoints *early* in the course of study based on protocol evaluation criteria, necessitating data reviewing committees to proffer early and frequent analyses with an obligation to provide cyclical efficacy, safety and risks versus benefits recommendations to stakeholders. Further in this form of research, befitting statistical designs and inferences are to be cogitated.

Research in hierarchical organizations as in the armed forces, institutions or hospital groups, here employees or students by nature of adjacency of work or association with investigators, may acquiesce to participate in *anticipation* of favoritism, consternation, retribution or compelling socioeconomic backgrounds.<sup>[4]</sup> ERBs need to be extra cautious to make safe the environment with exigencies involved, to ensure participants be neither pressured nor persuaded. *Declination* to participate should not affect their careers and credits.

When the protocol sample study population incorporates the vulnerable subset of patients, rationale for their representation, scientific significance and contributions are to be discussed.<sup>[4]</sup> Further, the analyses of results and the envisioned bearings of study to this segment of population require to be elucidated. The pillars of vulnerable participant safeguards are to be specifically expounded in the protocol and ICD. Gold standards of randomized controlled blinded trials are considered scientifically robust and well accepted ethically for unbiased evaluation of therapeutic credits to this population.<sup>[7]</sup> Defined, rigid research entry criteria ensure clinical safety to vulnerable participants. Well-formulated monitoring plans with data validity maybe appended to the protocol. The higher the severity of risks encountered in this sample population, the more aggressive the monitoring.

# **CONCLUSION**

Investigators require factual guidance from regulatory with reference to practical difficulties confronted during conduct of these forms of research. The need of the day is responsible, experienced, sensitive researchers<sup>[21]</sup> guiding conscientious teams to treat vulnerable communities with concern, patience, respect, equitably, allowing free will, ruling out any form of inducement, enticements, insensitivity or prejudice.

The goals of clinical research whether privately or publicly funded are to represent the best interests of this community within the framework of the protocol and by adherence to the principles of GCP. Presentation<sup>[21]</sup> of authentic information forms an integral aspect of patient's rights in decision making. In general, accurate definitions of groups of representatives' example, viable infant or nonviable fetus, and other technical terminologies and special procedures pertinent to sub-populations should clearly be defined without ambiguity<sup>[16]</sup> which aids both, study personnel and subjects in consent discussion.

Awareness through continued education of stakeholders including media and public would result in better attitudes and approach to this form of sensitive research. Watchdog panels overseeing vulnerable participant protection should remain in an open ongoing dialogue with stakeholders, monitoring compliancy to advocated precautions and norms. Enhancing the interaction between the ERBs and investigators may expand their ability to comprehend the trends involved and engage in greater understanding of ongoing safeguards of these populations. Compassionate

use of therapeutic interventions may be made available to vulnerable subjects following completion of research. Comprehensive mandatory pharmacovigilance and targeted risk management plans during post marketing are cardinal.

Good science with responsible research provides an authentic groundwork to heighten best practices in medical management of vulnerable populations. Nevertheless, clinical research is metamorphosing and escalating in complexity, blurring the line between potential risks and benefits encumbering the development of comprehensive robust monitoring systems.

We all walk down this inconstant dynamic path of research. But walk it we must.

## **REFERENCES**

- WMA Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects-59<sup>th</sup> WMA General Assembly, Seoul, Korea, October 2008.
- CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects. Available from: http://www.cioms.ch/ publications/layout\_guide2002.pdf. [Last accessed on 2012 Aug].
- 3. ICH GCP International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use ICH Harmonised Tripartite Guideline, Guideline for Good Clinical Practice E6(R1) Current Step 4 version dated 10 June 1996.
- 4. Indian Council of Medical Research Ethical Guidelines for Biomedical Research on Human Participants, New Delhi, 2006.
- Politics and Clinical Trials: The Inclusion of Women. In: Goldenberg MM, editor. Vol. 28. December 2003. Available from: http://www.pharmscope.com/ptjournal/fulltext/28/12/PTJ2812791. pdf. [Last accessed on 2012 Aug].
- 6. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, published in the Federal Register on 18 April 1979. Available from: http:// www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4178b\_09\_02\_ Belmont%20Report.pdf. [Last accessed on 2012 Aug].
- The Establishment and Operation of Clinical Trial Data Monitoring Committees for Clinical Trial Sponsors. Guidance for Clinical Trial Sponsors - Establishment and Operation of Clinical Trial Data Monitoring Committees. Available from: http://www.fda.gov/ RegulatoryInformation/Guidances/ucm127069.htm. [Last accessed on 2012 Aug].
- Reviewing Clinical Trials: A Guide for the Ethics Committee, In: Karlberg JP, Speers MA, editors. Clinical Trials Centre, The University of Hong Kong, Hong Kong SAR, PR China. Association for the Accreditation of Human Research Protection Programs, Inc. Washington, DC, USA. Available from: http://www.pfizer.com/files/

research/research\_clinical\_trials/ethics\_committee\_guide.pdf. [Last accessed on 2012 Aug].

- Schedule Y: Clinical Trial Regulation in India, Drugs and Cosmetics (IInd Amendment) Rules, 2005 Ministry of Health and Family Welfare (Department of Health) Notification New Delhi, 20th January, 2005
- US Department of Health and Human Services Office of Human Research Protections (OHRP), Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects Subpart C, Code of Federal Regulations Title 45, Part 46 Protection of Human Subjects.
- Guidance for Industry on Submission of Clinical Trial Application for evaluating safety and efficacy. Available from: http://cdsco.nic.in/ CDSCO-GuidanceForIndustry.pdf. [Last accessed on 2012 Aug].
- Nind M. Conducting qualitative research with people with learning, communication and other disabilities: Methodological challenges. Southampton, England: University of Southampton; Nov 2008.
- Monitoring Informed Consent Procedures: An Exploratory Record Review by Faden RR, Lewis C, Rimer B, http://www.research. va.gov/resdev/resources/pubs/informed\_consent/pdf/informed\_ consent\_ruth\_faden.pdf. [Last accessed on 2012 Aug].
- Making written information easier to understand for people with learning disabilities Guidance for people who commission or produce Easy Read information, revised ed. Department of Health U.K. Available from: http://odi.dwp.gov.uk/docs/iod/easy-readguidance.pdf. [Last accessed on 2012].
- Consenting of the vulnerable: The informed consent procedure in advanced cancer patients in Mexico. In: Verástegui EL, editor. Published: 13 December 2006, BMC Medical Ethics. Available from: http://www.biomedcentral.com/1472-6939/7/13. [Last accessed on 2012 Aug].
- US Department of Health and Human Services Office of Human Research Protections (OHRP) Subpart B, Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research, Code of Federal Regulations Title 45, Part 46 Protection of Human Subjects.
- 17. Guideline on the Exposure to Medicinal Products during pregnancy: Need for post-authorization data, EMEA 2006, EMEA/ CHMP/313666/2005.
- Title 21 Code of Federal Regulations Sec. 50.25 Elements of informed consent. Available from: http://www.accessdata.fda.gov/scripts/ cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50andshowFR=1andsub partNode=21:1.0.1.1.19.2. [Last accessed on 2012 Aug].
- US Department of Health and Human Services Office of Human Research Protections (OHRP)-IRB OHRP, Additional Protections for Children Involved as Subjects in Research, Subpart D, Code of Federal Regulations Title 45, Part 46 Protection of Human Subjects.
- 20. Title 21 Code of Federal Regulations Sec. 50.24 Exception from informed consent requirements for emergency research. Available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/ cfcfr/CFRSearch.cfm?CFRPart=50andshowFR=1andsubpartNo de=21:1.0.1.1.19.2. [Last accessed on 2012 Aug].
- 21. Liamputtong P. Researching the Vulnerable. California: SAGE Publications; 2007.

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