Research with vulnerable participants

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Sabahans feeling vulnerable
Abduction at seafood restaurant has Sandakan folk in jitters

SANDAKAN: The latest abduction of two Malaysians by Filipino gunmen at a popular restaurant has made Sabahans feel very vulnerable as it occurred hardly 3km from the high-profile security presence in the east coast under the Eastern Sabah Security Command (Esscom).

The bold kidnapping of Ocean King Seafood Restaurant co-owner Thien Nyuk Fun and a customer, Bernard Then Ted Fen late on Thursday was the first such crime on the mainland. Previous kidnappings had occurred on remote islands or boats in Lahad Datu and Semporna.

Former Sabah deputy chief minister Datuk Tham Nyip Shen said the raid at the popular eatery patronised...
Definition

Malaysian GCP Guidelines  3rd ed. 2011

1.67 **Vulnerable subjects**

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 if refusal to participate
Vulnerable subject

• Is it ethical to conduct research and clinical trial on vulnerable subjects?

• Is it ethical **not** to conduct research and clinical trial on vulnerable subjects?
  - search for identify effective and appropriate treatment
  - avoid unsuccessful and/potentially harmful treatment
History of research abuse

- Tuskegee syphilis study
  - poor sharecroppers Blacks
- New York Willowbrook hepatitis B studies
  - mentally retarded children 1960’s
- Jewish Chronic Disease Hospital live cancer cells
  - uninformed elderly patients
Helsinki Declaration 1964 by World Medical Assoc.
- To benefit both researchers and research subjects through adoption of ethical rules of practice
- Review
  • best-proven method of treatment for controls
  • highest attainable and sustainable treatment
  • social context (developing vs developed world)
    - socially disadvantaged can be easily exploited
    - CIOMS “lack of alternative means of obtaining medical care or other expensive necessities” identifies vulnerable subjects. They lack basic rights and freedoms that form an essential part of choosing the basic course of their life.
• HK Beecher described studies conducted at major institutions which had placed research subjects at considerable risk and failed to get consent, 1966
• Belmont report, 1983: protecting human subjects from harm, coercion, or un-consented experimentation.
Vulnerable subject

Vulnerability occurs when a person’s ability to protect himself is absent or diminished, risking him intentional or inadvertent harm.

Legitimate concerns about the capacity to understand information presented to decide and to make informed choice

Through coercion, undue influence, inducement, manipulation and persuasion
Types of undue influence
use of his/her power to exploit the trust, dependence, or fear of others

Coercion  A credible threat of harm or fore to a research subject
Manipulation  Influencing a research subject’s decision by altering the available options or information
Persuasion  Guiding a research subject to your way of thinking through the disclosure of truthful information, but in a manner that if meant to get the person to think or act in a preferred manner
Counter Measures

1. The research should directly address real health needs thought to be important by the subjects themselves.

2. Research specifically focus on inherent characteristics of the subjects which are important on the research design.

3. Process to ascertain that subjects had not consented out of coercion or desperation, and genuinely understand the research incl risk/benefit.

4. The research should analyse its long-term consequences through debriefing and follow-up.
## Vulnerable and Special Research Population

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WHO 2008
Children

Do 1 or both parents need to give consent?
- Does the procedure involves greater than minimal risk to the child?
- Is there a prospect of direct benefit to the child?

Minimal risk means the “probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological exams or tests.

Children are legally unable to give valid consent, but they may possess the ability to assent to or dissent from participation.

formation given to the child should be age-appropriate, understandable, and tailored to the child’s emotional and cognitive maturity. Dissent should be honored, and children should be allowed to withdraw at any time. The ability to give assent requires cognitive ability and the ability to engage in abstract thinking, which depend not on chronologic age but on developmental achievement.
Research with children

• Children are persons who have not yet attained the legal age for consent to treatment or procedures (involved in research)
• Children autonomy and competence to give informed consent is less than that of adults
• Excluding children from research is not appropriate as that would exclude finding new treatment or prevention methods beneficial to them and to protect them from untested, harmful practices
Research in children

Approach - preliminary studies in animals, adults and older children

Does one or both parents need to give consent?
Depends on:
1. Research procedures involve greater than minimal risk to the child?
2. Is there prospect for direct benefit to the child?

Children are legally unable to give valid consent, but they possess the ability to assent to or dissent from participation. Assent is recommended if the research is unlikely of benefit to them. Info: age-appropriate, understandable, and tailored to the child’s emotional and cognitive maturity. Dissent should be honoured, and children should be allowed to withdraw anytime
Minimal risk

Probability and magnitude of harm or discomfort anticipated in the research are not greater in or of themselves than those ordinarily encountered in daily life of an otherwise healthy child or during the performance of routine physical or psychological exams or - US DHSS 2001
Research on Women of Child-Bearing Potential

- Concern on the potential risk to the foetus
- 1970s FDA essentially excluded women of childbearing potential from research participation
- """"Justice – deprives such women of benefits from participation"
- 1993: FDA eliminated the restriction of the 70’s, emphasising the need for representation of both men and women in clinical trials
- 1994: NIH follows suit
- Protection of vulnerable persons to autonomy of individuals (eg. Living wills, advanced directives, shared decision-making)
- Research subjects should be protected against risk, but should not be deprived of potential benefits
Research on Women of Child-Bearing Potential - safeguards

1. Reproductive-toxicity studies completed before CT
2. Precautions against inadvertent exposure to foetus, inform the female subjects of potential risks and need for precautions against becoming pregnant or breast feeding
3. Pregnancy testing detects unsuspected pregnancy
4. Start of study during or immediately after menses
5. Reliable contraception
6. If pregnancy occurs, discontinue study
7. Information abt animal reproductive toxicity study
Measures for women as research subjects

In General

Ensure that women are appropriately represented in research studies

Review animal studies: drug effects on reproduction and development, dose-response relationship and mechanisms of toxicity

Expand access to experimental drugs used to treat serious and life-threatening diseases to all women
Measures for women as research subjects

Women of child-bearing potential

Do not exclude

Inform the potential risks to reproduction and foetus in the PIS including birth control

Monitor subjects for pregnancy during the trial; withdraw the subject when pregnant

Monitor the subjects for reproductive and/or developmental toxicity if pregnancy occurs
Measures for lactating and pregnant women who participate in studies

Lactating women
  Do not exclude
  Provide adequate information during consent process on potential risks to the child

Pregnant women
  Eligible for clinical studies as competent adults
  Exclude if no potential benefits and potential risks to foetus
  Ensure adequate information on potential risks to themselves, their pregnancies and foetuses
Research on Pregnant Women

• Vulnerable because of potential risk to them and their foetus
• Liberalisation on their participation but strict and detailed guidelines enforced
• Research on the health the pregnant woman and/or her foetus, exclude if risks are greater than minimal
• 10% of 15-44 year old become pregnant annually
  - new medical problems develop or old ones become more severe during pregnancy
Research on Pregnant Women

- Review on studies on animals and non-pregnant women
- Risk is minimised – to woman and her foetus
- Research directed on the foetus: consent from both mother and father
- Research directed to the mother or mother and foetus – consent from mother alone
Research with prisoners

• Prisoners were readily and easily available
• Physical and psychological abuse
  - 1940’s: 400 prisoners in Chicago infected with malaria
  - MK-ULTRA project with hallucinogens
• Until early 1970s, 90% of all pharmaceutical and cosmetic products were tested on prisoners
• Changed after Holmesburg prison where prisoners were paid to be tested with dioxin for dandruff, and exposed to radioactive, hallucinogenic, and carcinogenic chemicals 1974
Research with prisoners

Prisoner – any individual involuntarily confined in a penal institution, including those detained pending arraignment, trial, or sentencing, and the institutionalized mentally retarded

**Measures**

1. Is it permissible to study prisoners?
   - only studies that have potential to benefit the prisoners are permitted
2. Recruitment is closely monitored by IRB
3. Prisoners be informed that their participation would not affect their well-being vis-à-vis parole board or prison warders
4. Financial incentives kept to a minimum
Research with Students and Employees

- Principle – participation in research is voluntary
- Unequal relationship between teacher/instructor or employer with student/trainee or employee
- Student/traininee or employee may feel compelled

Measure
1. Investigator need to consider the interests of the student/trainee or employee and the value of the research
2. Recruitment strategy is free of coercion and respect privacy and confidentiality of subject
3. Participation is voluntary. No pressure
4. Own students/trainee – get someone else to get permission and/or flyers
5. Ample time for subject to consider participating
Research on cognitively impaired persons

Diminished capacity for judgment and reasoning
- Psychiatric, cognitive, developmental disorders
- Unconscious or critically ill
- Capacity vs competence

Measures
- Involve them only if they are the only appropriate subjects
- Research question focusses on issues unique to them
- Minimal risk
- More than minimal risk is permissible if there is prospect of direct therapeutic benefit to the subjects
- Consider how to assess decision-making capacity:
  i. Who to administer
  ii. What instrument to administer
  iii. How formal the assessment procedure
- Surrogate consent.
  Can’t consent if there is no expected benefit if it has more than minimal risk
- Use of assent. Objection should be binding unless the research is expected to be of direct benefit to the subjects or the intervention could not be obtained otherwise.
- Simplified study summary – focus on major points, frequently asked questions
Consent and the vulnerable participant

• Informed consent is a legal, moral and ethical requirement
• Consent renders actions ethically and morally permissible that would otherwise be unacceptable
• Informed consent is authorization of an activity based on an understanding of what that activity entails and in the absence of control by others
• Values: respect of persons’ autonomy and their right to define their own goals and make choices designed to achieve those goals
Challenges:

1. Cultural norms eg paternalistic Asian culture
   - loyalty, compassion, solidarity > autonomy

2. Respecting persons includes respecting their social values. What limit?
   
   Lisbon Declaration of WMA on Rights of the Patient emphasises that patients everywhere have a right to information and self-determination

3. Informed consent involves among others disclosure, comprehension, voluntary choice, and authorization
   
   - capacity to understanding: scope and level of detail of info, how to assess comprehension, what constitutes necessary and sufficient understanding for valid consent, how to know choices are sufficiently voluntary, documentation of consent (is a signature suffice?)

surrogate decision maker vs oversight mechanism (the consent to be governed)

4. Autonomous authorization vs institutionally or legally effective authorization

5. Advanced technologies and expanded research opportunities

6. Changing demographics: increasing age, social an population mobility, social heterogeneity and complexity
Strategies to improve patient understanding

- Physicians taught communication skills
- Simplified PIS
- Time spent explaining to patients
- Time given for patients to reflect
- Decision aids and decision-making tools
- Use of non-physicians
Conclusions

• Excluding vulnerable participants from research is not ethically and morally acceptable
• Vulnerable participants defined and identified
• Special measures implemented especially in taking informed consent and care during the research
• Protects and benefits the participants, researchers, and the society at large
• Much work yet need be done to update our own research guidelines
References

• Protect vulnerable subjects by excluding them from research: no longer medically or morally acceptable

• Vulnerability occurs when a person’s ability to protect himself is absent or diminished, exposing them to intentional or inadvertent harm

• People with psychiatric, cognitive or developmental disorders when there are legitimate concerns about their capacity to understand information presented to them or to make informed choices