

ETHICAL CHALLENGES IN RECRUITMENT FOR PHASE 1 TRIALS

Dr Yves DONAZZOLO, MD, MSc

EUROFINS OPTIMED

1, rue des Essarts

38610 GIERES

FRANCE

The VoIREthics initiative



- VoIREthics = Volunteers in Research and Ethics
- A French Inserm initiative set up in 2022 on ethical issues related to the participation of healthy volunteers in biomedical research all over the world
- This initiative is now supported by numerous international partners incl. UNESCO
- EUFEMED participation in VoIREthics initiative : mission to promote the interest of early clinical development, develop standards and guidance documents...

History of Ethical perception of clinical trials

Often new legal requirements follow accidents or dramatic events

- **1937: Elixir sulfanilamide case leading to the « Food, Drug & Cosmetic Act » (1938) : animal testing and FDA authorization required before marketing a new drug**
- **Code of Nuremberg 1947-1949 : voluntary consent of participants, protection of subjects, qualification of staff...**
- **1960's: *Thalidomide case : preclinical research and pharmacovigilance***

History of Ethical perception of clinical trials

- **1932 – 1972: *Tuskegee Syphilis Experiment* : 600 African American men enrolled without free informed consent and without treatment even after 1943 to follow the natural history of syphilis**

- **1979: Belmont Report (USA):**
 - respect for persons, informed consent
 - benefit : maximazing benefits for the project, minimazing risks for the participant
 - justice considerations
 - foundation of the Office for Human Research Protection

In summary :

Are the essential principles still guaranteed all over the world to protect the rights and well-being of healthy volunteers and to ensure that the knowledge gained from clinical research is reliable and beneficial to society ?

A new perception of risks

- Absence of risk is an illusion
- Acceptance of an intrinsic element of uncertainty : « Level of uncertainty »
- Adaptation of the rules to mitigate the risk (guideline EMA 2017-2018)

The VoREthics initiative



- Healthy volunteers should be recognized as a specific “vulnerable group that should receive specifically considered protection” all over the world
- To lead the sharing and discussion of practices at international level, so that each country can decide on the best way to protect its healthy volunteers
- To issue recommendations to ensure respect for the rights, well-being, and safety of healthy volunteers in biomedical research.

<https://www.inserm.fr/en/ethics/volrethics/>

SEVERAL REGIONAL MEETINGS : some findings

- Economic and educational vulnerability of participants
- Undue inducement : a situation of significant vulnerability creates the conditions for potential coercion and exploitation
- Food as compensation
- Healthcare access as a motivation
- Sometimes need for
 - acts of legislation
 - independent ECs
 - national guidelines for fair compensation
 - conditions for confinement/well-being
 - Ensure protocols align with ethical standards
 - Higher education/training for research teams

SEVERAL REGIONAL MEETINGS : some findings

- Disproportionate number of minoritized participants in phase 1 or Bioequivalence Trials
- Mostly lower income, low education
- Many with a history of incarceration
- Many are immigrants without work permits
- Participants are punished for withdrawing consent
- Completion bonuses

RISKS OF BEING EXPLOITED

- Permitted means of recruitment of volunteers ;
- Inability to freely decide to participate : economic vulnerability, literacy level, pressure from family, peers, lack of access to healthcare... ;
- Insufficient or excessive financial compensation ;
- Insufficient information on risks and benefits ;
- Insufficient attention to well-being during the study ;
- Insufficient information on right to withdraw

RISKS OF BEING HARMED

- Inability of IRBs and CA to assess quality of research, justification to involve HV, assessment of risks ;
- Concealed participation in multiple projects ;
- Legal standards for study personnel and study sites to ensure safety and well-being of participants ;
- Insufficient insurance coverage ;
- Risk of ethical dumping

SEVERAL REGIONAL MEETINGS : Key points

- Healthy volunteers definition
- Volunteers motivations
- Registries to prevent over-volunteering
- Ways to Respect, Reduce, Refine and Replace healthy volunteers

CONCLUSION

- New challenges in phase 1
- Geographical differences to be kept in mind
- Prevention of risk to be exploited
- Prevention of risk to be harmed
- May lead to a consensus to ensure respect for the rights, well-being, and safety of healthy volunteers in biomedical research.

