Ethics in
Clinical Research

Module 3 Topic 2

Topics

- Ethics in Clinical Research
- Ethics Codes
- Informed consent in research
- Vulnerable subjects
- IRBs and ECs
- Trials in Special Population (Paediatric, Geriatric & Pregnant)
- Compensation for subjects

What are Ethics?

- A system of moral principles
- A norm of behavior set for a particular profession
- A code of conduct for a set of people
- Usually set by others and not self imposed, but when it is self imposed it is often known as “morals”

Unethical Ethical

Protection

- Code of conduct to protect the weak against the strong.
- In every walk of life there are the weak and the strong.
- Protection of the weak is the hallmark of civilization.

Legal System

Education

Healthcare

Why Ethics in Research

Ethics

- **Promote the** aims of research, such as knowledge, truth, and avoidance of error.
- Promote the **values that are essential to collaborative work**, such as trust, accountability, mutual respect, and fairness.
- Help to ensure that researchers can be held **accountable to the public**.
- Help to build **public support** for research.
- Promote a variety of important **moral and social values**, such as social responsibility, human rights, animal welfare, compliance with the law, and public health and safety.

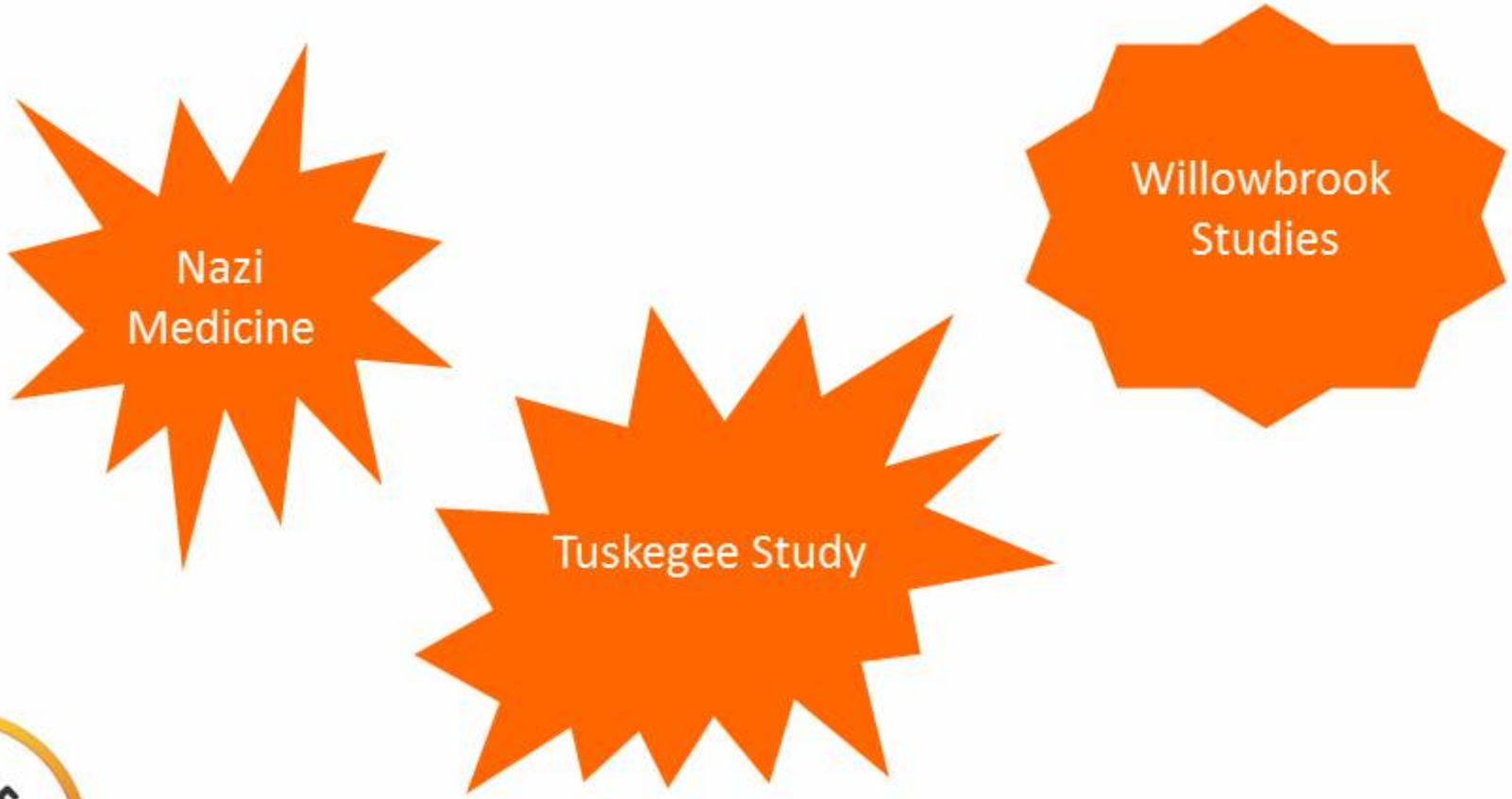
Clinical Research

- Human participants are used in research
- They usually lack adequate knowledge about their disease or treatment
- They are often sick and suffering, dependent on their doctors
- In a fiducial relationship with the medical fraternity
- They are the weakest link in healthcare system

History

- Very painful experiments were conducted on people to develop better surgical techniques.
- Painting shows Dr. Marion Sims with his patient, a slave Anarcha. She was subjected to 30 surgeries without anesthesia, none of which she needed.

Examples Galore



Codes of Ethics

Every major ethical violation, prompted the development of a new ethical code.

- The Berlin Code 1900
- Guidelines for Human experimentation 1931
- The Nuremberg Code 1947
- The Declaration of Helsinki 1964
- The Belmont Report 1978
- CIOMS Guidelines 2006
- ICMR Guidelines 2017

The Berlin Code 1900

- The code was a fall out of the infamous experiments of Albert Neisser on syphilis. In which he injected the spirochetes in commercial sex workers, without their consent.
- A commission headed by Rudolf Virchow found him guilty of misconduct and fined him 300 Marks.
- The code was published by the committee and included the first reference to informed consent.
- The code also put a bar on the use of children (below 18) in any experimental studies.

Guidelines for Human Experimentation

- Followed the Lubeck disaster in which 251 were inoculated with a vaccine against Tuberculosis. 72 children died of tuberculosis and 5 of other causes.
- Guidelines issued by the Weimar Government in 1931 to protect participants of “Innovative Therapy”. These guidelines remained in force till 1945, but were not followed by the Nazis.
- Enunciated many ethical principles that form the basis of current guidelines, but never acknowledged.

Nuremberg Code

- Medical experts at the Nuremberg Doctors Trial prepared a 10 point charter of "Permissible Medical Experiments"
- These were incorporated in the Nuremberg code, whose authorship is not known accurately.
- Many of the points of the code appear to have been lifted from the Guidelines for Human Experimentation of 1931, without acknowledgement.
- Has no legal standing but serves as the foundation for development of other ethical codes.

The Declaration of Helsinki

- Adopted by the World Medical Association at the 18th Annual meeting at Helsinki in 1964.
- Among the few "live" codes, in the sense that it is reviewed and revised regularly, last revision at Fortaleza, Brazil 2013.
- Prepared by synthesizing the Nuremberg Code with the Declaration of Geneva and the Vienna convention. Presently has 37 sections.
- The most widely followed code of ethics, India too is a signatory to this Declaration.

Belmont Report

- The US President set up the National Research Commission after the exposé of the Tuskegee Study (1932-72)
- The report of the commission was published in 1978 as the Belmont report, this is the guiding force behind all research in the United States.
- Enunciates the main principles of ethics viz. Respect, Beneficence and Justice.
- Childress and Beauchamp introduced the fourth principle of Non Malfeasance.

Principles

Respect for Persons.

- The principle of respect for persons divides into two separate moral requirements:
- Individuals should be treated as autonomous agents, and
- Persons with diminished autonomy are entitled to protection.

Application of this principle:

- **Informed Consent**. - Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them.

Principles

Beneficence.

- Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being.
- Two general rules have been formulated as complementary expressions of beneficent actions in this sense:
  - do not harm and
  - maximize possible benefits and minimize possible harms.

Principles

Application of this principle

- **Assessment of Risks and Benefits** - A method for determining whether the risks that will be presented to subjects are justified.

Justice.

- Fair distribution of burdens and benefits
- The selection of subjects should not be based on their easy availability, or compromised position
- Advantages be not restricted to those that can afford them and research should not involve persons unlikely to be beneficiaries of the research

Principles

Application of this principle

- **Selection of Subjects** –there be fair procedures in the selection of research subjects.

Two levels of justice relevant to the selection of subjects:

- Social - Social justice based on burdens of the class to which participants belong.
- Individual - Individual justice in the selection of subjects would require that researchers exhibit fairness:

CIOMS Guidelines

- The Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental, non-profit organization established jointly by WHO and UNESCO in 1949.
- International ethical guidelines for health-related research involving humans first published in 1982 latest revision in 2016.
- Very elaborate guidelines, consists of 25 guidelines, each elaborating a single principle.
- Covers issues not included in most guidelines, such as control groups, and medical reimbursement and compensation.

ICMR Guidelines

- 'Policy Statement on Ethical Considerations Involved in Research on Human Subjects' in 1980
- 'Ethical Guidelines for Biomedical Research on Human Subjects' in 2000
- 'Ethical Guidelines for Biomedical Research on Human Participants' in 2006
- 'National Ethical Guidelines for Biomedical and Health Research Involving Human Participants' in 2017

Principles of ICMR Guidelines

- **1.1.1 Principle of essentiality** whereby after due consideration of all alternatives in the light of existing knowledge, the use of human participants is considered to be essential for the proposed research. This should be duly vetted by an ethics committee (EC) independent of the proposed research.

Principles of ICMR Guidelines

- **1.1.2 Principle of voluntariness** whereby respect for the right of the participant to agree or not to agree to participate in research, or to withdraw from research at any time, is paramount. The informed consent process ensures that participants' rights are safe guarded.

Principles of ICMR Guidelines

- **1.1.3 Principle of non-exploitation** whereby research participants are equitably selected so that the benefits and burdens of the research are distributed fairly and without arbitrariness or discrimination. Sufficient safeguards to protect vulnerable groups should be ensured.

Principles of ICMR Guidelines

- **1.1.4 Principle of social responsibility** whereby the research is planned and conducted so as to avoid creation or deepening of social and historic divisions or in any way disturb social harmony in community relationships.

Principles of ICMR Guidelines

- **1.1.5 Principle of ensuring privacy and confidentiality** whereby to maintain privacy of the potential participant, her/his identity and records are kept confidential and access is limited to only those authorized. However, under certain circumstances (suicidal ideation, homicidal tendency, HIV positive status, when required by court of law etc.) privacy of the information can be breached in consultation with the EC for valid scientific or legal reasons as the right to life of an individual supersedes the right to privacy of the research participant.

Principles of ICMR Guidelines

- **1.1.6 Principle of risk minimization** whereby due care is taken by all stakeholders (including but not limited to researchers, ECs, sponsors, regulators) at all stages of the research to ensure that the risks are minimized and appropriate care and compensation is given if any harm occurs.

Principles of ICMR Guidelines

- **1.1.7 Principle of professional competence** whereby the research is planned, conducted, evaluated and monitored throughout by persons who are competent and have the appropriate and relevant qualification, experience and/or training.

Principles of ICMR Guidelines

- **1.1.8 Principle of maximization of benefit** whereby due care is taken to design and conduct the research in such a way as to directly or indirectly maximize the benefits to the research participants and/or to the society.

Principles of ICMR Guidelines

- **1.1.9 Principle of institutional arrangements** whereby institutions where the research is being conducted, have policies for appropriate research governance and take the responsibility to facilitate research by providing required infrastructure, manpower, funds and training opportunities.

Principles of ICMR Guidelines

- **1.1.10 Principle of transparency and accountability** whereby the research plan and outcomes emanating from the research are brought into the public domain through registries, reports and scientific and other publications while safeguarding the right to privacy of the participants. Stakeholders involved in research should disclose any existing conflict of interest and manage it appropriately. The research should be conducted in a fair, honest, impartial and transparent manner to guarantee accountability. Related records, data and notes should be retained for the required period for possible external scrutiny/audit.

Principles of ICMR Guidelines

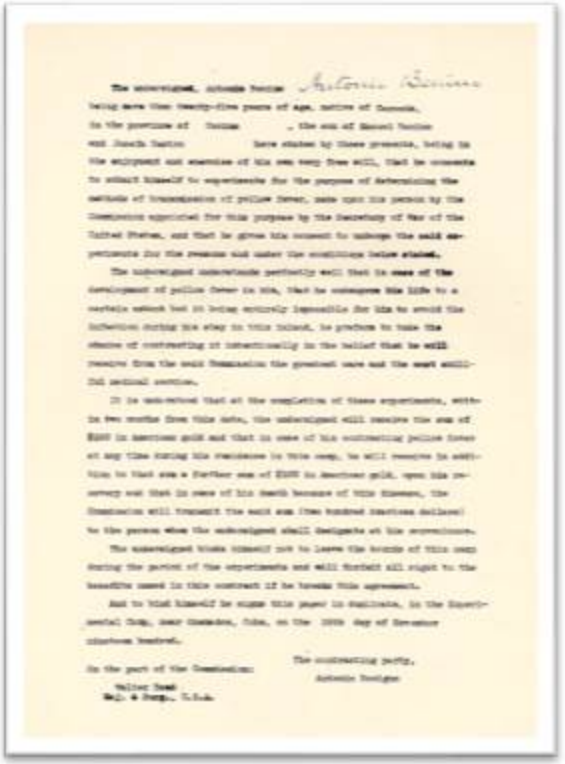
- **1.1.11 Principle of totality of responsibility** whereby all stakeholders involved in research are responsible for their actions. The professional, social and moral responsibilities compliant with ethical guidelines and related regulations are binding on all stakeholders directly or indirectly.

Principles of ICMR Guidelines

- **1.1.12 Principle of environmental protection** whereby researchers are accountable for ensuring protection of the environment and resources at all stages of the research, in compliance with existing guidelines and regulations.

Informed Consent

- The need for informed consent was hinted in the Berlin Code of 1900.
- This was given primacy by the Nuremberg Code and the Declaration of Helsinki.
- Walter Reed used a written informed consent form in his studies on yellow fever in 1900.



Consent

- The Nuremberg Code begins with - “The voluntary consent of the human subject is absolutely essential.”
- Elaborating further that - This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved, as to enable him to make an understanding and enlightened decision.

Vulnerable Population

DoH States as follows:

- Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm. All vulnerable groups and individuals should receive specifically considered protection.
- Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

CDSCO Classification

Vulnerable persons

- Members of a group with hierarchical structure (e.g. prisoners, armed forces personnel, staff and students of medical, nursing and pharmacy academic institutions),
- Patients with incurable diseases,
- Unemployed or impoverished persons,
- Patients in emergency situation,
- Ethnic minority groups, homeless persons, nomads, refugees, minors or others incapable of personally

Extra Protection for Vulnerable

Several provisions to protect vulnerable individuals:

- Special attention of ethics committee before approval of studies
- Use of "Legally Authorized Representatives" to consent on behalf
- In some cases use of "witness" for consent process. In India use of AV recording of the consent process.*
- Experts familiar with the problems of the vulnerable persons to advise Ethics Committee.
- Assent in addition to parental consent in case of children above 8 years of age.

*For certain trial types only.

Informed Consent Process

- All documents to be prepared using simple, non legal or medical language.
- Documents in languages that the participants are familiar with.
- Ample time to read and understand and take advice of friends or family.
- Investigator to explain trial procedures, allowing adequate time for questions and doubts.
- Must contain all essential elements as given in Appendix V of the Schedule Y.

AV Recording

- Informed consent process in all trials on New Drugs, involving vulnerable subjects must have audio video recording.
- Trials on AIDS/ HIV and Leprosy to have audio recording only.
- AV recording must be consented to by participants
- AV recordings to be stored in a secure place by PI
- Access to AV recordings to be restricted to members of EC, representatives of CDSCO and on orders of a court.
- AV recording protects both the participants and the investigators.

Ethics Committees

- The Declaration of Helsinki introduced the concept of Independent Review Boards to review and approve studies in 1975.
- In India the boards have been designated as Institutional Ethics Committees and Independent Ethics Committees.
- Every center proposing to perform clinical trials should have its own Ethics Committee. Institutional EC allowed to review and approve clinical trials, Independent ECs to review and approve BA/BE Studies
- Composition, registration and function of EC as per Rule 122 DD.
- EC to be accredited by NABH.

EC Composition

- Chairperson (who is from outside the Institution)
- Basic medical scientists (preferably one pharmacologist).
- Clinicians
- Legal expert
- Social scientist / representative of non-governmental voluntary agency /philosopher / ethicist / theologian or a similar person(s)
- Lay person from the community.
- Member Secretary

EC Powers

- To review all studies submitted to it.
- To approve/demand modification/disapprove studies (EC shall provide written reasons for disapproving studies)
- Conduct periodic reviews of ongoing studies
- Receive feedback/complaints from participants other staff about studies
- Audit studies in progress
- Conduct self appraisal periodically

EC Responsibilities

- To protect the rights, safety and well being of trial participants
- Review all study related documents to assess protection of rights, well being and safety of participants
- Ensure that trials are conducted as per protocol, guidelines and regulations
- Review protocol deviations design and ensure implementation of CAPA
- Review all SAEs, opine on causality and recommend medical reimbursements and compensations to participants/nominees.

Chairperson's Responsibilities

- Conduct EC meetings at the proper frequency and in the approved method
- Ensure that Guidelines and regulations are faithfully followed
- Ensure that all members participate in review process
- Appraisal of members, recommending change in membership
- Correspond with the Drugs Controller General on issues of medical reimbursement and compensation.
- Ensure timelines of communication and reporting are met.

Special Studies

- Certain populations that are sensitive to ill effects of drugs are generally excluded from clinical trials.
- These people may be included if the drug under investigation has special relevance to them or is meant for them,
- These include
  - Infants and children
  - Pregnant and lactating women
  - People with compromised hepatic or renal function
  - Geriatric populations

Children

- Ordinarily not included in studies, but should be included after safety in adults has been demonstrated and the drug is likely to benefit this population too.
- The stage at which children are included in studies will depend on the need of the drug by children:
  - If the drug is meant predominantly or exclusively for children
  - If meant to treat serious or life threatening conditions in children
  - If the drug has potential for use in children

Children

- Types of studies done in children include
  - Clinical studies
  - Bioequivalence studies between pediatric and adult formulations in adults
  - Definitive pharmacokinetic studies in different ages of pediatric cases
- If the drug is a major therapeutic advance for children's diseases, children should be included in the early phase of development.
- Children are vulnerable population, all care should be taken to protect their rights and well being, while protecting them from risk of long term harm.

Geriatric Studies

- With the rise of greying population in all countries, there is need to test most drugs in geriatric populations for their PK/PD and safety.
- Geriatric patients may be included in Phase II or III of studies, if the disease to be treated is:
  - Characteristically a disease of ageing
  - Population to be treated includes geriatric patients
  - More likely to be encountered in the elderly
- Or if the drug is likely to alter the response in the elderly (with respect to both safety and efficacy) compared to younger adults.

Pregnancy and Lactation

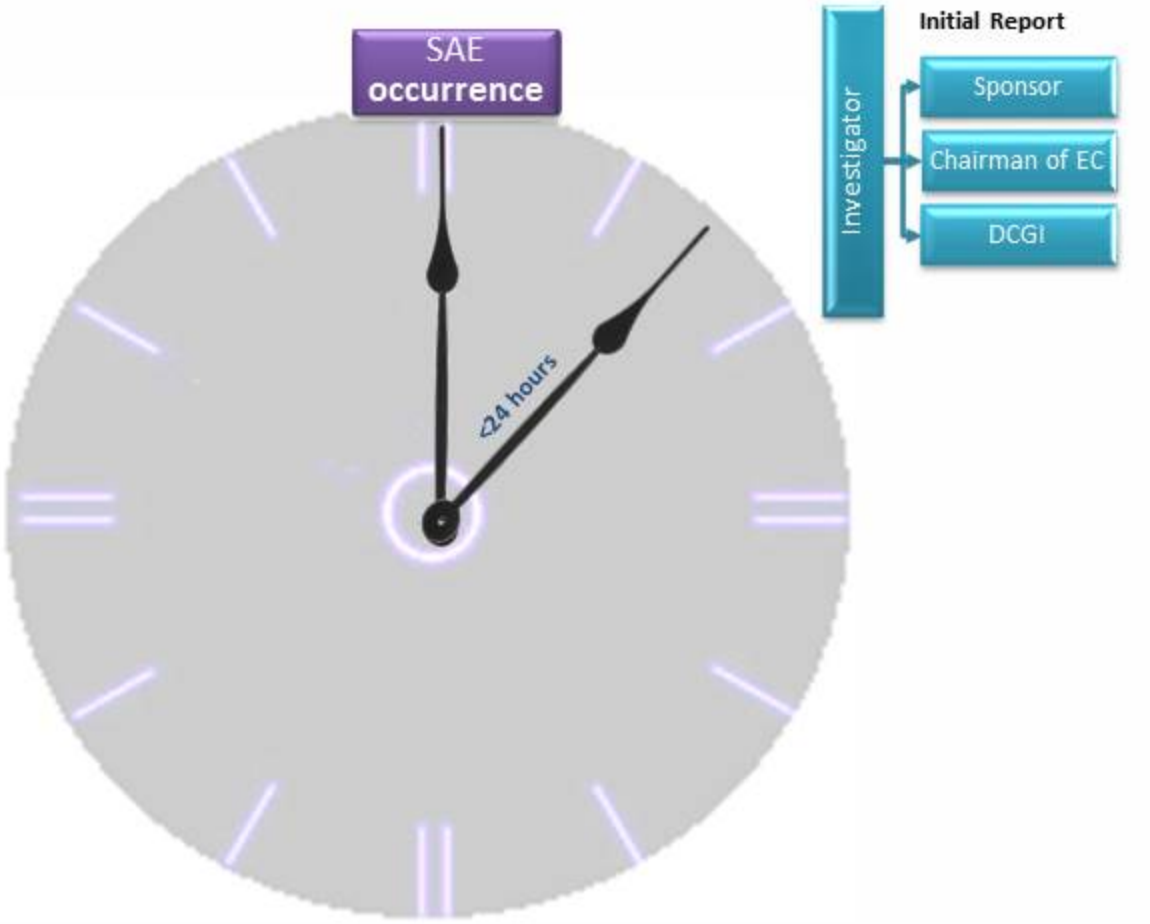
- Pregnant individuals or patients are avoided in all studies since the drug is likely to reach the fetus, and produce damage. In lactating women the drug may pass on to the child through the milk.
- These subjects may be specifically chosen for studies on drugs that:
  - are specifically needed by this population
  - may be needed to treat such patients and data from non pregnant women is not suitable
- For drugs to be used in lactating women, studies on drug in breast milk should be studied and infants monitored for drug effects.

SAE

- An adverse events that leads to any of the following conditions, is deemed to be a Serious Adverse Event.
  - Death
  - Is life threatening
  - Hospitalization, or prolongation of hospitalization
  - Permanent injury
  - Damage to the unborn child
- The sponsor may include other adverse events in this definition with justification.

New SAE Reporting Process

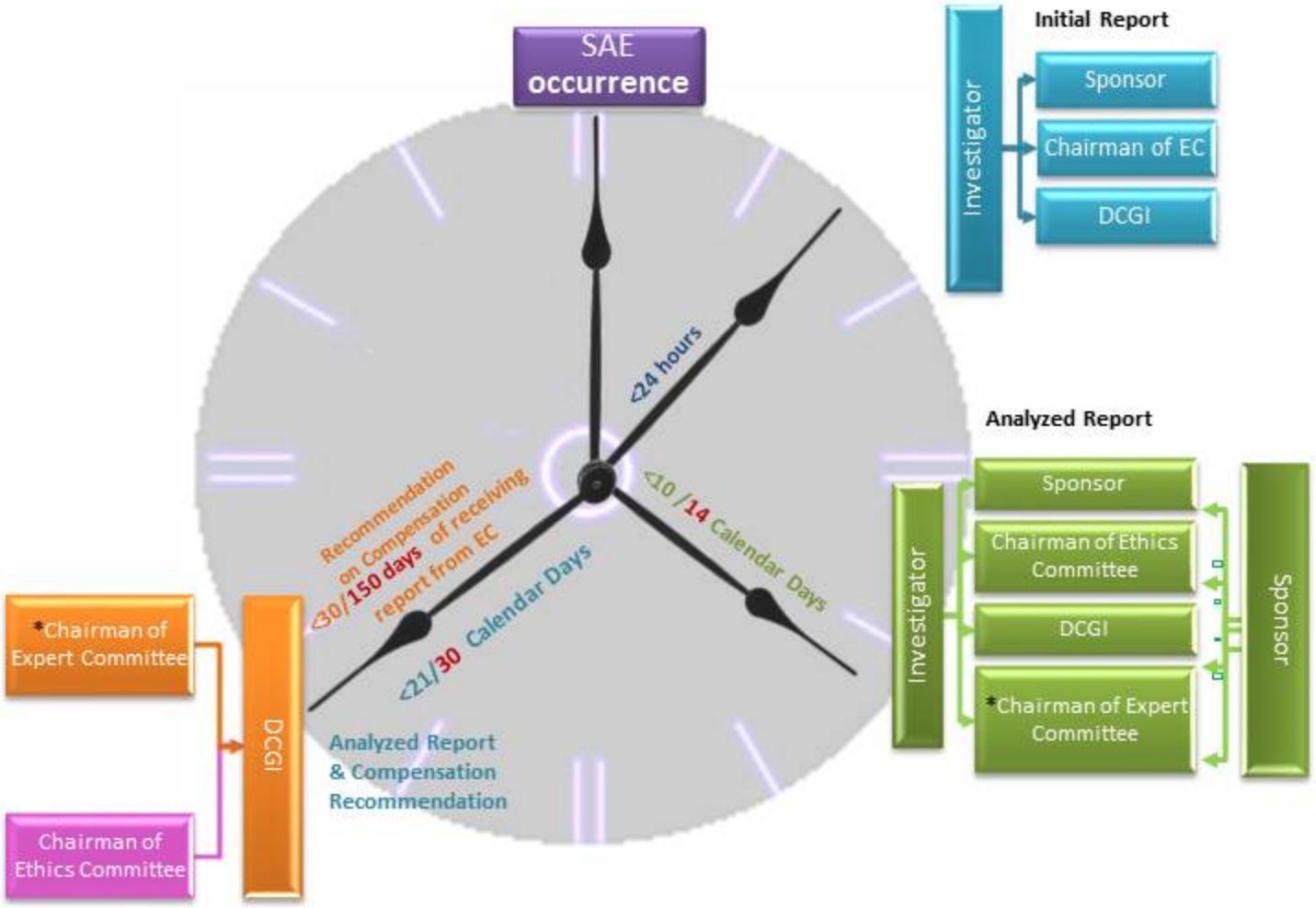
New SAE Reporting Process



New SAE Reporting Process

* In case of Death

New SAE Reporting Process



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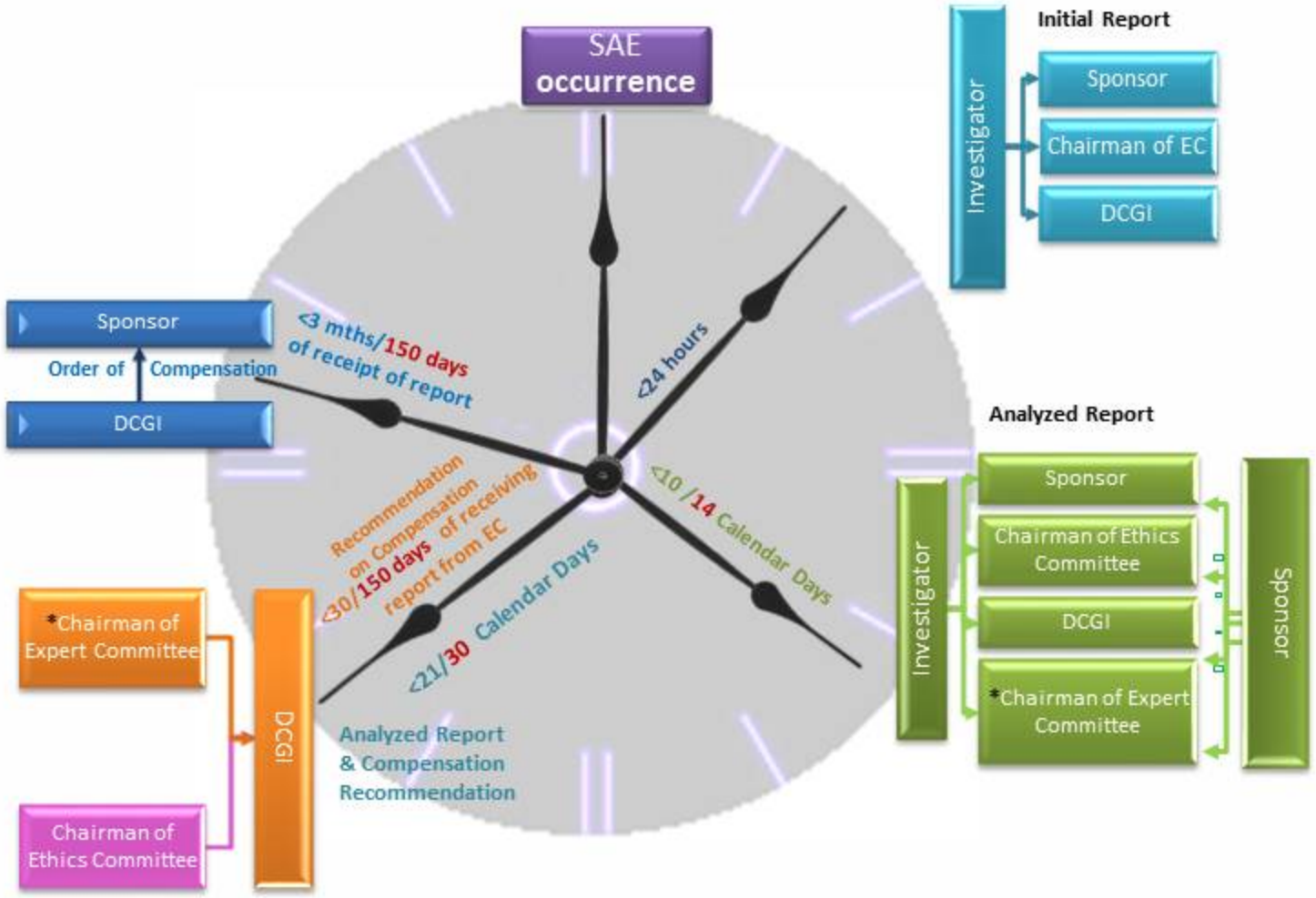

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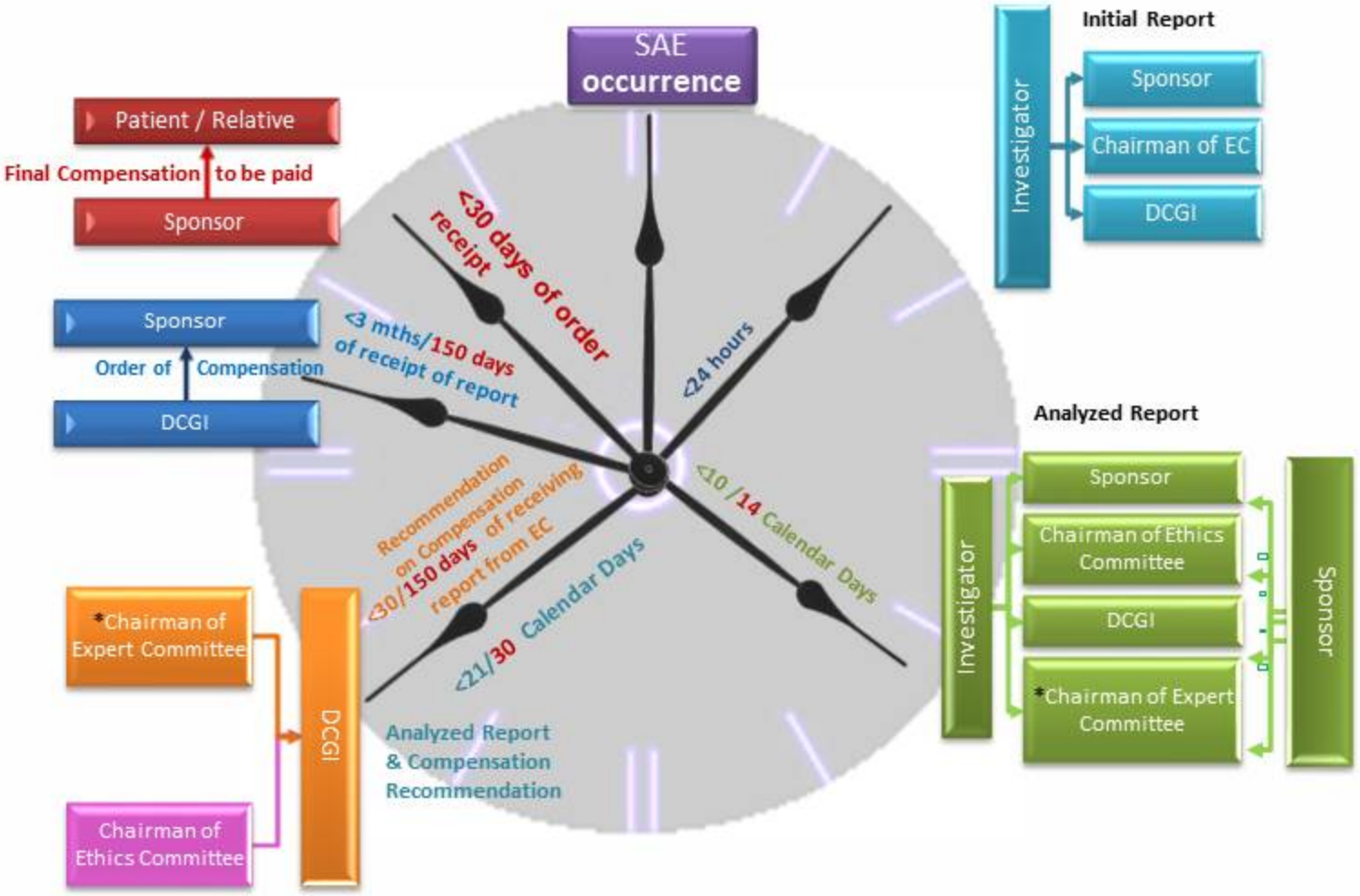

* In case of Death

Reimbursement

- Reimbursement of medical/surgical expenses for treatment of SAE is required to be paid by the sponsor(for as long as required) if the SAE is caused by the trial drug or procedures.
- If the SAE is unrelated, reimbursement must be paid till it is proved that the SAE is unrelated.
- Reimbursement is to be recommended by the EC and the final call is to be taken by the Drugs Controller.
- Payment must be made within 39 days of the receipt of the order from the DCGI.

Injuries Related to Trial

Injuries due to the following reasons are considered to be trial related:

a) Adverse effect of investigational product

b) Violation of the approved protocol, scientific misconduct or negligence by the sponsor or his representative or the investigator

c) Failure of the investigational product to provide intended therapeutic effect, where standard care, though available was not provided to the subject as per the protocol

Injuries Related to Trial

d) Use of placebo in a placebo controlled trial, where standard care, though available was not provided to the subject as per the protocol

e) Adverse effects due to concomitant medication excluding standard care, necessitated as part of the approved protocol

f) For injury to a child in utero because of the participation of parent in clinical trial

g) Any clinical trial procedure involved in the study

Compensation shall be paid by the sponsor, in addition to reimbursement of medical expenses in all the above situations.

Causality

- On the occurrence of an SAE, the investigator opines about the causality.
- The EC considers the PI's opinion and makes its own assessment about the causality, based on this assessment the EC recommends reimbursement of medical/surgical expenses and compensation, according to the formulae suggested by the government.
- The EC opinion must reach the Drug Controller within 30 days of the occurrence of the SAE.
- Causality assessment can be done using standard algorithms like the one of Naranjo or the WHO.

Naranjo's Algorithm

S.No	Question	Yes	No	Don't Know	Score
1	Are there previous conclusive reports on this reaction?	+1	0	0	
2	Did the AE appear after the suspected drug was administered?	+2	-1	0	
3	Did the AE improve on discontinuation or use of antagonist?	+1	0	0	
4	Did the adverse event reappear when the drug was re administered?	+2	-1	0	
5	Are there alternative causes that could have caused the reaction?	-1	+2	0	

Naranjo's Algorithm

S.No	Question	Yes	No	Don't Know	Score
6	Did the reaction reappear when a placebo was given?	-1	+1	0	
7	Were toxic levels of the drug detected in blood or body fluids?	+1	0	0	
8	Was the severity of the reaction related to the dose?	+1	0	0	
9	Did the patient have a similar reaction this or same drug in the past?	+1	0	0	
10	Was the adverse event confirmed by any objective evidence?	+1	0	0	

Interpretation

Score	Interpretation of Scores
Total Score >9	**Definite.** The reaction (1) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, (2) followed a recognized response to the suspected drug, and (3) was confirmed by improvement on withdrawing the drug and reappeared on re exposure.
Total Score 5 to 8	**Probable**. The reaction (1) followed a reasonable temporal sequence after a drug, (2) followed a recognized response to the suspected drug, (3) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.

Interpretation

Score	Interpretation of Scores
Total Score 1 to 4	**Possible.** The reaction (1) followed a temporal sequence after a drug, (2) possibly followed a recognized pattern to the suspected drug, and (3) could be explained by characteristics of the patient's disease.
Total Score ≤0	**Doubtful.**. The reaction was likely related to factors other than a drug.

Compensation

- In addition to medical reimbursement the sponsor is required to compensate the participant/nominee for:
  - Loss of wages due to hospitalization
  - Injury leading to permanent damage
  - Injury leading to in utero damage to fetus
  - Death of a participant

- The EC must recommend compensation as per the formula and the recommendation needs to be ratified by the expert committee appointed by the Drug Controller.

Compensation Formula

Death

$$\text{Compensation} = \frac{B \times F \times R}{99.37}$$

Where
B - Basal rate Rs. 8,00,000
R - Risk Factor assigned at recruitment
F - Age related factor

Minimum Compensation Rs. 2,00,000
Maximum Compensation Rs. 73,60,000

Compensation

Permanent Injury

SAE causing permanent disability to the subject.

$$\text{Compensation} = \frac{D \times 80 \times C}{100 \times 100}$$

where, D = percentage disability the subject has suffered,

C = quantum of compensation which would have been due for payment to the subject's nominee(s) in case of death of the subject.

Compensation

SAE causing congenital anomaly or birth defect leading to.

a) Still birth
b) Early death due to anomaly
c) No death but deformity which can be fully corrected through appropriate intervention
d) Permanent disability (mental or physical)

Initial compensation of Rs. 4,00,000

For (c) and (d) medical management as long as required

Compensation

SAE causing life-threatening disease

Compensation =N x W

where N = number of days for which the trial subject remained in a life-threatening situation requiring medical care, irrespective of number of days of hospitalization;

W = minimum wage per day of an unskilled worker.

Compensation

Reversible SAE if it is resolved

Compensation = 2 x N x W

where N = number of days for which the trial subject remained in a life-threatening situation requiring medical care, irrespective of number of days of hospitalization;

W = minimum wage per day of an unskilled worker.

Failure to pay

- In case the sponsor fails to provide medical management or financial compensation for clinical trial related injury; or compensation to the subject's nominee in case of clinical trial related death, the Licensing Authority may after a show cause notice suspend or cancel the clinical trial and/or restrict the sponsor to conduct any further clinical trials in the country or take any other action deemed fit under the rules.