Indian Clinical Trials- The Unaddressed Challenges of Regulatory Amendments

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What Is Schedule Y

- It is “Schedule under Part X-A of Drugs & Cosmetics Rule 1945 describe the information/data required –

  Requirements and guidelines for permission to import and/or manufacture of new drugs for sale or undertake clinical trials

Salient Features of Schedule Y

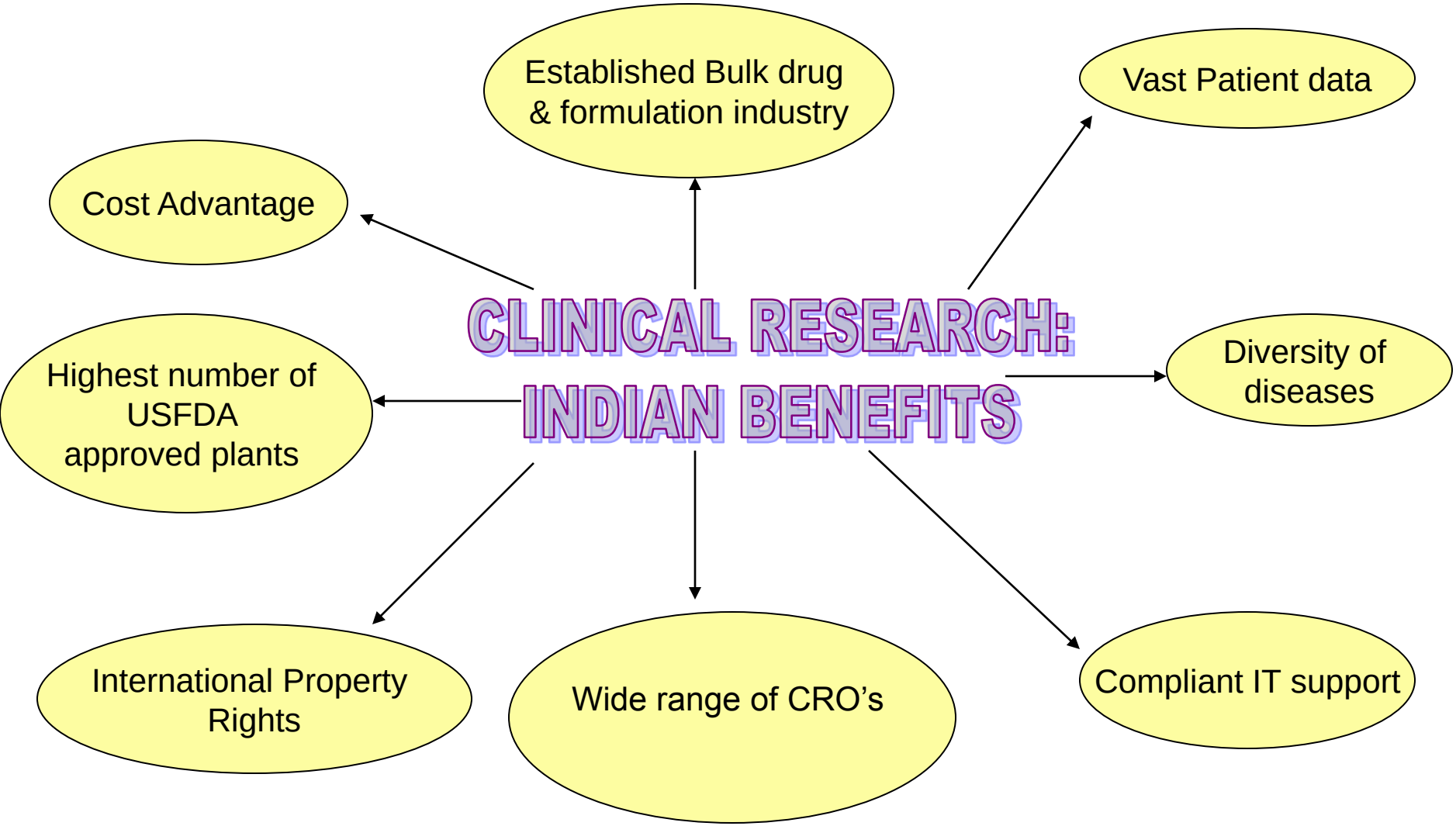
- Concurrent phase global clinical trials permitted,
- Phase I (first-in-human) study of New Drug substance discovered outside the country, not permitted(Repeat Phase I is permitted)
- Provides statutory support to Indian GCP Guidelines
- Stipulates responsibilities of EC, Investigators and Sponsor.
- Structure, contents and formats for CT protocols, reports, EC approvals, ICF, SAE reporting are incorporated .

Legal Provisions for regulation of Clinical Trials

Requirements and Guidelines - Schedule Y

Rule 122 DA	Permission to conduct clinical trial
Rule 122 DAA	Definition of Clinical trials
Rule 122 DAB	Compensation in case of trial related injury or death
Rule 122 DAC	Conditions of Clinical Trial permission & Inspection
Rule 122 DD	Registration of Ethics Committee
Rule 122 E	Definition of New Drugs

Advantages of conducting Clinical Trials in India



Schedule-Y Amendments - Long Overdue

- The amendment has brought in several good changes - EC/CRO registration, GCP Compliance and other related quality changes.
- Safeguard the safety of trial participants and to improve the following much criticized inefficiencies:
  - Misconduct, fraudulent cases of several clinical research players including CROs, investigators, ECs, regulators and sponsors.
  - Ethical lapses in informed consent issues, protocol violations, compensation issues among others.

Committees for Evaluation of Applications

- IND Committee – Evaluation of Investigational New Drugs (new molecules discovered in India). Chaired by DG, ICMR & Secretary, Department of Health Research.

- 12 New Drug Advisory Committees (NDACs) – Evaluation of all applications of clinical trials and new drug approvals except IND, subsequent approval of approved new drug, Bioequivalence study for export purpose
  - NDAC- Oncology & hematology
  - NDAC- Cardiovascular and renal
  - NDAC-Metabolism & endocrinology
  - NDAC- Antimicrobial, Antiparasitic & Antifungal, Antiviral
  - NDAC- Reproductive & Urology
  - NDAC-Gastroenterology & Hepatology
  - NDAC-Dermatology & Allergy, immunology
  - NDAC- Pulmonary
  - NDAC- Neurology & Psychiatry
  - NDAC- Analgesic, Anesthetics & Rheumatology
  - NDAC- Ophthalmology
  - NDAC- Vaccines

Evaluation of Clinical Trial Applications

- In compliance to the Hon'ble Supreme Court's order dated 03.01.2013, in the matter of Swasthya Adhikar Manch, a system of supervision of clinical trial has been put in place by constituting an Apex Committee under Chairmanship of Secretary, Health and Family Welfare and a Technical Committee under Chairmanship of DGHS.

- Presently applications are evaluated by the New Drugs Advisory Committees (NDACs) / Investigational New Drugs (IND) committee. The recommendations of these committees are finally reviewed by the Technical Committee and then approved by the Apex Committee on the basis of recommendations of the Technical Committee.

Recent Amendments in D &C Rules

- **Amendment vide G.S.R. 53(E) dated 30-01-2013 –**
  - analysis of SAEs,
  - provisions for payment of compensation,
  - expansion of responsibilities of Investigator, Sponsor and EC,
  - amendment in ICD.

- **Amendment vide G.S.R. 63(E) dated 01-02-2013**
  - conditions for conduct of CT,
  - authority for CT inspections
  - actions in case of non-compliance

- **Amendments vide G.S.R No. 72(E) Dated 08.02.13 –**
  - requirements and guidelines for registration of Ethics Committee

G.S.R. 53(E) dated 30-01-2013

Rule 122DAB

- In case of injury subject shall be provided free medical management as long as required.
- In case of CT related injury or death subject is entitled for financial compensation as per order of DCG(I).
- The expense on medical management and financial compensation shall be borne by the Sponsor.
- Sponsor shall give an undertaking along with the CT application to provide compensation in case of CT related injury or death.
- In case of failure to provide medical management and/or compensation
  - CT can be suspended / cancelled
  - Sponsor can be restricted from conducting future CTs

G.S.R. 53(E) dated 30-01-2013

Rule 122DAB

- Injury or death due to following shall be considered as clinical trial related injury or death:

  - Adverse effect of investigational product(s);
  - Violation of the approved protocol, scientific misconduct or negligence by the Sponsor or his representative or the investigator;
  - Failure of investigational product to provide intended therapeutic effect;
  - Use of placebo in a placebo-controlled trial;
  - Adverse effects due to concomitant medication excluding standard care, necessitated as part of approved protocol;
  - For injury to a child in–utero because of the participation of parent in clinical trial;
  - Any clinical trial procedures involved in the study.

G.S.R. 53(E) dated 30-01-2013

Amendment in ICD

- Essential elements of ICD have been amended to include statements that –
  - in the event of injury, free medical management as long as required
  - in case of CT related injury or death, financial compensation

G.S.R. 53(E) dated 30-01-2013

Amendment in ICF

- The Format of ICF have been amended to include-
  - address,
  - qualification,
  - occupation,
  - annual income of the subject and
  - name & address of his nominee.

- Mandatory for Investigator to hand over a copy of duly filled ICD to the subject or his/her attendant.

G.S.R. 53(E) dated 30-01-2013

Expansion of Responsibility of Investigators

- Investigator shall report SAEs to the DCG (I), Sponsor and Ethics Committee within 24 hr.

- The report of SAE of death, after due analysis shall be forwarded within ten calendar days to:
  - Chairman of the EC
  - Chairman of the independent Expert Committee with a copy to DCG(I)
  - Head of the Institution where the trial has been conducted.

G.S.R. 53(E) dated 30-01-2013

Expansion of Responsibility of Investigators

- The report of SAE other than death, after due analysis shall be forwarded within ten calendar days to:
  - **Chairman of the EC**
  - **DCG(I)**
  - **Head of the Institution where the trial has been conducted.**

- The Investigator shall provide information through informed consent process to the subject about
  - **Essential elements of the clinical trial as per Appendix-V**
  - **Right to claim compensation in case of trial related injury or death.**
  - **Right to contact the applicant for the purpose of making claims in the case of trial related injury or death.**

G.S.R. 53(E) dated 30-01-2013

Expansion of Responsibility of Sponsor

- The report of SAE of death, after due analysis shall be forwarded within ten calendar days to:
  - **Chairman of the EC**
  - **Chairman of the independent Expert Committee with a copy to DCG(I)**
  - **Head of the Institution where the trial has been conducted.**
- The report of SAE other than death, after due analysis shall be forwarded within ten calendar days to:
  - **Chairman of the EC**
  - **DCG(I)**
  - **Head of the Institution where the trial has been conducted.**
- In case of clinical trial related injury or death compensation to be paid within thirty days of order of DCG(I).

G.S.R. 53(E) dated 30-01-2013

Expansion of Responsibility of EC

- The report of SAE of death, after due analysis along with its opinion on the financial compensation, if any, shall be forwarded within twenty one calendar days to:
  - **Chairman of the independent Expert Committee**
  - **Copy to DCG(I)**

- The report of SAE other than death, after due analysis along with its opinion on the financial compensation, if any, shall be forwarded within twenty one calendar days to:
  - **DCG(I)**

G.S.R. 53(E) dated 30-01-2013

Appendix XII

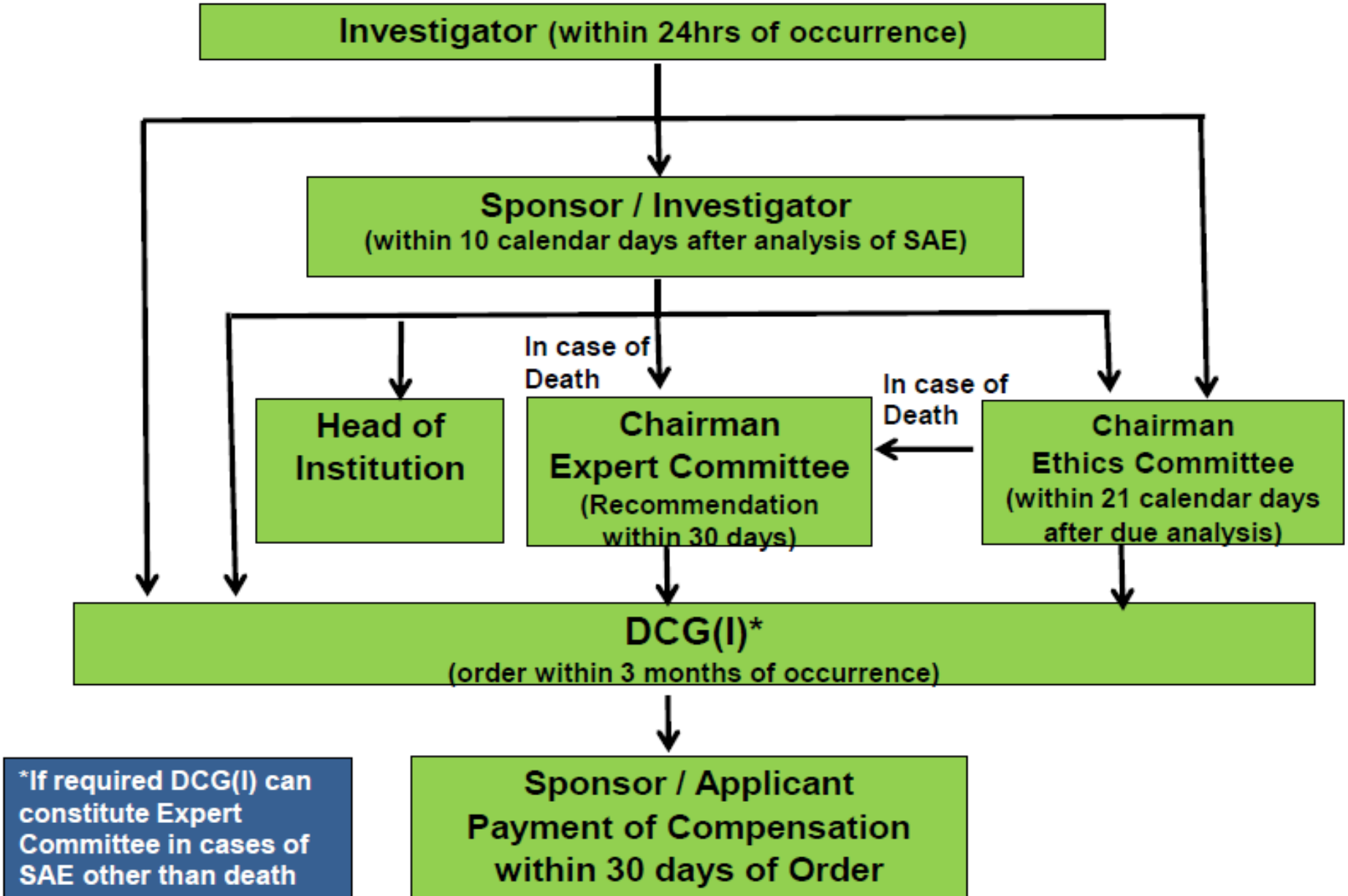
- **Procedure for examination of SAEs:**
  - Investigator shall report SAEs to the DCG (I), Sponsor and EC within 24 hrs.
  - In case of death, independent Expert Committee constituted by DCG (I) shall examine and recommend to DCG (I).
  - The Expert Committee, while examining may take into consideration reports of the Investigator, the Sponsor and the EC.

G.S.R. 53(E) dated 30-01-2013

Appendix XII

- **Procedure for examination of SAE's (Contd...) :**
  - DCG (I) after considering the recommendations of the Expert Committee, shall determine the cause of death and decide quantum of compensation within three months of receiving the report of SAE of death.
  - In case of Serious Adverse Events (SAEs) other than death, the DCG (I), after considering the reports of the Investigator, the Sponsor and the Ethics Committee, shall determine the cause of injury and also decide the quantum of compensation within three months of receiving the report.
  - Sponsor shall pay the compensation within thirty days of order of DCG(I).

Procedure for Examination of SAE



G.S.R. 63(E) dated 01-02-2013

Rule 122DAC

- Clinical trial shall be conducted in compliance with the approved protocols, requirements of Schedule Y, Good Clinical Practice Guidelines for conduct of clinical trials in India and other applicable regulations;
- Approval of the Ethics Committee shall be obtained before initiation of the study;
- Clinical trial shall be registered at Clinical Trials Registry of India before enrolling the first patient for the study;
- Any Report of SAE after due analysis shall be forwarded within 10 days of its occurrence in compliance with the procedure prescribed in Schedule-Y.

G.S.R. 63(E) dated 01-02-2013

Rule 122DAC (Contd…)

- Authority of CDSCO for inspection of clinical trial sites of Sponsor & Investigator.

- In case of non-compliance by the sponsor, Investigators and clinical trial sites LA can take following actions:

  - Recommend that study may be rejected or discontinued;
  - Suspend or cancel the clinical trial permission;
  - Debar the Investigator(s), Sponsor including his representative to conduct any clinical trial in future.

G.S.R. 72(E) dated 08-02-2013

Rule 122DD – Ethics Committee Registration

- No Ethics Committee shall review and accord its approval to a clinical trial protocol without prior registration with DCG (I).
- An application for registration of Ethics Committee is required to be made to DCG(I) as per Appendix VIII of Schedule Y.
- The Ethics Committee shall approve the CT and conduct periodic review as per the provisions of Schedule Y and the GCP Guidelines and other applicable regulations.

G.S.R. 72(E) dated 08-02-2013

Rule 122DD – Ethics Committee Registration

- In the case of any SAE, the Ethics Committee shall analyse and forward its opinion as per procedures specified under Appendix XII of Schedule Y.
- CDSCO can inspect the facilities, records, documents etc. of Ethics Committees.
- The registration of an EC shall be valid for a period of three years.
- If the EC fails to comply with any of the conditions of registration, DCG (I) may suspend or cancel the registration.

Concerns on Compensation Rules

- Providing medical management as long as required in case of any injury to clinical trial subjects.
- Payment of compensation in case of injury or death in clinical trials due to
  - Failure of investigational product to provide intended therapeutic effect
  - Use of placebo in a placebo controlled trial
  - Use of concomitant medication

Concerns on Compensation Rules

- Requirement for Investigator to report the SAEs to the CDSCO, Sponsor and Ethics Committee within 24 hours of their occurrence.
- Liability of sponsor to pay compensation for injury or death due to negligence / protocol violations/ misconduct by Investigator.
- Requirements of Sponsor to report the SAEs, after due analysis, within ten days.
- Overall time lines to be followed by the Ethics Committee, Independent Expert Committee and CDSCO for examination of SAEs to determine the cause of injury or death and to decide the quantum of compensation to be paid by the sponsor or his representative in case of clinical trial related injury or death.
- DTAB has deliberated these issues and submitted its recommendations for consideration of the Ministry.

Concerns on Compensation Rules

- Compensation has to be paid irrespective of whether or not the SAE is causally linked to IP.
- If this compensation is not provided, this may lead to the company suspending/losing the license to conduct CT in India on a case-by case basis. This is acting as a deterrent for many pharma MNCs.
- DTAB meeting on May 16th, 2013- causality issue/ if the standard care is denied in case of placebo trials/ failure of IP to act /streamline the timelines – these recommendations are highly required to be enacted

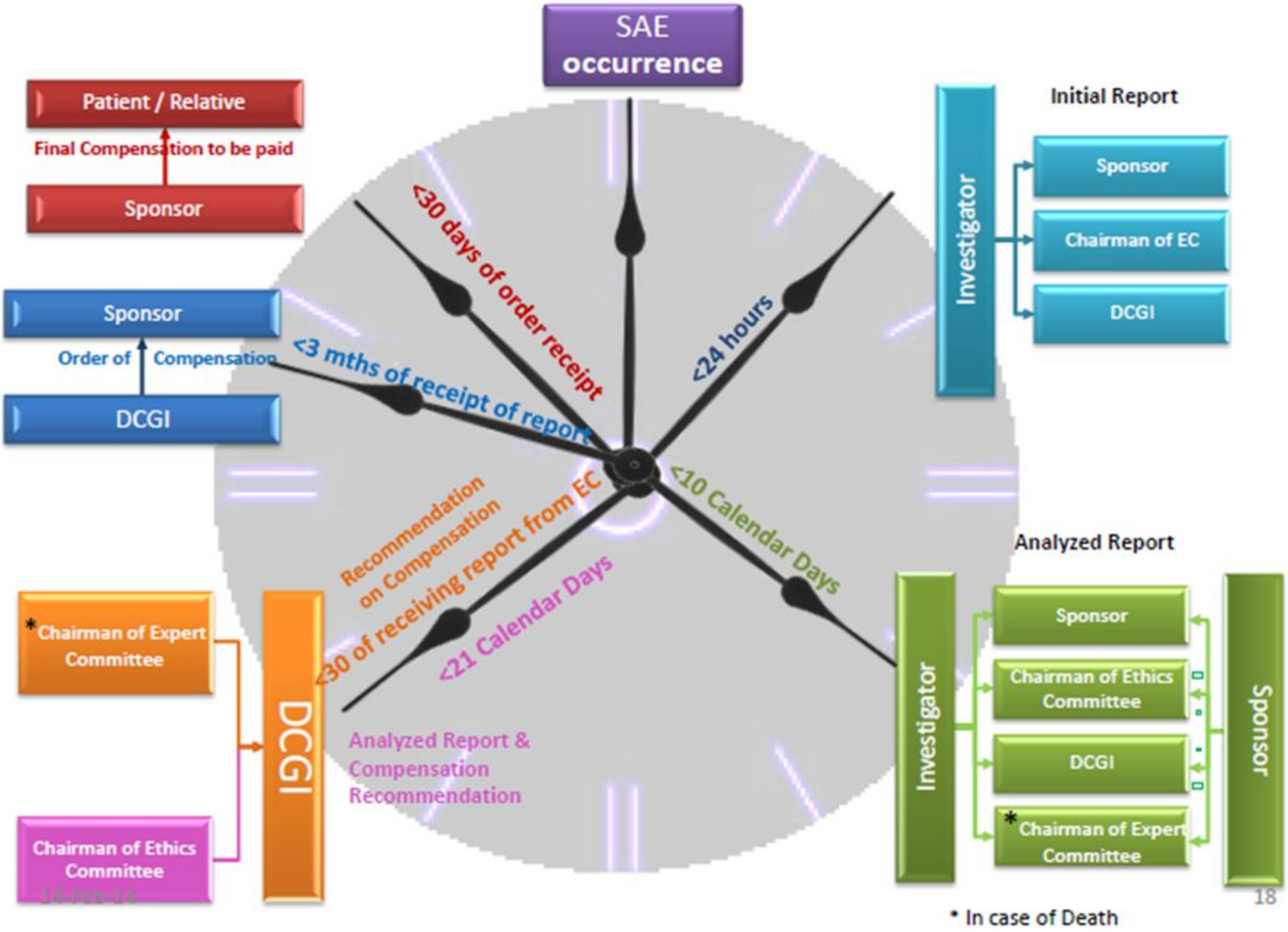
GSR No 53(E) dt 30 Jan 2013
Additions in Schedule Y



Inform the participant regarding compensation provisions during Informed consent process

Order by CDSCO for compensation to Sponsor within 3 months of receiving the report on ADR

New SAE Reporting Process



CONCLUSION

- These amendments have brought sudden change to the CT regulations.
- Many of these amendments were long overdue and were very much required however without too many lacunas.
- These changes should have been done in consultation with the stakeholders (Public, Sponsors, CROs, Academia, Ethics Committees, Regulators and Ministry) to avoid the anguish that the CT industry is undergoing currently.

THANK YOU

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