Safety Review

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Principles of ICH GCP

Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

Principles of ICH GCP (cont.)

Freely given informed consent should be obtained from every subject prior to clinical trial participation.

All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting Interpretation, and verification.

The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

Systems with procedures that assure the quality of every aspect of the trial should be implemented.

COMPARISON OF CLINICAL TRIAL PHASES

	PHASE I	PHASE II	PHASE III	PHASE IV
OBJECTIVES:	Determine the metabolic and pharmacological actions and the maximally tolerated dose	Evaluate effectiveness, determine the short-term side effects and identify common risks for a specific population and disease	Obtain additional information about the effectiveness on clinical outcomes and evaluate the overall risk-benefit ratio in a demographically diverse sample	Monitor ongoing safety in large populations and identify additional uses of the agent that might be approved by the FDA
FACTORS TO BE IDENTIFIED:	-Bioavailability -Bioequivalence -Dose proportionality -Metabolism -Pharmacodynamics -Pharmacokinetics	-Bioavailability -Drug-disease interactions -Drug-drug interactions -Efficacy at various doses -Pharmakodynamics -Pharmakokinetics -Patient safety	-Drug-disease interactions -Drug-drug interactions -Dosage intervals -Risk-benefit information -Efficacy and safety for subgroups	-Epidemiological data -Efficacy and safety within large, diverse populations -Pharmacoeconomics
DATA FOCUS:	-Vital signs -Plasma and serum levels -Adverse events	-Dose response and tolerance -Adverse events -Efficacy	-Laboratory data -Efficacy -Adverse events	-Efficacy -Pharmacoeconomics -Epidemiology -Adverse events
DESIGN FEATURES:	-Single, ascending dose tiers -Unblinded -Uncontrolled	-Placebo controlled comparisons -Active controlled comparisons -Well-defined entry criteria	-Randomized -Controlled -2-3 treatment arms -Broader eligibility criteria	-Uncontrolled -Observational
DURATION:	Up to 1 month	Several months	Several years	Ongoing (following FDA approval)
POPULATION:	Healthy volunteers or individuals with the target disease (such as cancer or HIV)	Individuals with target disease	Individuals with target disease	Individuals with target disease, as well as new age groups, genders, etc.
SAMPLE SIZE:	20 to 80	200 to 300	Hundreds to thousands	Thousands
EXAMPLE:	Study of a single dose of Drug X in normal subjects	Double-blind study evaluating safety and efficacy of Drug X vs. placebo in patients with hypertension	Study of Drug X vs. standard treatment in hypertension study	Study of economic benefit of newly-approved Drug X vs. standard treatment for hypertension

Data Safety Monitoring

- Defined as a planned, ongoing process of reviewing data collected in a clinical trial with the primary purpose of protecting the safety of trial participants, the credibility of the trial, and the validity of trial results

- Independent group consisting of at least 3 members with pertinent experience

History of DMC

- Almost 44 years of history on DMC's
- Soon after the era of modern randomized clinical trials began (1950's): Coronary Drug Project (CDP)
- NIH external advisory group (Greenberg report 1967) first introduced the concept of a formal committee
- After the CDP, DSMB became a more frequent component to large, multi-center trials sponsored by NIH
- Veteran Affairs began to include the use of DMC's with formal guidelines developed in mid-70's
- NCI began adopting DMC's in early 1980's
  - Still considered valuable despite being completely independent and using open therapies
- Adopted more frequently by industry in early 1990's

History of DMC

- 1996- Adoption by Internatinal Conference of Harmonisation (ICH)of GCP guidelines that recommended DSMBs in randomised trials
- 1998 - Medical Research Council of UK made the establishment of independent DSMB mandatory for all trials
- 1998- NIH guidelines states establishment of DSMBs for multi-site clinical trials involving interventions that entail potential risks to participants
- 2001- Indian GCP guidelines
- 2006- ICMR Ethical guidelines for Biomedical Research on Human subjects recommend setting up of independent DSMBs

Study Risk Definitions

Minimal-risk:

One standard definition is: *A study where the magnitude of harm or discomfort is not greater than that encountered in daily life or the performance of routine physical or psychological examinations or tests.*

Non-therapeutic trials such as survey research, questionnaires, blood samples, or observations.

Moderate-risk:

Phase II or phase III multi-intuitional industry sponsored trials with independent data monitoring

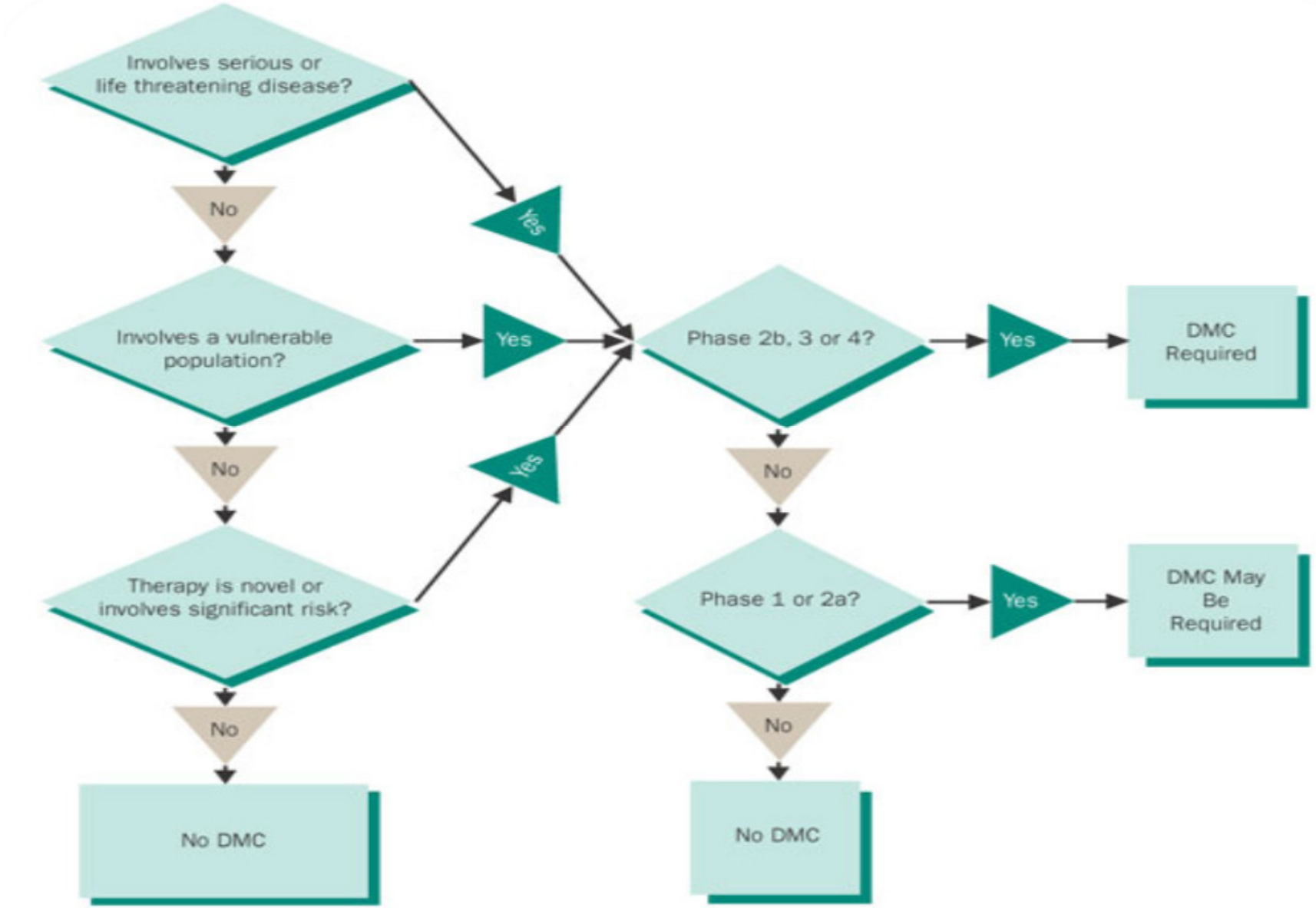
High-risk:

Clinical trials with investigational agents, phase I clinical protocols, investigator initiated INDs, manufacturing of product on campus, some phase II clinical trials, and investigator initiated phase III clinical trials.

Trials that Need a DMC

- Mortality or major Morbidity as primary or secondary endpoints
- Studies evaluating the clinical efficacy and safety of new intervention to reduce severe morbidity/mortality
- Early study of high risk intervention
- Early clinical phases of novel intervention with limited information on clinical safety or where prior information raises concerns regarding potential serious adverse outcomes eg.dose escalating studies
- Design or expected data accrual is complex, or ongoing questions with regards to impact of accrued data on study design and participants safety
- Data could justify early termination eg. Case of an intervention intended to reduce severe morbidity/mortality might turn out to have adverse effects that resulted in increase in morbidity/mortality
- Studies in vulnerable populations and emergency situation

Identifying Trials that Need a DMC



Expertise on DMCs

- Clinical medicine (appropriate specialty)
- Biostatistics
- Biomedical ethics
- Basic science/pharmacology
- Clinical trial methodology
- Epidemiology
- Law
- Patient advocate/community rep

Functions of the DMC

- Protect safety of trial participants
- Identify unacceptably slow rates of accrual
- High rates of ineligibility determined after randomization
- Protocol violations that suggest clarification or changes to protocol are needed
- Unexpectedly high dropout rates that threaten the trials ability to produce credible results
- Ensure credibility of study
- Ensure validity of study results

Utilityof DMC: Example

Withdrawal of Vioxx (Rofecoxib)by Merck & Co

- **APPROVe (Adenomatous Polyp prevention on Vioxx) trial** initiated in 2000 to investigate the efficacy of Vioxx in preventing recurrence of colon polyps

  Eighteen months into the trial DSMB recommended stopping the trial as patients taking the drug were found to have increased risks of serious cardiovascular events as compared to placebo

- Similar findings reported from **VIGOR (Vioxx GI Outcomes research) study** primarily designed to compare gastrointestinal adverse events profile of Vioxx and Naproxen

  Drug was voluntarily withdrawn from market

DMC Responsibilities

- Evaluating accumulating data with regard to safety & efficacy
- Recommending trial termination or continuation
- Recommending other modifications
- Reviewing and approving protocol
- Assessing trial conduct
- Recommending additional analyses

DMC Recommendations

- Continue Trial / Protocol Unmodified
- Modify Protocol
- Terminate Trial

Reasons for Early Termination

- Serious toxicity
- Established benefit
- Futility or no trend of interest
- Design, logistical issues too serious to fix

Key concerns of a DMC

- Avoiding two unethical decision:
  - Incorrectly stopping a trial of a good Rx
  - Failing to stop a trial of a bad Rx

Why the increasing use of DMC

- Growing number of industry-sponsored trials with mortality and major morbidity endpoints
- Increasing collaboration between industry and government in sponsoring major clinical trials
- Heightened awareness within scientific community and lay public of problems in clinical trial conduct

DMC Independence

- Many advantages to independent DMC
  - ensures that DMC not influenced by sponsor/ investigator interests
  - preserves ability of sponsor to make needed changes in trial without biasing results
  - protects sponsor from pressures to release interim data (e.g., SEC)
- Independent DMC does not mean sponsor has no contact with DMC
  - open sessions
  - sponsor can provide valuable information
- Preparation and presentation of interim analyses external to sponsor & study leadership allows for interim protocol changes

Data Safety Monitoring Sub Committee
Tata Memorial Centre

- The Data Safety Monitoring Sub-Committee is a sub-committee of the Hospital Ethics Committee
- Multidisciplinary membership
- 19 Members including Clinicians- representatives from every departments/DMG, pharmacologist and statistician
- Each project assigned to 2 reviewers
- Restructured every 2 years
- Meets on 2nd Tuesday of every month for SAE Review

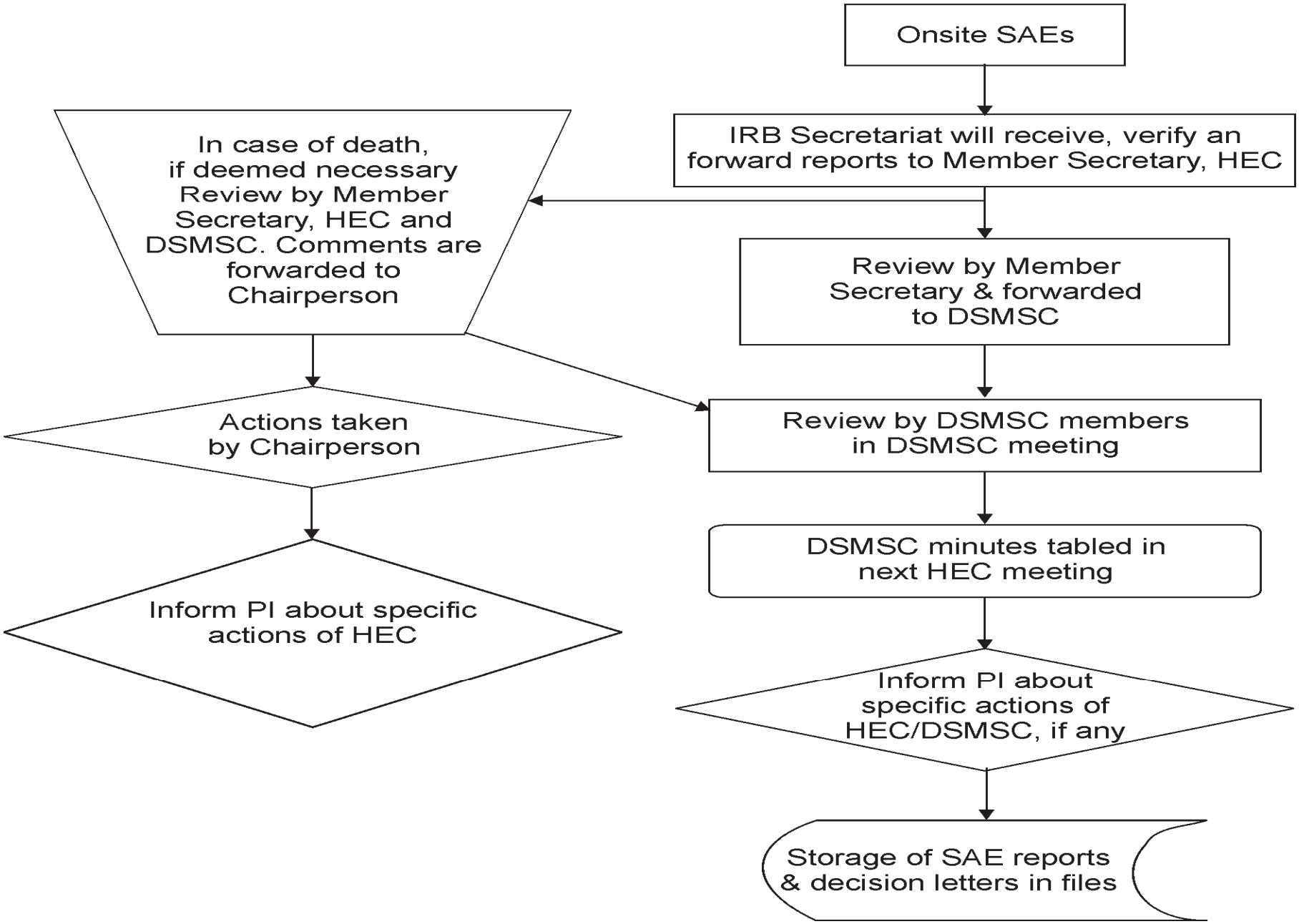
Mandate

- Monitor the overall progress of institutional clinical trials and for ensuring adherence to clinical trial and procedural requirements.
- Ensure the safety of participants, validity of data, projected accrual goals are maintained.
- Ensure that eligibility and evaluation criteria are followed, that risks are not excessive.
- Adverse events are appropriately monitored and reported to the appropriate agencies.
- Enhance the quality of the research by providing the investigator with constructive criticism.
- Provide regular reports to the Hospital Ethics Committee , address regulatory queries

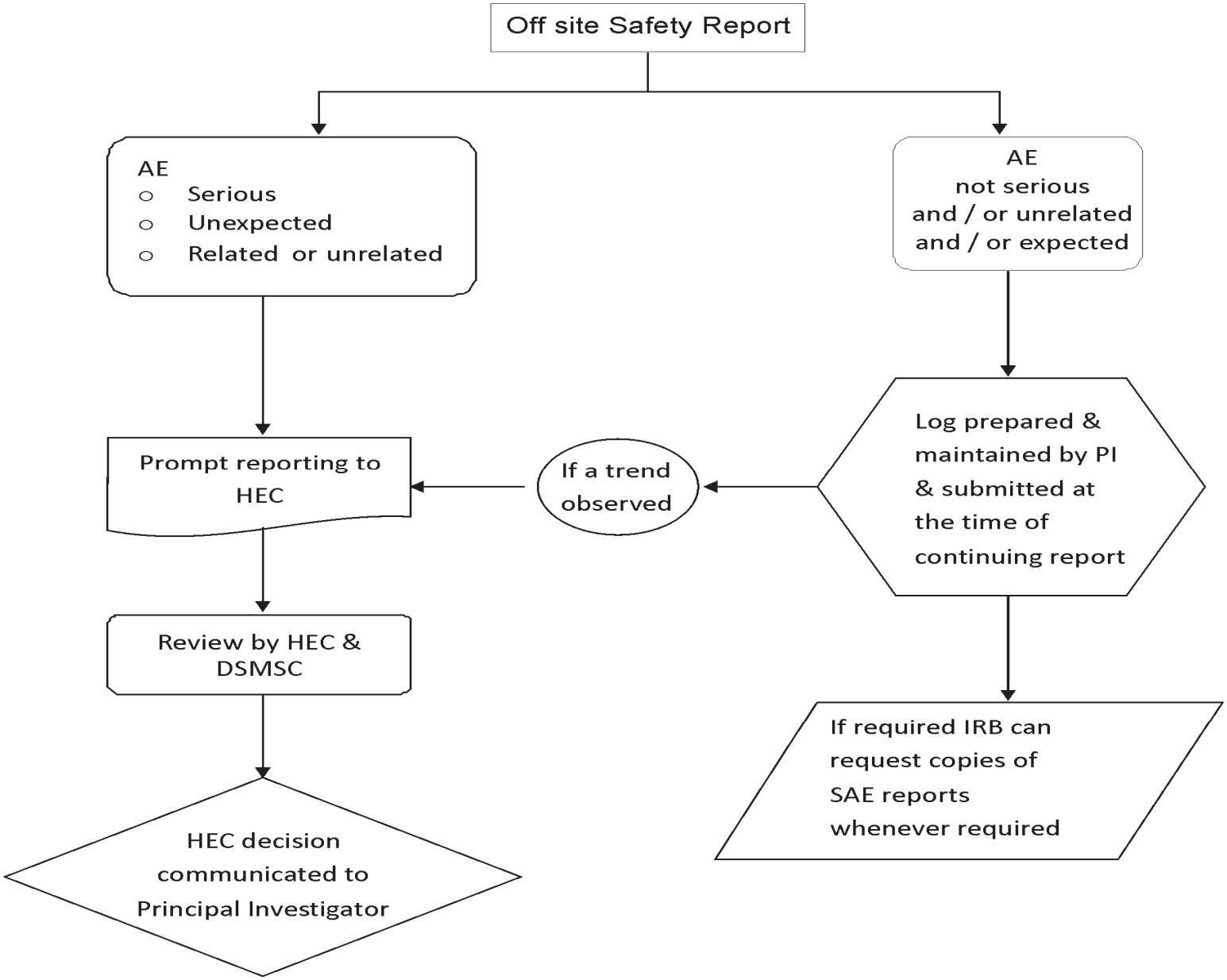
Functions

- Serious Adverse Event Review
- Monitoring of Investigator initiated trials and Sponsor trials (when necessary)
- Continuing review of trials

Flow Chart


Onsite SAEs
IRB Secretariat will receive, verify an forward reports to Member Secretary, HEC
In case of death, if deemed necessary Review by Member Secretary, HEC and DSMSC. Comments are forwarded to Chairperson
Review by Member Secretary & forwarded to DSMSC
Actions taken by Chairperson
Review by DSMSC members in DSMSC meeting
DSMSC minutes tabled in next HEC meeting
Inform PI about specific actions of HEC
Inform PI about specific actions of HEC/DSMSC, if any
Storage of SAE reports & decision letters in files

Flow Chart


Off site Safety Report
AE
Serious
Unexpected
Related or unrelated
AE
not serious
and / or unrelated
and / or expected
Prompt reporting to
HEC
If a trend
observed
Log prepared &
maintained by PI
& submitted at
the time of
continuing report
Review by HEC &
DSMSC
HEC decision
communicated to
Principal Investigator
If required IRB can
request copies of
SAE reports
whenever required

On- Site SAE Facts - 2010

- Total projects (SAEs received) 60
- Total SAE Reports* 872
  - Hospitalization 435
  - Increased hosp. stay 189
  - Deaths 163
  - Others ** 85

* includes initial, follow up and final reports

** important medical events, grade IV Lab abnormality, disease reoccurrence, life threatening events, persistent /Significant disability

Issues while review

- Death due to disease progression – need not be reported
- Over dose –Role of DSMSC
- Rapid event rates: Death, other medical problems
- Death of participant – withdrawn / out of trial status – Action by DSMSC
- Review of offsite /PSUR/Quarterly/ Annual safety reports
- Issues in discussion –
  - Drug action, interaction
  - Prohibited medication used
  - Statistical significance
  - Expected /unexpected events
  - Causality assessment: Related /unrelated

Increasing DCGI Vigilance

- Against increasing number of trial-related deaths
- Queries requesting EC opinion on past SAEs (> than 1year old)
- Compensations paid for trial related deaths
- TMH has received a total of **23 DCGI queries in 2010** and 32 till date (2010-11)
- Led to DCGI's stand to include a line in the informed consent form, assuring the patient/volunteer that he will be provided complete medical care and compensation for any clinical trial-related injury or death

Challenges

- Not an independent body
- Uniqueness of disease and treatment modality
- Causality Assessment
- Large number of trials – One DSMSC for all trials
- Tagging and flagging of real time events
- AE Reporting/Offsite SAE review
- Increasing number of Industry trials with several new molecules

- Continuous, ongoing process
- Interactive
- Dynamic process: changes, training
- Increasing awareness & vigilance

THANK YOU