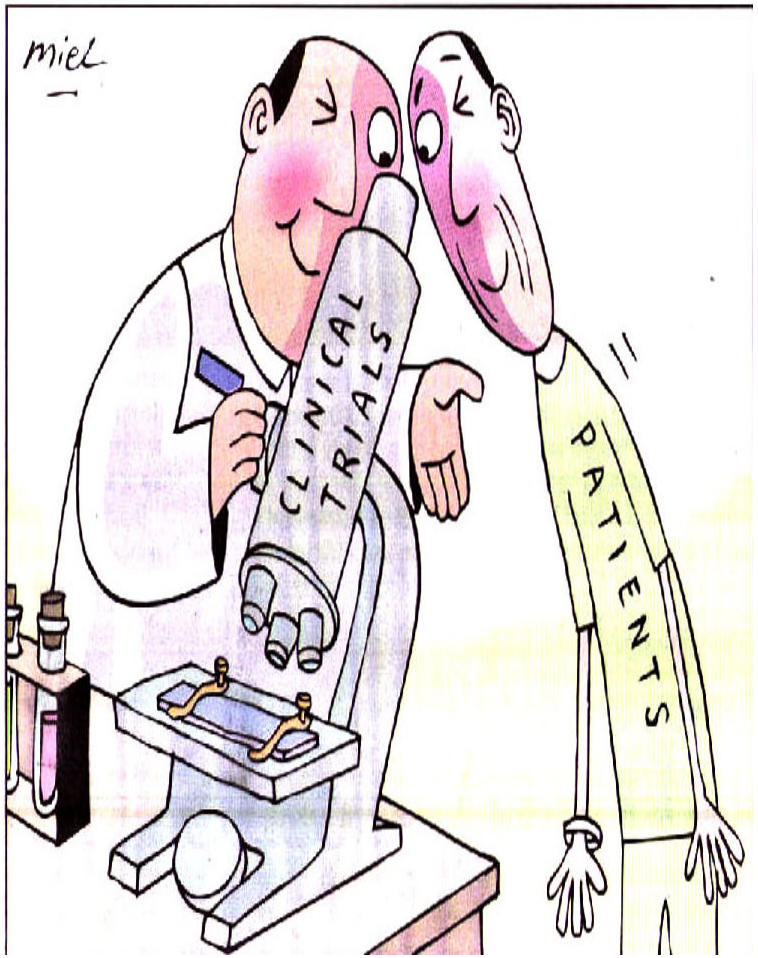
Multi-center Clinical Trials and Monitoring

"3rd International Conference and Exhibition on Pharmacovigilance & Clinical trials"27 Oct-29 Oct 2014 , Hyderabad, India

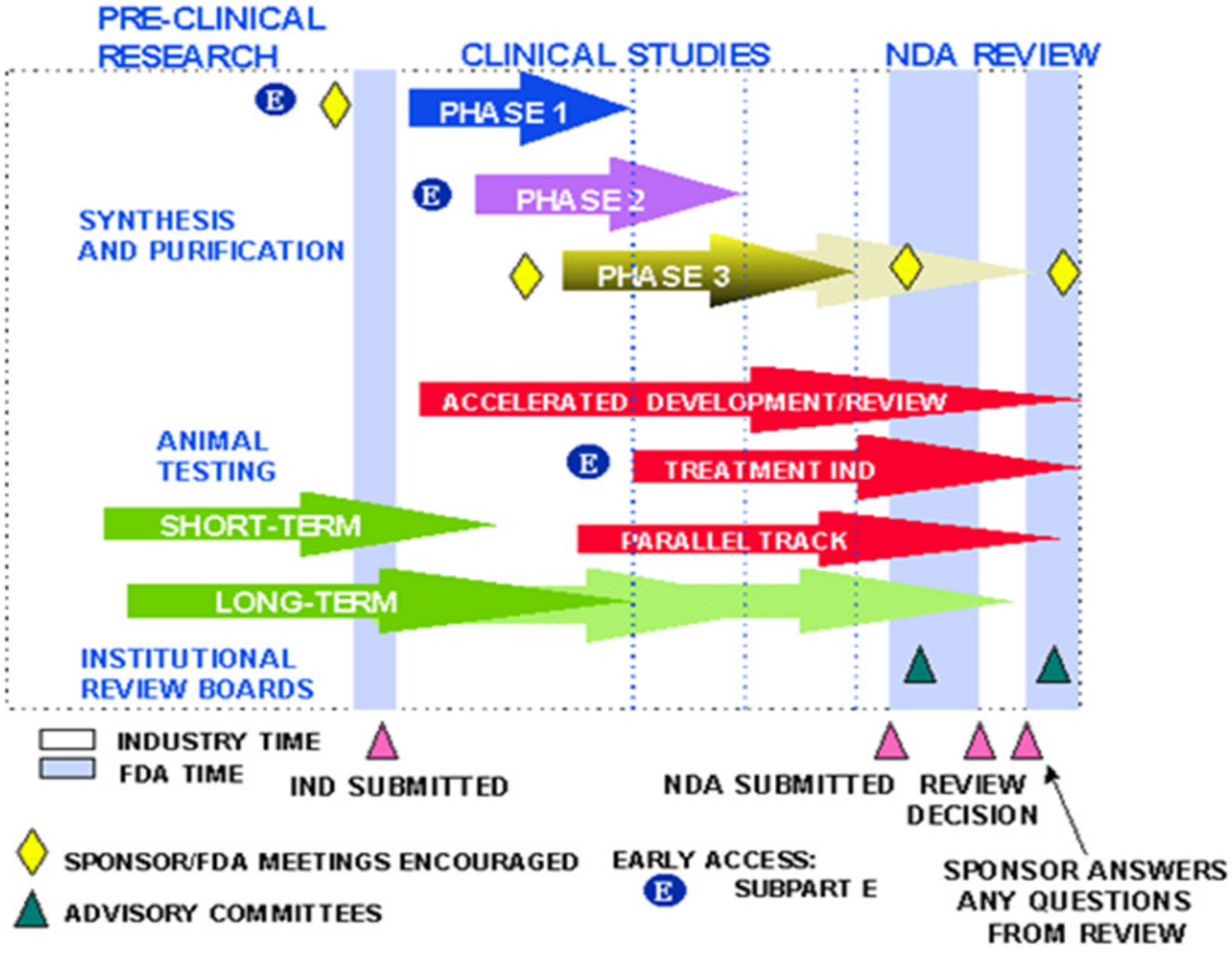
Dr.Anju Gopan
Senior Clinical Research Physician
ICON Clinical Research India
27Oct 2014

Contents

- Relevance and introduction
- Multicenter clinical trail/Investigator initiated MCT
- Monitoring-Centralized Monitoring
- Risk based Monitoring
- Experience with Monitoring/Risk based monitoring and Centralised Monitoring
- Experience with centarlised Safety monitoring
- Future of MCT and Monitoring
- Take home points



Clinical trial in a picture



Relevance of MCT: Regulatory updates

- **The FDA** has released an action plan aimed at encouraging **more diverse patient participation** in drug and medical device clinical trials(later half of 2013)
- FDA regulations already require some amount of reporting on **patient demographics(**later half of 2013 and early 2014**)**
- Companies submitting investigational new drug applications must provide the FDA with annual reports tabulating **patients' age, race and gender.**
- Drug- and device makers are also encouraged to enroll patients whose age, gender, race and **ethnicity reflect the most affected populations**
- Include these information in study protocols

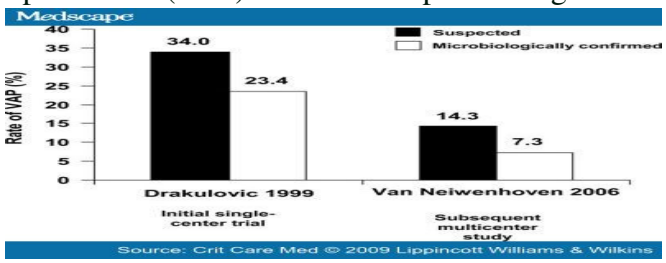
- ***FDA-Diversity in Clinical Trial Participation-Action plan in aug 2014***

Monitoring the Quality of Conduct of Clinical Trials: A Survey of Current Practices," Clinical Trials, Vol. 8, No. 3, pp 342–349, June 2011, http://ctj.sagepub.com/content/8/3/342

Guidance Webinar Video, Transcript from FDA Webinar Session, Oct. 24, 2012.

Multicenter Clinical trials-Facts

- 2007- the FDA revised the label on the common blood-thinning **drug warfarin** (Coumadin) to explain that a **person's genetic makeup might influence response to the drug** → **Labeling** on Warfarin(induvidualised according to PT/INR)
- Drug **Transtuzumab (Herceptin**). This therapy works only for women whose tumors have a **particular genetic profil**e → Benefit for high risk specific group(over expr of HER2) of breast cancer women **(Personalised medicine)**
- Chemotherapy drugs- gefitinib (Iressa) and erlotinib (Tarceva), work much better in lung cancer patients whose tumors have a **certain genetic change**(EGFR expression) → Evaluate EGFR expression –treat patients who **benefits(No blanket treatment reduce unnecessary side effects**)
- **Tacrolimus** : retrospective comparison in kidney transplant patients - black (African-American) patients **required higher tacrolimus doses than whites** → Difference in treatment **dosing.**
- Variability in the rates of ventilator associated pneumonia(VAP)in recumbent positioning → Single center VS Multi center results



(:*Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling* DIA, Clinical Forum, Dublin, 7 October 2013.Fergus Sweeney, Head, Inspections and Human Medicines Pharmacovigilance-Ref:Safety labeling)

Why MCT is the need of the hour?

- **Emergence of different variants, resistant strains, and genetic mutations of common and uncommon diseases**
- Biggest barrier to completing clinical trials- **not enough people take part in them.**
- Increase the **generalizability** of the study by including a wider range of population groups
- More **efficient** clinical investigators at different sites is better than a single investigator for **recruiting patients**
- (According to the Pharmaceutical Research and Manufacturers of America (PhRMA), more than 1000 cancer medicines were being tested in clinical trials in 2012.Not all of these drugs will prove to be useful, but those that are **may be delayed in getting approved because so few adults volunteer)**

- Ability to **compare** results among centers
- To recognize the **efficacy safety in varying** populations
- Avoid unnecessary **exposure of patients** to ineffective drugs
- Increasing **demand i**n evaluating a drug in **different genetic pool**
- **Develop personalised medicine**



In many cases, efficacy will vary significantly between population groups with different genetic, environmental, and ethnic or cultural backgrounds ("demographic" factors); normally only geographically dispersed trials can properly evaluate this.

Factors leading to a successful MCT

- A promising **molecule/treatment** regime
- A well trained and planned **team**
- Single **well-planned and designed protocol** conducted at more than one location
- Inter-Institutional **Agreements**
- Determine **Authorship** Policies
- **Register** trial with clinicaltrials.gov
- Oversee **regulatory** documents
- **Adverse Events Reporting** - Central Monitoring Body
- **Site** and Centralised Monitoring

A vigilant & dedicated team of Investigators

Sponsor/CRO

Multi –center clinical trials

Advantages :

- Larger **sample size** and quicker **patient accrual**
- Broader **interpretations of results** because of the multiple participants involved in the study across various geographic regions (this adds to external validity)
- Increased **scientific merit** of the trial because of collaborations among experienced clinical scientists involved in the design and implementation of the study.

Disadvantages

- Planning is more **complex**
- **Expensive**
- **compliance to clinical protocol across all centers**
- **Quality control and data cordinating centers must** be implemented for taking measurements and recording data
- **All investigators involved** and motivated
- Avoidance of passive investigators
- Compromise between quantity and quality of centers
- **Leadership to coordinate efficiently**



Transform into advantage

MCT-Sharing of responsibilities

1-Sponsor and CRO responsibility

- **Organizational structure** :

leadership / communication/ performance criteria / a process for monitoring performance goals/ providing feedback

- **Develop** Financial plan/Monitoring plans/Regulatory plans/DSMB committee/Interim analysis team/Safety monitoring Plans/ Plan to handle unexpected events

- **Safety** /study Monitoring **team**

- **Adequate** site selection and follow up

- **Train** sites and retrain when needed

- **Oversight and Review** of study results at interval
- Safety **reporting and analysis**
- Regular Monthly evaluation of study and safety
- Adequate **technology** incorporated at various aspects of study

2--Investigator's Responsibilities

1 Investigator's qualifications and agreements

- Education, Training, Experience
- Be familiar with protocol and IB

2 Adequate resources

- Do you have the time?
- Staff and facilities
- Can you recruit patients under the recruitment period?

3 Medical care of subjects

- Medical decisions
- Adverse events

4-Communication with IRB

5 Protocol compliance and IP

6 Inventory, records (dates, quantities, batch/serial numbers, expiration date)

7 Informed consent of trial subjects

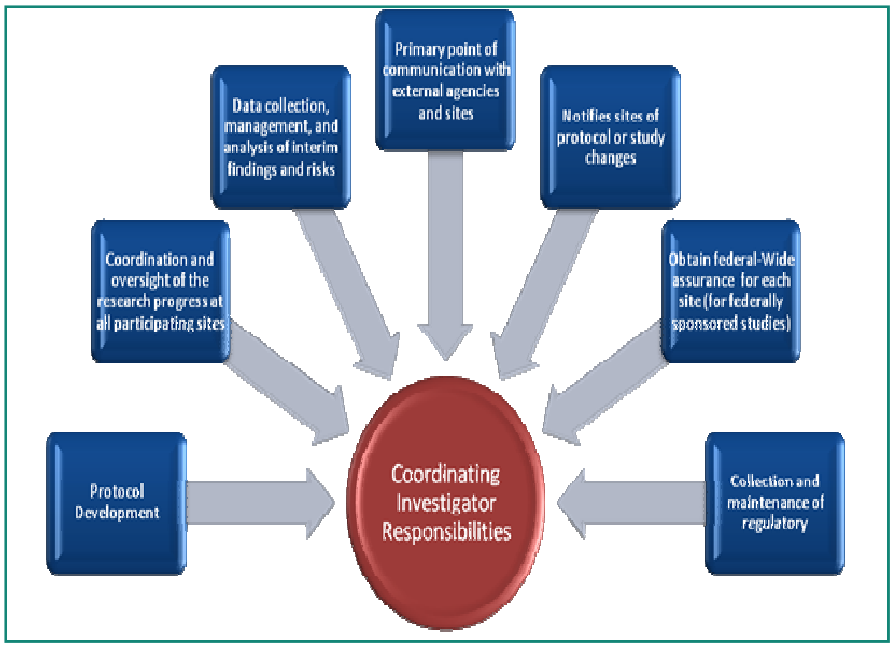
8 Records and reports

9 Patient safety

Investigator initiated Multicentric clinical trials

A-Coordinating Center

B-Research committee



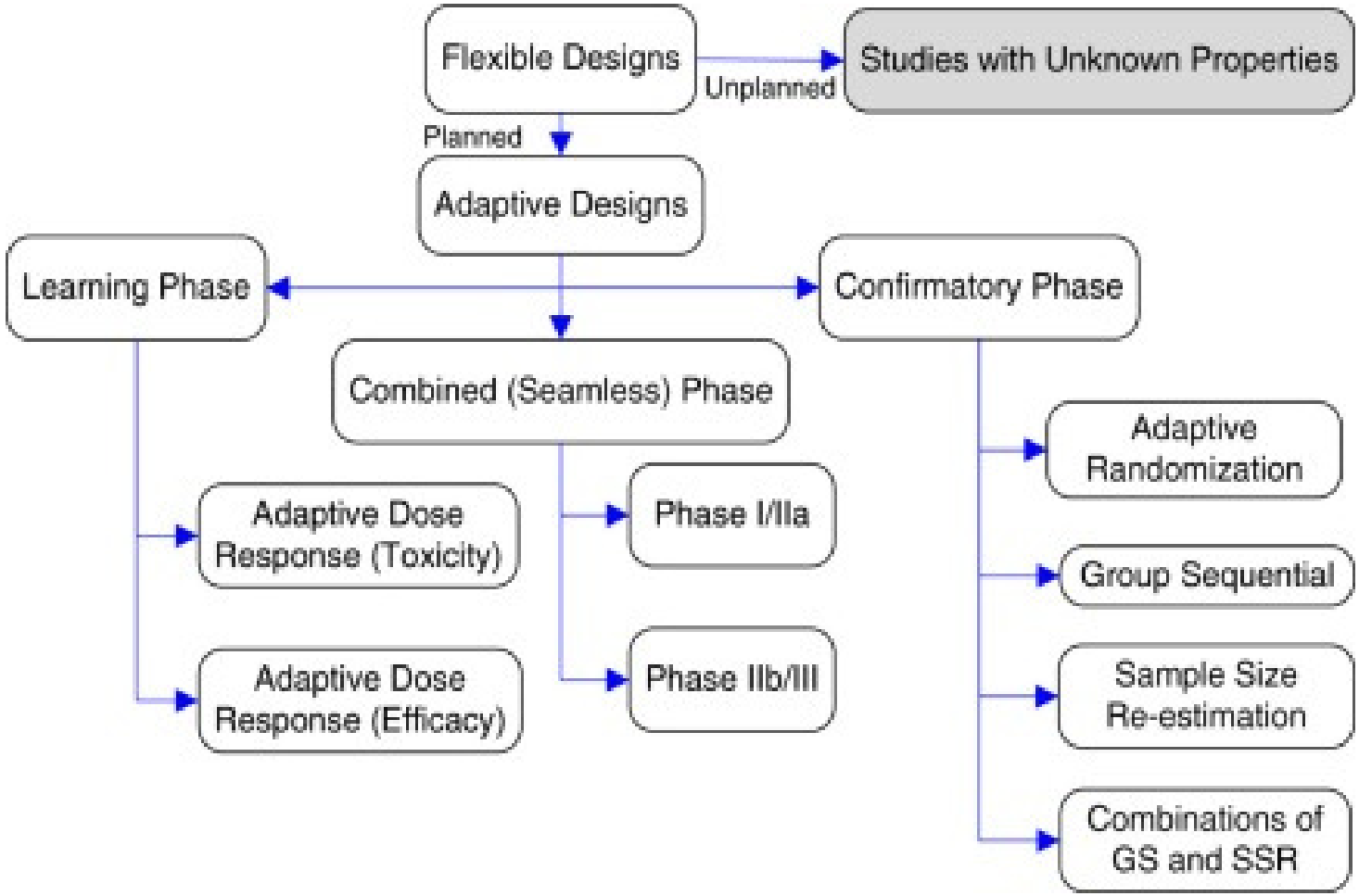
Monitors :

- Adverse event reporting
- participant safety
- Recruitment
- Delivery of the interventions
- Collection of assessments
- Completeness and timeliness of transfer of data to the coordinating center

C-Performance criteria to be determined:

- Provide the principal investigators, study sponsor and Data and Safety Monitoring Board with feedback on conduct of the trial
- Site performance criteria to be evaluated periodically

Protocol design. How to evaluate



DSMB-Data Safety Monitoring Board

- A DSMB(Data Safety Monitoring Board/Committee)typically examines the following issues when assessing the worth of a multi-center clinical trial:

  - Are the treatment groups comparable at baseline?
  - Are the accrual rates meeting initial projections and is the trial on its scheduled timeline?
  - Are the data of sufficient quality?
  - Are the treatment groups different with respect to safety and toxicity data?
  - Are the treatment groups different with respect to efficacy data?
  - Should the trial continue?
  - Should the protocol be modified?
  - Are other descriptive statistics, graphs, or analyses needed for the DSMB to make its decisions?

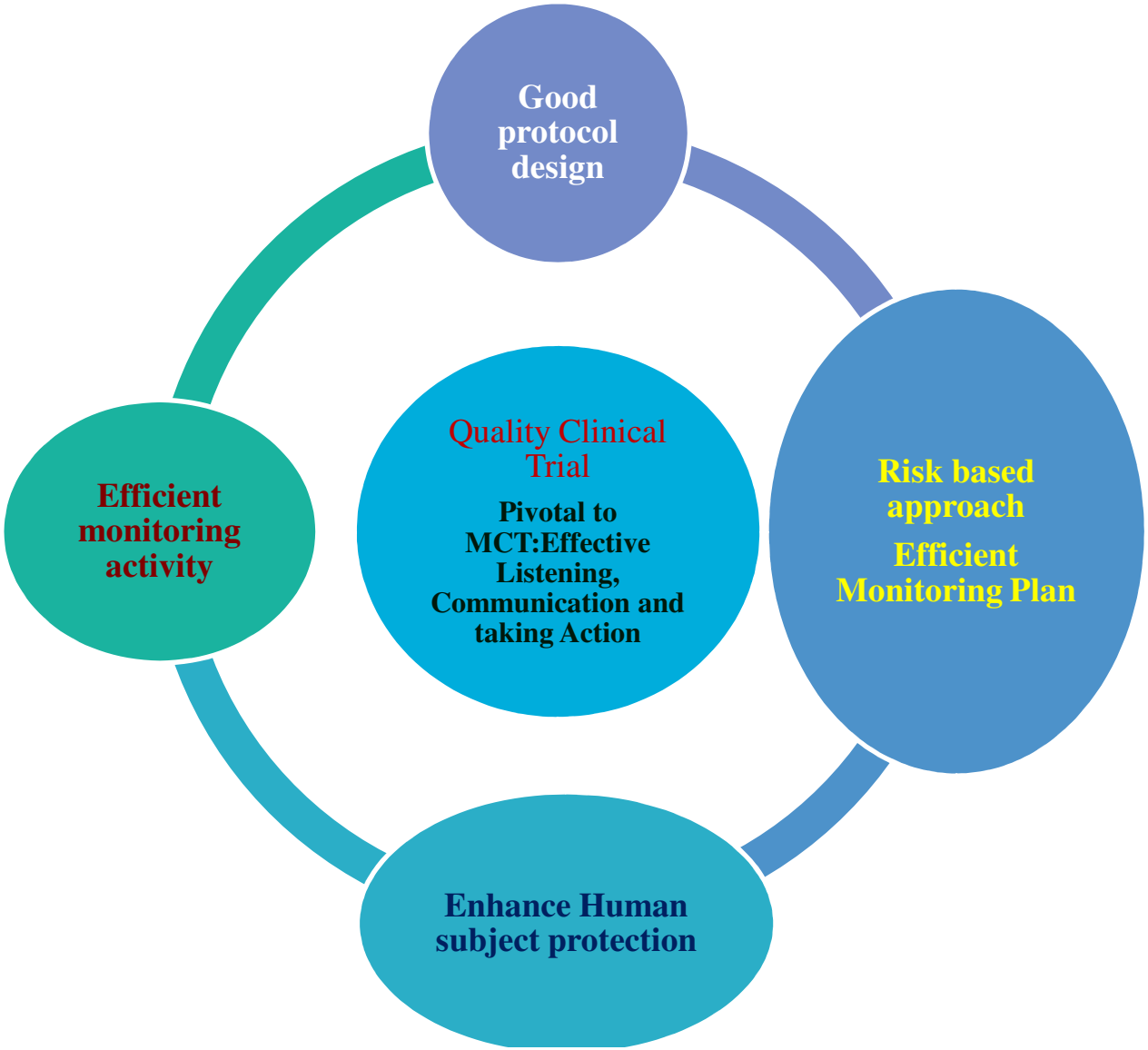
Handling of Unexpected Events or Unanticipated Problems

- A **plan** to manage issues from participating sites should also be developed in **advance**

- For example, the plan should address how the following will be handled:
  - concerns of **non-compliance**
  - unanticipated problems involving **risks to subjects or others**
  - interim results requiring **changes to the research study or early study termination**
  - **site termination** due to non-compliance or violation of contract/protocol
  - receipt and evaluation of **deviations and protocol exceptions**

(Ref:Sponsors may also appoint other individuals and groups to ensure compliance and proper clinical trial monitoring as well as evaluate the accumulating outcome data. The FDA guidance, The Establishment and Operation of Clinical Trial Data Monitoring Committees for Clinical Trial Sponsors, defines a Data Monitoring Committee (DMC), also known as Data Safety Monitoring Boards (DSMBs) or Data and Safety Monitoring Committees (DSMCs), as a group of individuals with pertinent expertise that reviews, on a regular basis, data from one or more ongoing clinical trials)

MCT and Monitoring



Goal of Monitoring

- **Human subject protection** and clinical trial **data quality**
- Focuses on **clinical investigators**' conduct oversight, and reporting of an investigator
- Sponsors/Investigator(Investigator initiated trials) - variety of approaches to fulfill **monitoring responsibilities**

  "No single approach to monitoring is appropriate or necessary for every clinical trial"
- Find the best way to monitor MCT

GCP inspections requested by EMA 2000-2012 Monitoring findings

Finding type	Critical	Major	Total
Monitor did not report/act on problems	8	20	28
Deficient SDV	9	15	24
Insufficient Monitoring	5	34	39
No action by sponsor	7	10	17
Failure to visit lab or other technical facility	2	7	9
Failure to visit sub-investigator sites	3	4	7
Late to start, big gaps, not to plan	11	32	43
IMP related issues	0	17	17

Monitoring in MCT-Present Scenario

- **On-Site Monitoring**-In person evaluation carried out by Sponsor/CRO personnel or representatives at the site

- **Centralized Monitoring**-Remote evaluation carried out by sponsor personnel or representatives at a location other than the site.

- Standard checks of range, consistency, completeness of data
- To identify unusual distribution of data
- To identify higher risk sites to target on-site monitoring
- Routine review of data in real time
- Any safety issues for immediate action
- Prevention is the goal

Best Strategy-Combination of both

Centralised monitoring

- Regulatory bodies **encourages greater reliance on centralised monitoring**
- **L**ess emphasis on on-site monitoring
- Utilise/create technology (new innovative soft ware for Monitoring and safety monitoring)
- With the proper system, centralised-**risk-based monitoring is an effective way** to meet the growing challenge of ensuring that the study protocol is being correctly interpreted and executed

Results :

- **Proper patient care**
- **Valid study results**
- **Reduced clinical trial costs**.

Effective monitoring

Monitoring Plan :

- Study specific-LOOK INTO:Subject protection ,Data integrity risks of the trial
- Focuses on critical study parameters
- Encourages use of a combination of monitoring activities
- Encourages greater reliance on centralized monitoring practices, where appropriate tools are used for risk assessment/safety assessment



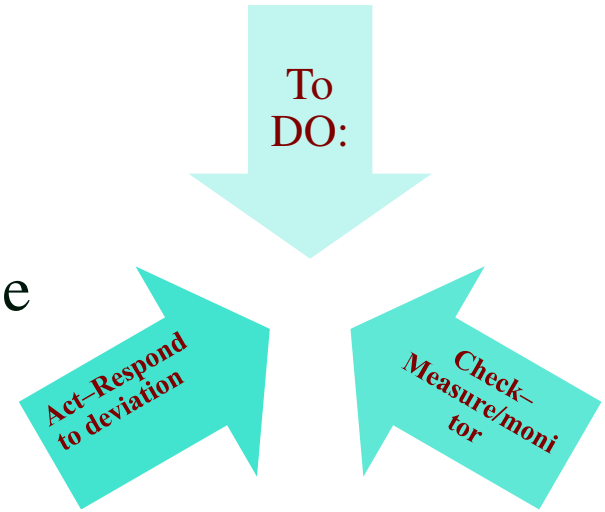
"Half the diabetics were given the new drug and responded well. The other half got a placebo and went into shock."

Describes:

- Monitoring methods
- Responsibilities
- Requirements

Focus on critical data and processes like:

- Complexity of study design
- Types of endpoints
- Clinical complexity of subjects
- Experience on the molecule/Disease
- Relative safety of product
- Quantity of data
- Stage of study
- Safety issues



Risk Assessment

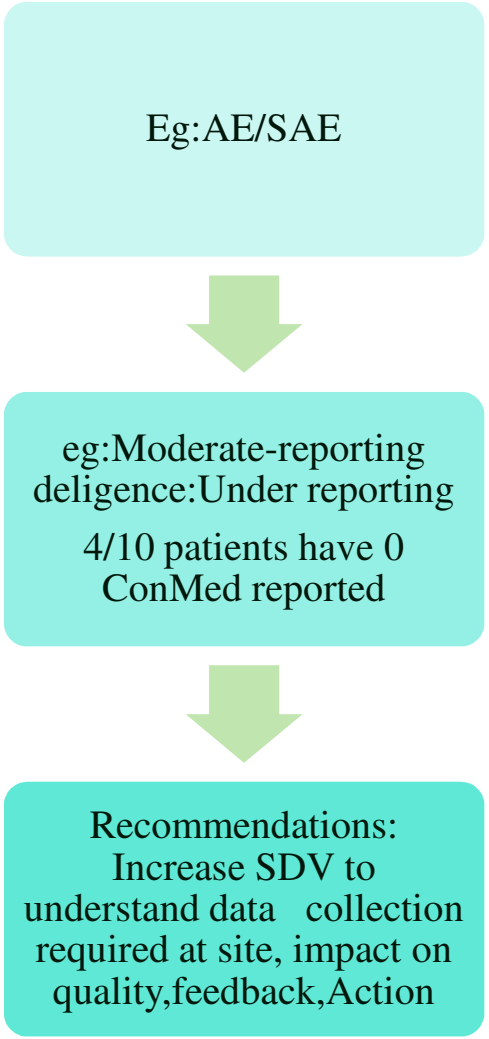
Perform and document a risk assessment process to identify risks through out the study, mainly on the critical data.

Consider following questions:

- What could go wrong?
- What would be the impact?
- Could we detect it?

Consider the following critical data:

- Endpoints
- Serious Adverse Events/AE
- Randomization/ Blinding
- Consent
- Eligibility Criteria



Experience :Centralised Monitoring and Centralised Safety monitoring

- Combination of *automation, analytical and visualisation tool, using human intelligence, and an established processes for corrective actions which has proven to be very effective and efficient at uncovering major sources of risk* that could and would, jeopardise the integrity of the data, and hence of the trial itself

- These include:

• Fraud and fabrication of data.

• Unreported or inaccurately reported data.

• Protocol deviations, ranging from mild to severe, that can be related to poor training, questionable competency, or a simple misunderstanding of the protocol

- **Supports** on site monitoring activities by CRA
- Enrich the **inference** on quality &compliance provided by the centralized analysis
  - **Verify & "Validate"**

  If the inference is wrong initiate **CAPA**s
  - **Audits** serve the purpose of an additional **test** for **robustness of the process**

- Centralised monitoring tools if planned and integrated properly is a very good **Safety monitoring tool for** Medical Monitors

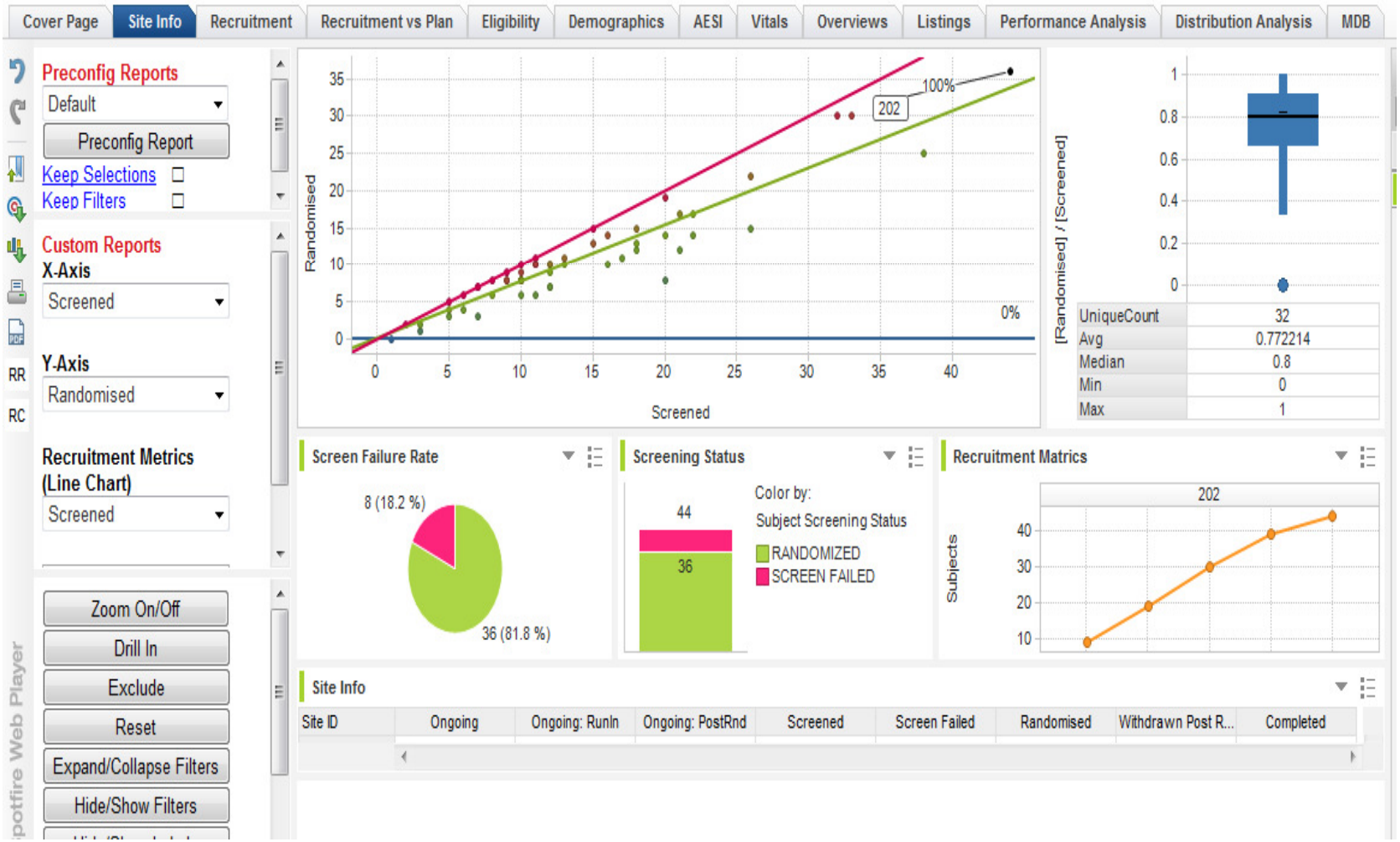
My Experience with centralised Monitoring tool : ICONS-ICONIK

- **An information platform that delivers clinical studies better, faster, safer and more cost effectively**

- ICONIK is a powerful integrated information platform that **consolidates, standardises and visualises operational and clinical data from multiple sources, to provide a single holistic view** of all study information, from study start-up to database lock.

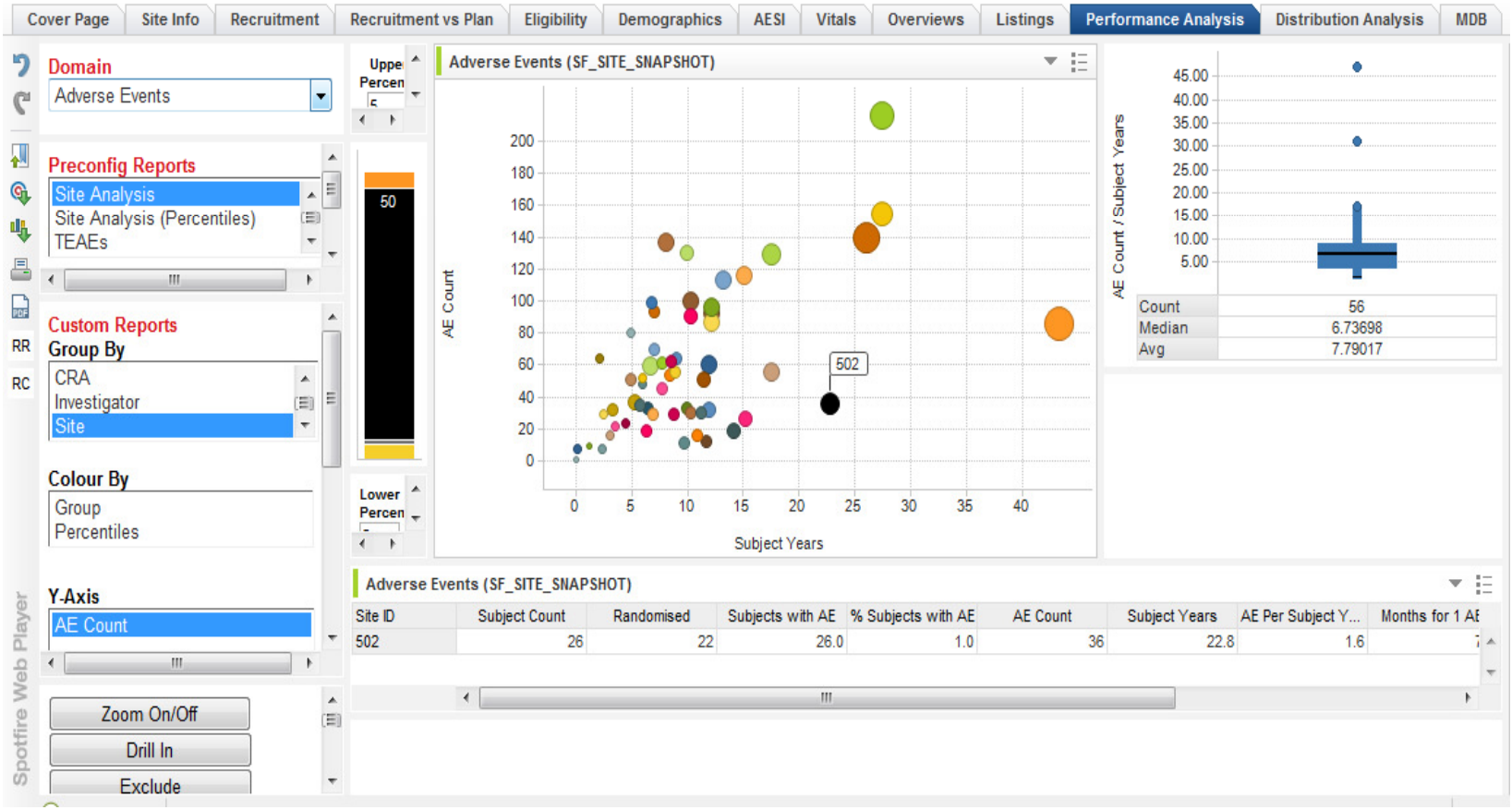
Site Info

Question answered: What is the current site status in terms of Screen failure rates, Screening status, recruitment etc…

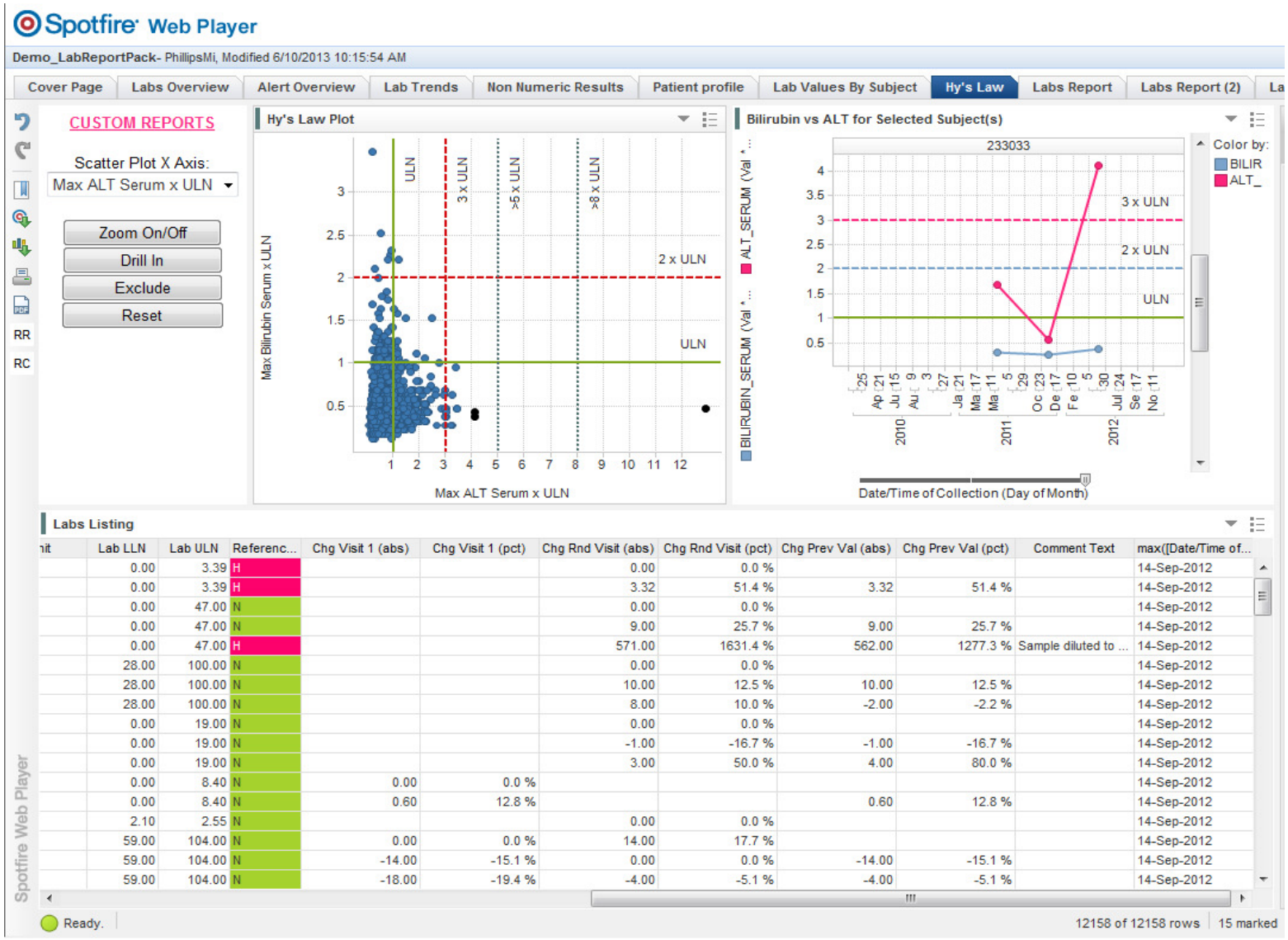


Performance Analysis

Where are the outliers from a quality perspective?
(Risk triggers, Dynamic percentile thresholds)
Underpinning Patient Centric Monitoring



Hy's law (DILI detection)



Summary: Take home

Prioritise:

- Protocol Design
- Monitoring Plans
- Monitoring tools
- **Centralised monitoring with risk assessment plans**

Anticipate

- Assess risks, accept or mitigate
- Revise design
- Implement
- Plan to handle unexpected events

Advisory/Safety monitoring bodies

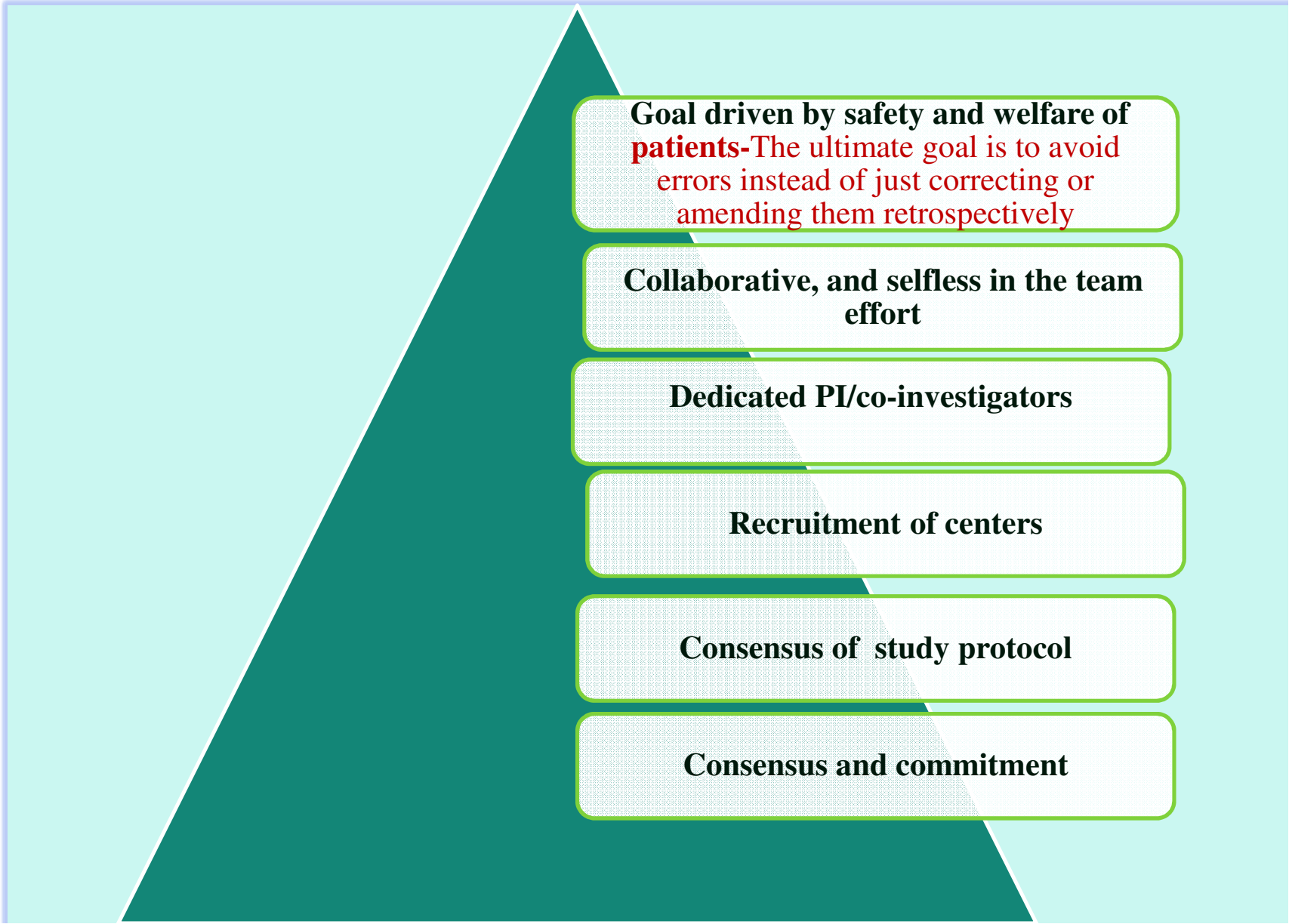
- DSMB

Train, Do, Check, Review, Adjust

Don't just think of Corrective Action
Implement with Preventive Action



Multicenter clinical trial



References: with thanks

Reflection Paper on Risk-Based Quality Management in Clinical Trials," European Medicines

Agency, Aug. 2011, EMA/INS/GCP/394194/2011.4

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, European Medicines Agency

Coordinating and monitoring multisite clinical trials that combine pharmacological and behavioral treatments.
Youngblood ME[1], Murray KT, Devine E, Latham PK, Hubatch S

Risk-Adapted Approaches to the Management of Clinical Trials of Investigational Medicinal

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Agency, Aug. 2011, EMA/INS/GCP/394194/2011.

"Guidance on Risk-Proportionate Approaches to the Management and Monitoring of Clinical Trials,"

Medicines and Healthcare Products Regulatory Agency, Oct. 6, 2011.Guidance for Industry Oversight of Clinical Investigations: A Risk Based Approach to Monitoring

- And many other references in PubMed/Medscape/Clinical trial journals
- Time to Change the Clinical Trial Monitoring Paradigm Results from a Multicenter Clinical Trial Using a Quality by Design Methodology, Risk-Based Monitoring and Real-Time Direct Data Entry
- Publish date: Jan 17, 2014
  By: Jules T. Mitchel, Timothy Cho, Dean A. Gittleman, Judith M. Schloss Markowitz, Yong Joong Kim, Joonhyuk Choi, Michael R. Hamrell, Dario Carrara, Sergio Dalla Nora

Reference :Monitoring

- In order to support the transformation of how the pharmaceutical industry manages the performance of clinical trials, in 2013, the **Food and Drug Administration (FDA) i**ssued its Final Guidance for Industry: Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring, and a Guidance for Industry: Electronic Source Data in Clinical Investigations.

- These guidance's are consistent with the **European Medicines Agency (EMA)** Reflection Paper on Risk Based Quality Management in Clinical Trials [3] and Expectations for Electronic Source Data and Data Transcribed to Electronic Data Collection Tools in Clinical Trials

- A **Risk-Based Approach to Monitoring** :U.S. Department of Health and Human Services Food and Drug Administration :August 2013 Procedural .

The FDA advises that any remote **monitoring plan(Centralised) should clearly define monitoring methods, responsibilities, and requirements for the trial**.

- **The guidance provides direction for addressing the main components of a monitoring plan, which include**:

(1) the description of monitoring approaches

(2) communication of monitoring results

(3) management of noncompliance

(4) ensuring quality monitoring

(5) monitoring plan amendment

The FDA believes that targeted risk-based approaches that **focus on the most critical data elements will result in more effective monitoring** and help to overcome many of the limitations of on-site monitoring

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Thank you

