Protocol deviations

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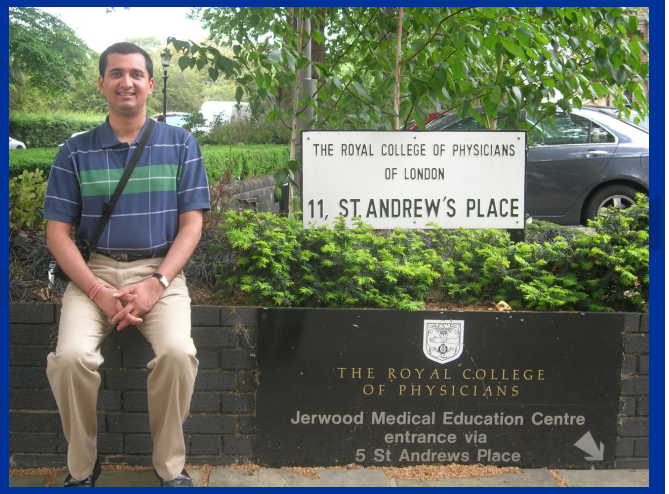


All opinions expressed in the presentation are entirely that of the presenter and not necessarily that of Sanofi

Opinions are based on evidence as well as experience

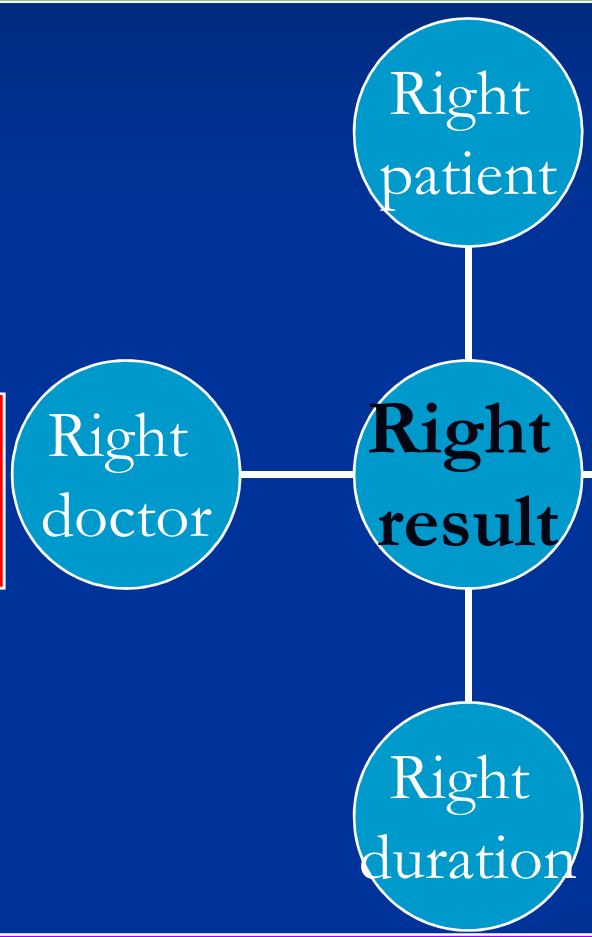
Flow of the discussion

- What is protocol deviation
- Significance of protocol deviations
- Role of stakeholders
- Managing protocol deviations

Converting data into evidence

Is he the true representative of the patient population?

Are all risk management plans in place?



Is the physician well qualified to conduct this research?

Is it the right dose given the physical characteristics of the patient ?

Is it given at right frequency and for right duration ?

Does it contribute to answer the research question

What is a protocol deviation?

Generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change

Who commits protocol deviations?

Sponsor	Lack of clinical understanding of the disease under study and the challenges
Investigator	Wrong selection of patient Not comfortable assessing few parameters
Patients	Missing doses Non-adherence to schedule of visits Non-compliance to protocol restrictions

Significance of protocol deviations

- Increases risk to patients
- Increased reporting of adverse events
- Bias in study results
- Discrepancy in study objectives and conclusion
- Negative impact on site quality and team reputation

Common protocol deviations

Patient is incorrectly included in the trial (does not meet inclusion criteria)
Patient receives wrong dose
Patient takes a forbidden comedication
Patient takes fewer or extra dose(s) of treatment than prescribed
Patient takes all doses but does not take them on time
Patient stops taking the treatment but remains on the study
Patient or clinical team does not comply with measurement times
Patient or clinical team misses some measurements but completes the study
Measurements are incorrect/missing
Measurement times are incorrect
Patient failing to comply with study requirements
Patient drops out before the end of the study

Impact on quality and speed of recruitment

L Sch Trop Med, 2008

Role of stakeholders

Sponsor

- Developing a pragmatic clinical study
- Identifying right sites with right skills
- Effective monitoring with identification of problems and trends
- Robust training program

Investigator

- Vigilant during patient screening and identification
- Training of support team members with focus on skills
- Proactive in identifying causes of deviations
- Remedial actions with clear plans

Ethics committee

- Review serious protocol deviations
- Identify trends and possible causes of the deviations
- Ensure adequate risk management plans in place
- Audit the site and possible review of approval if required

What does the law state?

- Sponsor: Include number and list of deviations in the final study report

  How will deviations be managed
- Investigator: Undertaking mentions responsibility of not conducting any deviation
- EC: Approval and review required for deviations if any

Schedule Y. www.cdsco.co.in

What do the guidelines state?

- Sponsor: Report all deviations to EC
  Clarify deviations, assess training need
  Include in monitoring report
- Investigator: Report to EC with details
- EC: Review and take required actions

Indian GCP guidelines. www.cdsco.co.in

What should the EC review?

- Is there a protocol deviation form mentioning all aspects of the deviation?
- What is the deviation and does it impart high risk to patients?
- Is it associated with an adverse event and safety issues?
- Is there a trend and possible identifiable cause?
- What action does it require?
- How to prevent such an episode in the future?

Summarizing possible approaches

Training	Right identification of team members Ongoing training of site members Ethics Committees to assess trends and responsibilities Patients and relatives to adhere to protocol
Managerial	Need for protocol amendments Ensure right flow of patients and systems to identify and manage risk Risk assessment of patients and risk management plan
Regulatory	Punitive actions if required Temporary halting of study

Case study

- 4 out of 8 patients recruited in a RA study had Hb less than 10 g. Investigator feels it is routine to find such levels and this is not low per Indian standards. No patient has developed any SAE. Is it a deviation?

- Monitoring of a study in psychiatry revealed that several patients did not FU till the end and discontinued medication. Co-ordinator reported that they were all fine and exposing them to further medications was unethical. How will you manage this?

Case study

- In a study of antihypertensive drug, BP is being taken by a nurse. All measurements are accurate but the protocol demands that it be taken only the treating physician. Is it a deviation?

- In a glaucoma study, 30% patients did not report for a day 3 visit. They complained of blurring vision, an analysis found that 90% of these were over 60 years. What will you do?

Key take home messages….

- Protocol deviations occur commonly
- Reflect on site and study quality
- EC has specific responsibilities on prevention and management of deviations
- Patient safety and quality of clinical trial data most significant