Good Clinical Practice & Effective Site Management

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Agenda

- Introduction
- Learning Objectives
- Defining the major steps and phases of the drug development process
- Evolution of Good Clinical Practice Guidelines (GCP)
  - History of GCP and current standards
  - Stakeholders in GCP
  - Understanding GCP and the Clinical Trial Process

Agenda

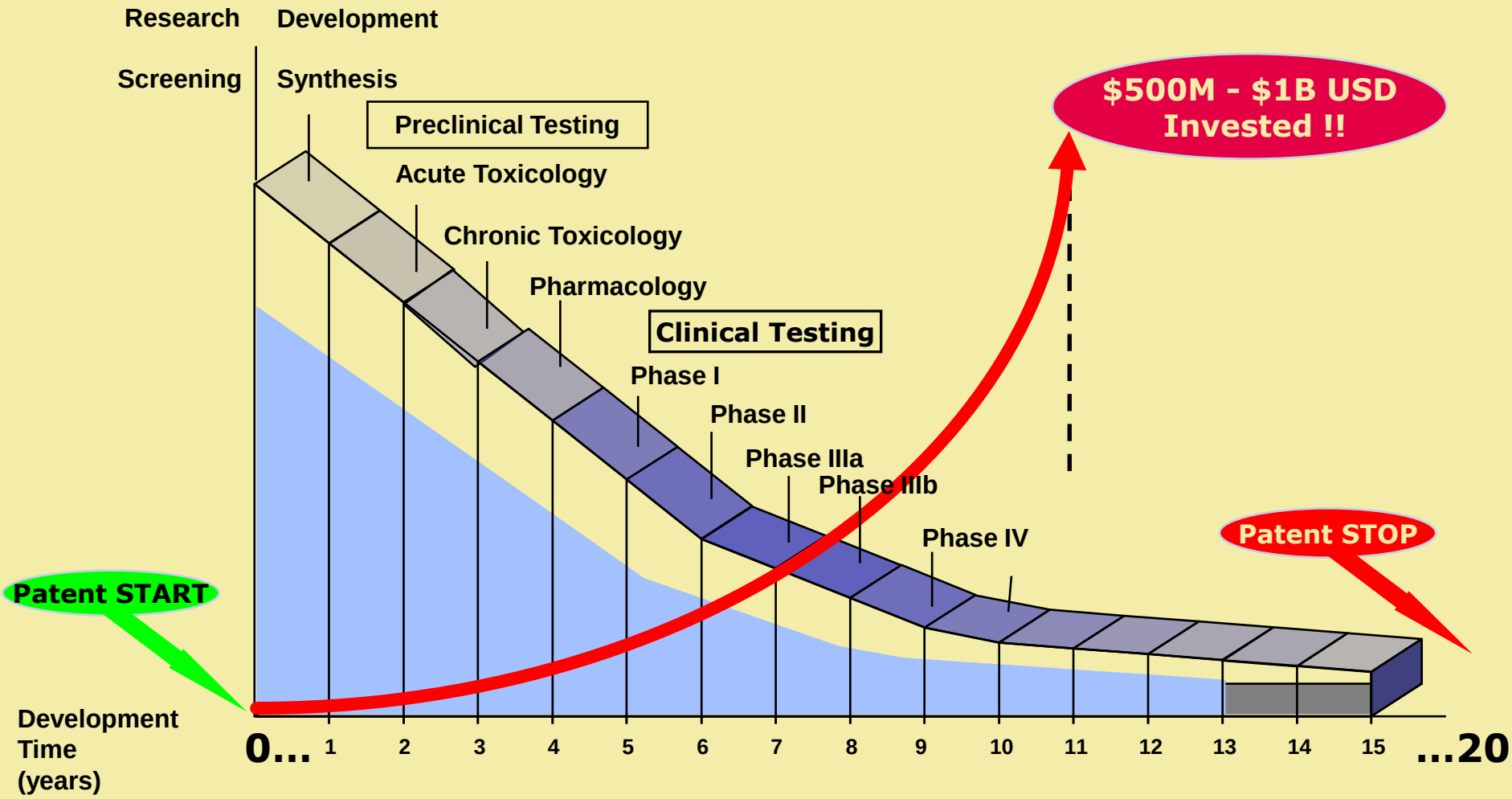
- The Clinical Trial Process
  - Roles involved in the Clinical Trial Process
  - Ensuring adequate source documentation
  - Informed consent process; including a role-play and interactive discussion
  - Succeeding with IRBs
  - ‘How-to’ guide to adequate source documentation
- Identification of current regulatory and ethical issues in clinical research
  - Current regulatory and ethical issues in clinical research
  - Applications of the regulations to practice

Learning Objectives

- Review the overall drug development process
- Review of Good Clinical Practice Guidelines
- Understand the overall impact of GCP on the clinical trial process including the respective roles and responsibilities of the Investigator and the Sponsor
- Understand the impact of GCP on overall study quality (e.g., source documentation, informed consent, IRB, etc.)

Drug Development Process

Drugs Development Overview



Developing New Drugs

- Potential “blockbuster”

  e.g. first effective therapy for a common and/or chronic disease and/or life-saving treatment

- Market size is LARGE
  - Broad patient population
  - Multiple therapeutic indications
    - Several products across several companies
    - Similar products on the market or in development
- Drug poor fit in manufacturer product portfolio
  - License or sell to another company sponsor

Pre-Clinical Drug Discovery

- Screening (Medicinal Chemistry)
  - Pharmacological and biological screening models
  - Computer modeling
  - Serendipity (Luck counts or “Do you feel lucky?”)
- Synthesize
  - Compounds that fit the biological target (e.g., receptor)
    - ~ 1 out of 100,000 may reach market
- Screening
  - Assess likelihood of safety and efficacy in humans using *in vitro* and *in vivo* testing

Pre-clinical Objectives

- Safety of drug
- Effective dose range
  - Organ(s) or organ system affected
  - Drug absorbed, distributed, metabolized and excreted (‘ADME’)
- Cx – drug assessed as a potential carcinogen
- Drug assessed for potential for producing:
  - birth defects
  - affects on fertility

Development
Benefit – Risk Assessment

If…

- Drug has what appears to be acceptable levels of safety and effectiveness in appropriate models

And…

- Potential market(s) exists for the drug

Then…

- Further development balances business and scientific merits

Development Plan

- Indication(s)
- Preclinical testing
  - Genotoxicity, mutagenicity, reproduction studies,
  - Sub-chronic, chronic
- Clinical studies
- Marketing research data / Sales projection
- Manufacturing issues
  - Scale-up, cost of goods
- Regulatory issues

IND / CTA

Investigational New Drug Application (IND; USA)
Clinical Trial Application (CTA; EU, Canada)

- Filed with regulatory authorities by the Sponsor
  - Intends to conduct clinical studies using the investigational drug
  - Investigational drug refers to a new drug or biological used in a clinical investigation OR a marketed drug that is not licensed for usage in the proposed indication
- Approval/no objection of the CTA or IND allows the investigational drug to be sent to sites for clinical investigations

Drug Development – Regulatory

- Regulatory authorities' goal worldwide
  - Safe and effective drug availability to the public
- Regulatory considerations
  - Global: worldwide standardized procedures and practices for drug development for all sites
  - Local: drug tested and responsibly marketed using local and international regulations and guidelines

Standard Operating Procedures (SOPs)

Sponsors of Investigational New Drugs

- Write standard operating procedures (SOPs)
- Ensure study activities follow regulatory requirements
- Ensure study activities follow GCP

Clinical Development Plan (CDP)

- Comprehensive plan
- Map out the development of the compound
- All development phases required for registration file preparation are included

International Regulatory

Major Regulatory Drivers

- US Food and Drug Administration
- ICH: International Conference on Harmonization
- Country-specific regulations

  (e.g. EMEA (EU), TPD (Canada)

Phases of Clinical Research

Phases of Clinical Research

		I	II	III	IV
	PRECLINICAL	CLINICAL			
		Pre-marketing			Post-marketing

PHASES OF DRUG DEVELOPMENT					
Average Time/Study	A few weeks – 2 years	0.25 - 1 month	A few months – 2 years	A few months – 4 years	A few months – several years
Number of Subjects		20 - 100	A few hundred	A few hundred – Several thousand	About 50 - Several thousand
Subject	Animals or Laboratory Models	Healthy Volunteers or Patients	Patients	Patients	Patients
Primary Purpose	Predict toxicity (humans)	Determine safe dose(s) (humans)	Determine dose(s) with acceptable level of efficacy and safety	Determine safety & efficacy in large subpopulation(s) during usage over longer periods of time Approval of a new indication	- Condition for approval - Test under real life situations in clinical practice

Clinical Development – Phase I

Objective

- Start to determine the drug compound's:
- Clinical Pharmacology of the Drug Compound:
  - Pharmacokinetics (Pk) i.e. what the body does to a drug
  - Pharmacodynamics (Pd) i.e. what a drug does to a body
    - Mechanism of action (MoA)
    - e.g. Drug interactions
    - How other drugs affect new compound
    - How new drug compound affect available marketed drugs
- Assess tolerability, side-effects with escalating doses
- Preliminary data to possibly predict efficacy

Clinical Development – Phase I

Need to Answer the Following

- Safe and effective doses
- Time for drug…

  Absorption

  Distribution

  Metabolism

  Elimination

- Organ or systems involvement in **ADME**

Clinical Development – Phase II

Need to Answer the Following

- Phase I dose(s) help predict efficacy and safety
- Efficacy
  - Expected indication(s) or uses

    i.e. under what exact clinical circumstances or disease diagnoses, etc. is the drug compound being proposed for use in patients?
  - Predicted minimum/maximum dose(s)
  - Same dose in mild, moderate and severe cases?
- Safety profile
  - Assess Phase II patient safety in proposed indications; use Phase I subject data to predict

Clinical Development – Phase III

Multiple protocol, multi-center studies

- Placebo control or active control
- Possible uncontrolled studies,
  e.g.Extension studies (chronic dosing, safety)
- Special populations
  e.g.Elderly, pediatrics
- New indication(s) for approved drugs

Clinical Development – Phase III

Need to Answer the Following

- Dose – as effective or more effective than ‘gold standard’ currently on the market
- Drug effective in broader usage, e.g.,
  - Elderly, combination therapy, etc.
- Drug effective for chronic usage without occurrence of drug tolerance
- Drug interaction risk assessment for concomitant medications?

Clinical Development – Phase IV

Objective

- Compare ‘effectiveness’ instead of efficacy
  - Assess in a larger population (500 to 10,000+)
  - Provide additional data to receive final approval (or new formulation/condition)
  - Continue assessment of drug in real-life setting post-marketing
  - Supportive data
    - Cost-effectiveness, QoL, comparison to other active agents (‘gold standards’)

Good Clinical Practice

International Conference of Harmonization (ICH)

Purpose of Harmonization

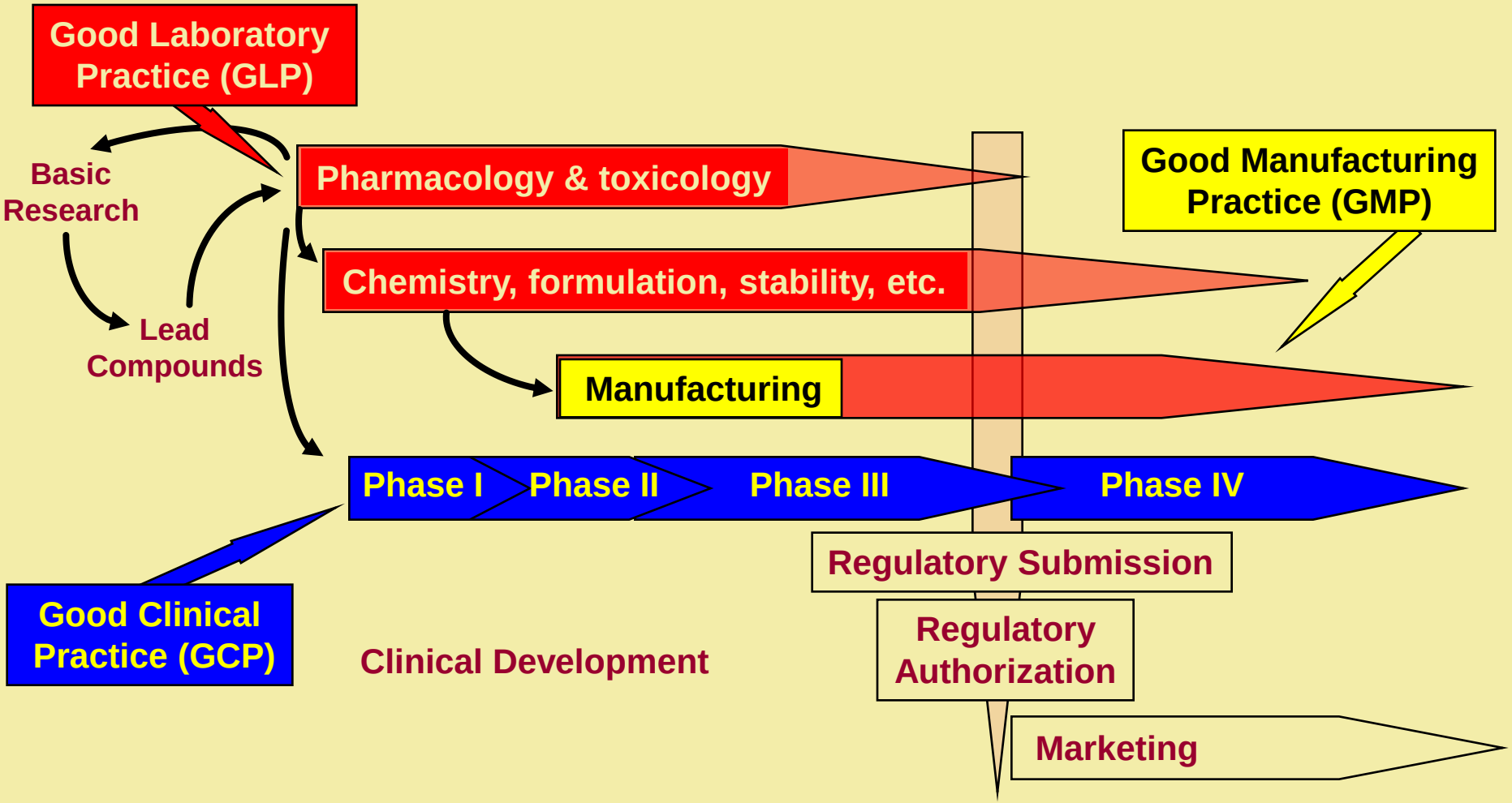
- Reduce the costs of the drug approval process
- Expedite the availability of new drugs to consumers
- Harmonization effort between USA, Japan & Europe

Declaration of Helsinki

- World Medical Association statement of ethical principles in medical research with human subjects
- Major driver towards development of GCP guidelines
- Response to the war crimes of World War II

  Experiments without patient consent are unethical
- All proposed studies must be evaluated by independent Ethics Committee

Drug Development



Good Clinical Practice

What are GCP Guidelines?

- International systematic approach
- Ensuring the scientific quality and ethical standard
  - Designing, conducting, recording and reporting of studies involving human subjects

GCP Principles

- **Compliance with the GCP Guidelines standards**
  - Study subject rights are protected
  - Data/reported results are credible, accurate

GCP Responsibilities

	GCP Quality Compliance	Data Accuracy & Integrity	Protection of Subjects' Rights
Ethics Committee (EC) / Institutional Review Board (IRB)	✓		✓
Investigator	✓	✓	✓
Monitor	✓	✓	✓
Sponsor	✓	✓	✓

Investigator Responsibilities

- Patient informed consent
- Site approvals
- Drug administration and accountability
- Relevant data
- AE reporting

Approvals & Documentation

Pre-study Approvals

- Internal approvals (Sponsor)
- Institutional Review Board/Ethics Committee approval
- Notification to and approval by FDA

Company Approvals

- Protocol
- CRF
- Study medication : packaging, labeling
- Budget / Contracts
- Others

  Choice of CRO / CLO

Ethics Committee / IRB Approval

Favorable opinion/approval required from the appropriate EC / IRB

- Before study medication sent to centres
- Before start of patient recruitment

Source Documents & CRFs

Site Responsibility

- Type of source documentation
  - First time an observation or data point is recorded
- Storage of source documentation or study documentation
  - Access & confidentiality
  - Direct access limited to study personnel
  - Record retention policy & conditions
  - Long-term records retention crucial after study completion
- Who is responsible for CRF completion?
  - Usually completed by the Study Coordinator
  - CRF data is either handwritten or in electronic form

Informed Consent (IC) Process

Investigator should

- Obtain IRB/EC written approval
- Adhere to GCP
- IC revised as new important information is made available
- IC vs. Coercion
  - Neither Investigator nor staff can unduly influence a subject to participate or continue in a study

Informed Consent (IC) Process

Investigator requirements:

- Submit an informed consent form
  - Content understood by a subject with a grade 6 (or less) education
- Non-technical in nature as much as possible
- Understandable by the subject's legal guardian where the subject cannot understand the IC
- Ensure the IC uses a subject's native language

  e.g. English, French, Spanish, Mandarin, etc.
- Comply with regulatory requirements

Informed Consent (IC) Process

Investigator requirements:

- IC language must not try to waive any legal rights
- IC wording cannot prejudice any future treatment if the subject does not agree to participate or withdraws consent

Informed Consent (IC) Process

- **ALL Subjects (or Legal Guardian) must sign and date the IC form**
- **IF Subject or legal guardian cannot read:**
  - Impartial witness present for entire consent discussions
  - IC form signed and dated by subject; same for the witness
- **Additional signatures may be required (Sponsor, IRB or local law)**

E.g. specific investigator or person conducting informed consent

Informed Consent (IC) Process

In Emergency Situations

(Prior consent not possible)

- Consent of subject's legal representative requested
- If no legal representative
  - Seek IRB/EC favorable opinion and support
  - Inform subject's legal representative as soon as possible

Informed Consent
< Exercise >

- Role-play and interactive discussion at end of presentation
- To follow…

Institutional Review Boards
Ethics Committees

Roles and Responsibilities

- Investigator
  - Report SAE to Ethics Committee
- Company
  - Inform all world-wide investigators of specific SAEs within study duration reported in Company safety report
  - Report AEs to study report or drug brochure

E.g. AEs > 2% frequency in study report

E.g. All AEs reported at the end of the study report

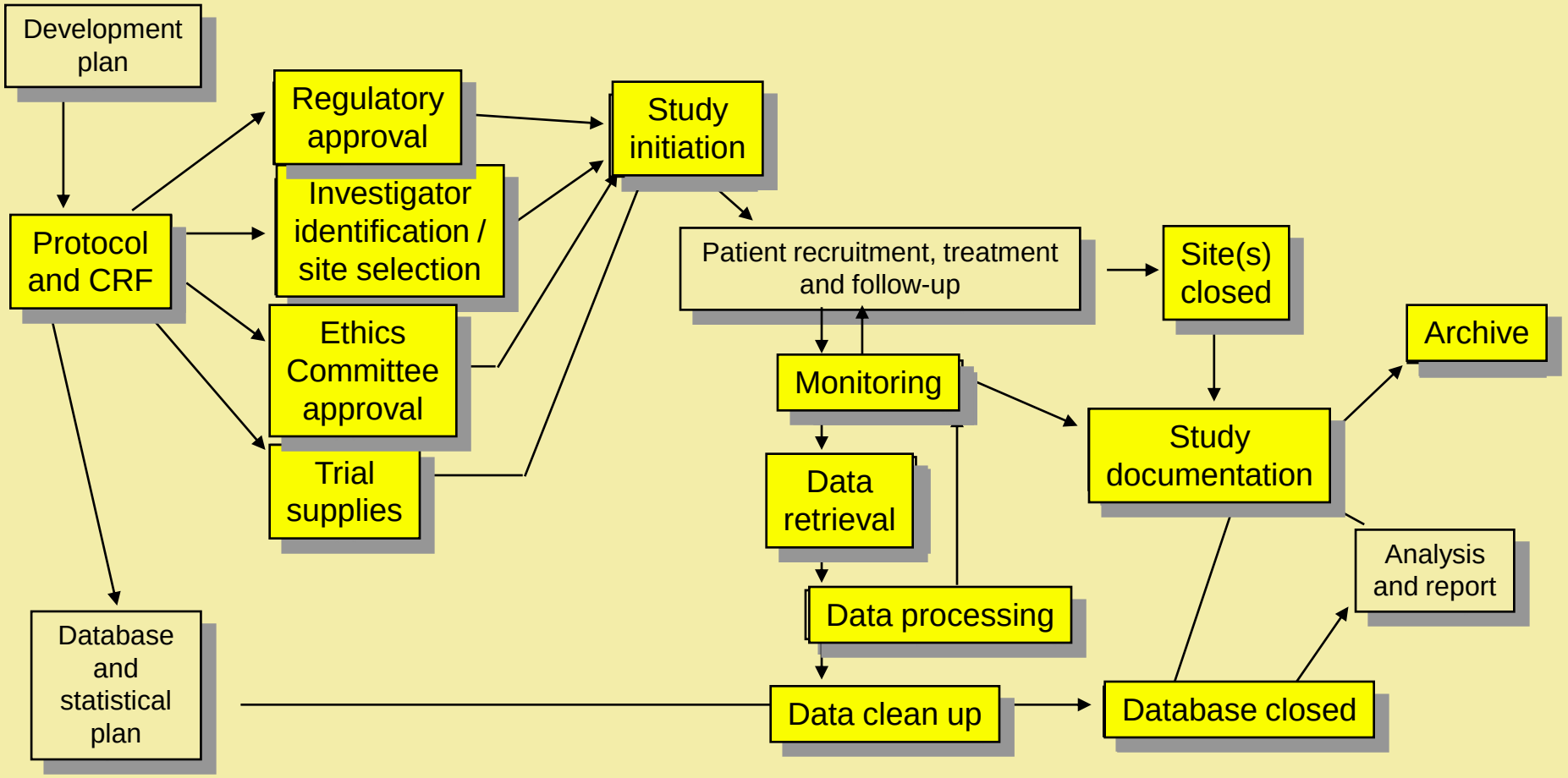
Institutional Review Boards / Ethics Committees

How to Succeed with IRBs

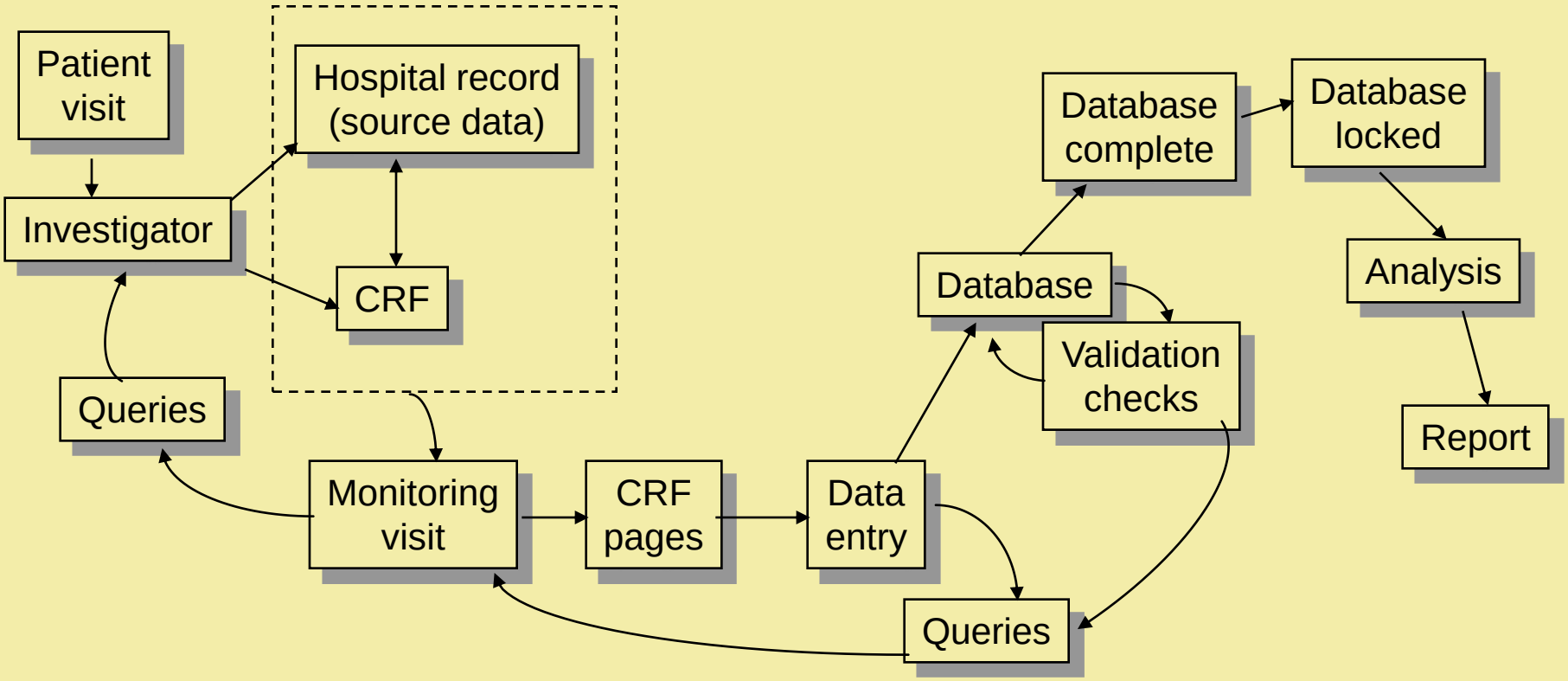
- Investigators – Be prepared!
  - CORRECTLY complete all IRB / EC Forms
    - Can be a major reason for study application rejection!
  - Contact IRB to be added to the agenda
    - Send IRB the correct number of copies of all documentation specified by your IRB
    - IRB will charge for review; IRB expenses included in your site budget?
  - Investigator attendance important during discussions at IRB to answer questions
  - Consult sponsor for questions you cannot answer

Clinical Trial Process

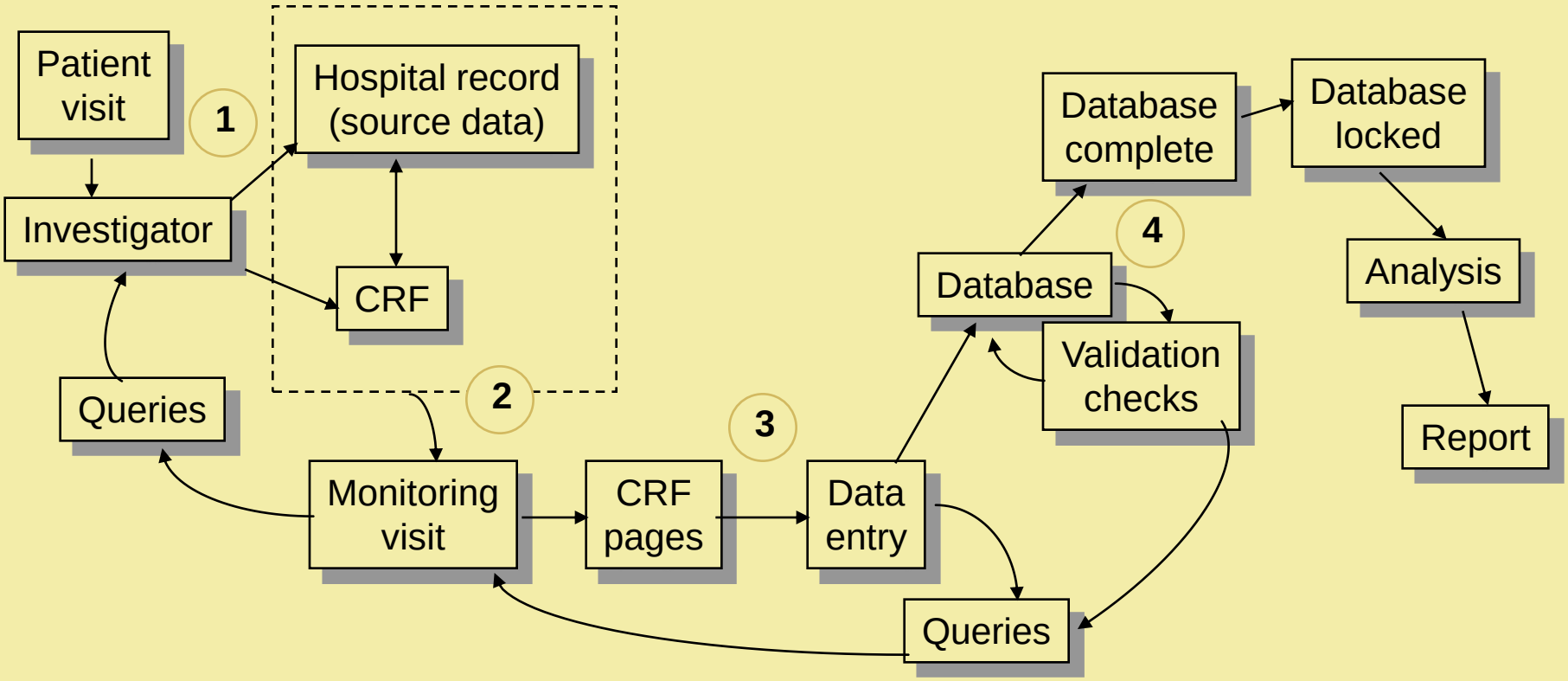
Clinical Trial Process



Traditional Data Flow



Data Quality
No errors

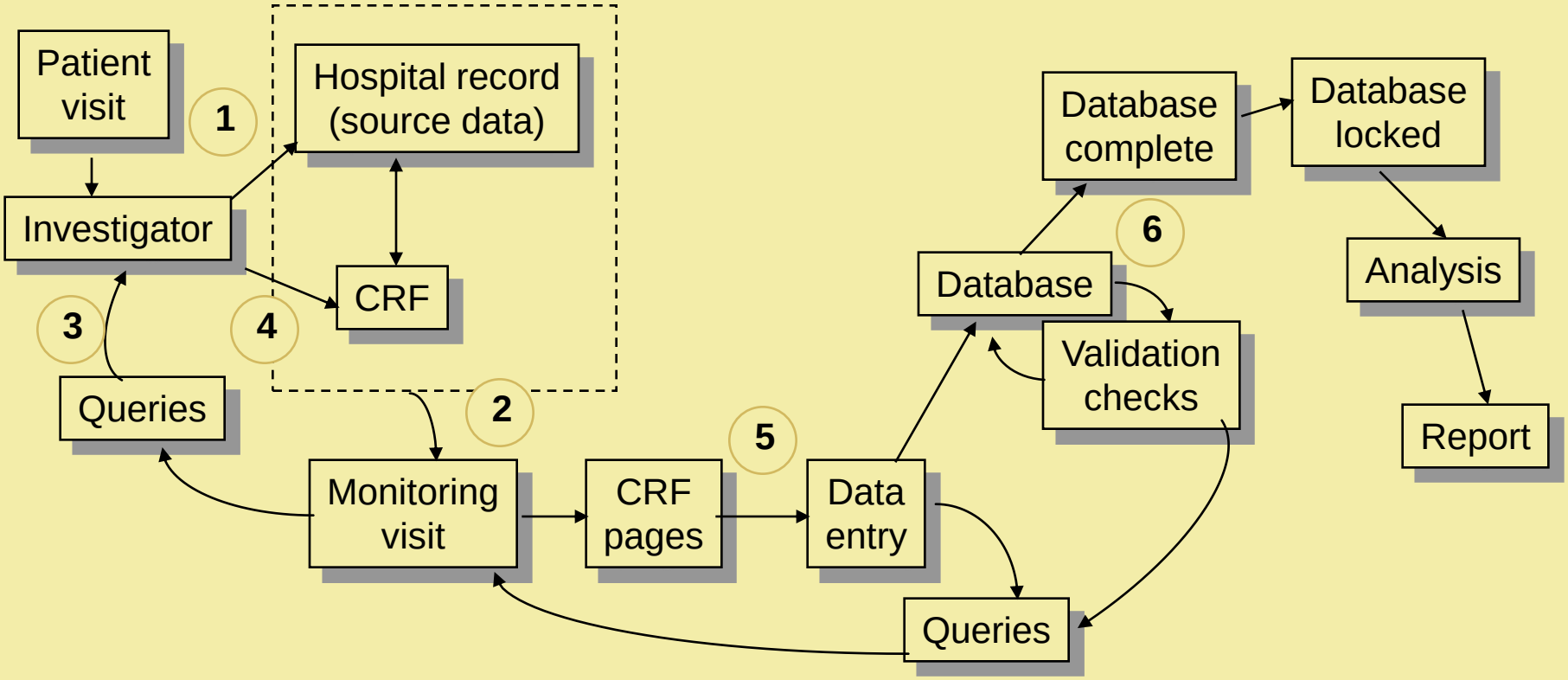


Total number of steps = 4

Data Quality

Impact of errors

Monitoring Visits Only

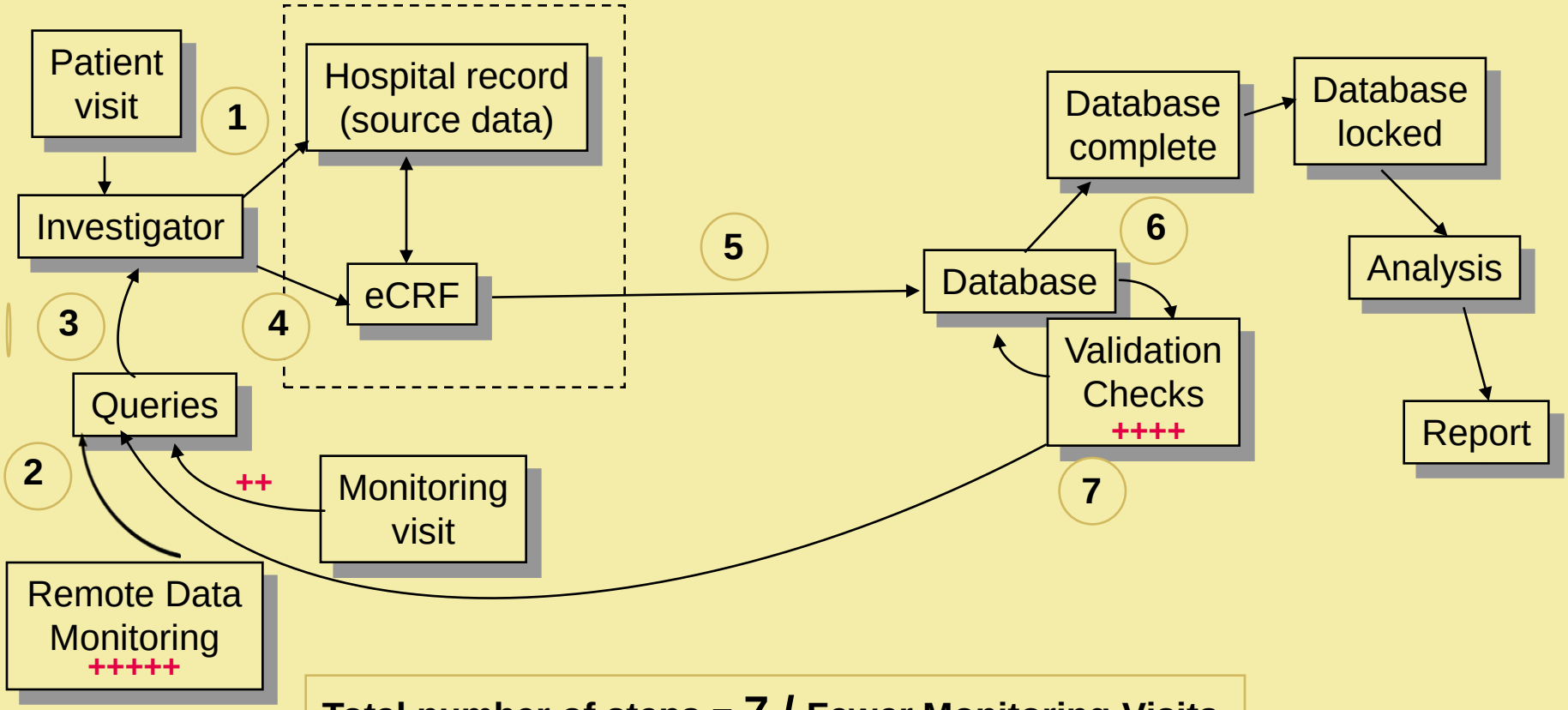


Total number of steps = 6

Data Quality

Impact of errors

RDM and Monitoring Visits



Total number of steps = 7 / Fewer Monitoring Visits

Conclusion

- Drug development aims to provide a framework for generating empirical evidence to support claims made regarding efficacy & safety
- Clinical development entails a dynamic process that is evolving to maximize ethical, scientific, regulatory and technical integrity of the resulting data quality