Quality standards in oncology pharmacy research and practice

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Step 1: Discovery and Development

New drugs are typically **discovered** through	**Development -** Experiments
• New insights into a disease process • stop or reverse the effects of the disease • Tests of molecular compounds to find possible beneficial effects • Existing treatments with unanticipated effects • New technologies - target products to specific sites or to manipulate genetic material	• How it is absorbed, distributed, metabolized, and excreted • Potential benefits and mechanisms of action • Best dosage • Best way to give the drug (such as by mouth or injection) • Side effects or adverse events - toxicity • How it affects different groups of people (such as by gender, race, or ethnicity) differently • Interaction with other drugs and treatments • Effectiveness compared with similar drugs

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Step 2: Preclinical Research

In vitro VS In vivo

FDA requires good laboratory practices (GLP) 21 CRF Part 58.1

- Basic requirements for
  - study conduct
  - personnel
  - facilities
  - equipment
  - written protocols
  - operating procedures
  - study reports
  - assure the safety of FDA-regulated product

Must provide detailed information on dosing and toxicity levels

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Good laboratory practice

- Quality system of management controls for research laboratories and organizations
- Propose
  - ensure uniformity, consistency, reliability, reproducibility, quality, and integrity of products in development
  - for human or animal health (including pharmaceuticals)
  - through non-clinical safety tests
  - from physio-chemical properties through acute to chronic toxicity tests

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GOOD LABORATORY PRACTICES PRINCIPLES.

1. Test Facility Organisation and Personnel.
2. Quality Assurance Programme(QAP).
3. Facilities.
4. Apparatus, Material and Reagents.
5. Test systems.
6. Test and Reference Substances.
7. Standard Operating Procedures(SOP).
8. Performance of The Study.
9. Reporting of Study Results.
10. Storage and Retention of Records and materials.

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Step 3: Clinical Research

Studies or trials done in people

- Investigational New Drug (IND) a process before clinical research begins

Designing Clinical Trials

- Answer specific research questions related to a medical product.
  - Specific study plan - **protocol** (prior information - research questions and objectives)
    - Who qualifies to participate (selection criteria)
    - How many people will be part of the study
    - How long the study will last
    - Control group? and other ways to limit research bias
    - How the drug will be given to patients - dosage
    - Assessments - when and what data will be collected
    - How the data will be reviewed and analyzed
- Phase 1, Phase 2, Phase 3 studies

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Good Clinical Practice (GCP)

- International guidelines that helps make sure that the results of a clinical trial are **reliable** and that the **patients are protected**.

National Cancer Institute

- International Council for Hasmonization Good Clinical Practices (ICH-GPC)
  - Provide unified standard of Clinical Research across for the globe to facilitate the mutual acceptance of clinical data by the regulatory authorities

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GPC - Guide how clinical trials are

designed | conducted | performed | monitored | audited | recorded | analyzed | reported

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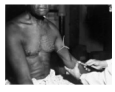
Historical background of GCP



460BC	Oath of Hippocrates
1930's	U.S. Food, Drugs and Cosmetic Act
1947	Nuremberg Code
Dec. 10th, 1948	Declaration of Human Rights
1962	Kefauver-Harris Amendment
1964, revised 2000	Declaration of Helsinki
1979	The Belmont Report
1982	International Guidelines for Biomedical Research Involving Human Subjects
1996	ICH-GCP guidelines issued
1997	ICH-GCP guidelines becomes law in some countries

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13 principles of ICH GCP

ETHICS
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)

Trial risk vs trial benefit
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

Trial participants – SAFETY FIRST
The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society

Information on the Medicinal Product
The available non-clinical and clinical information on an Investigational Product should be adequate to support the proposed clinical trial

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13 principles of ICH GCP

Good quality trials - PROTOCOL
Clinical trials should be scientifically sound, and described in a clear, detailed protocol

Compliance with the study protocol - IRB
A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion

Medical decisions
The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist

Trial staff
Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s)

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

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13 principles of ICH GCP

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

Confidentiality
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)

Good Manufacturing Practice
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

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

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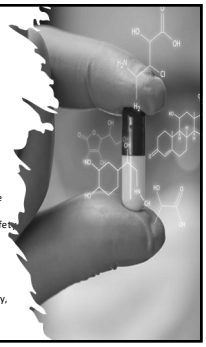
The Investigational New Drug Process

IND application

- Animal study and toxicity data (side effects that cause **great harm**)
- Manufacturing information
- Clinical protocols (study plans) for studies to be conducted
- Data from any prior human research
- Information about the investigator

FDA IND Review Team

- ***Project Manager*** - primary contact for the sponsor
- ***Medical Officer*** - reviews clinical study data before, during, and after the trial is complete
- ***Statistician:*** interprets trial designs and data - evaluate protocols and safety and efficacy
- ***Pharmacologist*** - reviews preclinical studies
- ***Pharmakineticist*** - drug's absorption, distribution, metabolism, and excretion processes
- ***Chemist:*** drug's chemical compounds (stability, quality control, continuity, impurities, etc.)
- ***Microbiologist*** - (antimicrobial product) assess response of microbes



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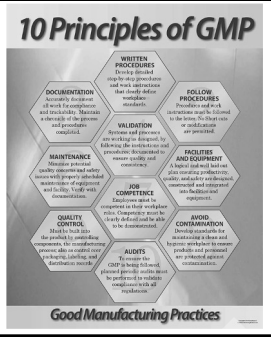

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IND Approval

- 30 days
- Protects volunteers from unreasonable and significant risk in clinical trials
- FDA responds to IND applications:
  - Approval to begin clinical trials.
  - Clinical hold to delay or stop the investigation
    - Participants are exposed to unreasonable or significant risk
    - Investigators are not qualified
    - Materials are misleading
    - Not enough information about the trial's risks
- FDA often provides comments intended to improve the quality of a clinical trial
- The developer must inform new protocols, serious side effects, final study reports
- Marketing application (2 large controlled clinical trials)

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Step 4: FDA Drug Review

Early tests and preclinical and clinical research - drug is safe and effective for its intended use

New Drug Application (NDA)

- Full story of a drug - drug safety and effectiveness for intended use in the studied population
  - preclinical data to Phase 3 trial data
  - proposed labeling
  - safety updates
  - drug abuse information
  - patent information
  - data from studies outside the United States
  - institutional review board compliance information
  - directions for use

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Step 4: FDA Drug Review

FDA Review

- full review
- FDA routine inspection - evidence of fabrication, manipulation, or withholding of data
- "action package." (record for FDA)

FDA Approval

- develop and refine prescribing information ("labeling")
  - describes the basis and best to use the drug
- issues need to be resolved before the drug marketing approval
  - address questions based on existing data - additional studies

FDA Advisory Committees

- questions - require additional consideration
- independent Advisory Committees - public comments
  - Patient Representative - input from the patient perspective

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Step 5: FDA Post-Market Drug Safety Monitoring

Clinical trials provide important information BUT it is impossible to have complete information about the safety of a drug at the time of approval

Supplemental Applications

- significant changes from the original NDA (formulation, labeling, or dosage strength)

INDs for Marketed Drugs

- new use, dosage strength, new form, or different form (injectable, oral liquid, etc), or conduct other clinical research or a post-market safety study

Manufacturer Inspections

- FDA routine inspections - manufacturing facilities (may be unannounced) assure good manufacturer practice

Drug Advertising

- FDA regulates prescription drug advertisements and promotional labeling

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Step 5: FDA Post-Market Drug Safety Monitoring

Generic Drugs

- patent protected - sponsor exclusivity
- other manufacturers can develop comparable to brand name drugs
- must have the same dosage, form, strength, safety, quality, performance characteristics, intended use
- don't conduct clinical trials to demonstrate product safety and effectiveness
  - bio-equivalence studies and file an Abbreviated New Drug Application

Reporting Problems

- MedWatch - report and learn new safety information or problems on medical products (drugs and devices) (MedWatch safety alerts)
- Medical Product Safety Network (MedSun) - monitors safety and effectiveness of medical devices (MedSun newsletter)

Active Surveillance

- Sentinel Initiative - national system to spot possible safety issues
  - Uses electronic health databases - electronic health records systems, administrative and insurance claims databases, and registries

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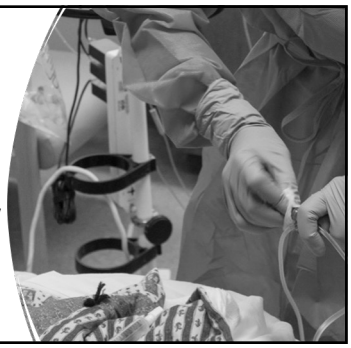
Safety requirements for the nursing administration of chemotherapy



- Safe administration of chemotherapy by nurses should be **evidence-based**
- Promote **patient and nurse safety** during nursing administration of chemotherapy
  - risk of adverse health outcomes
- Chemotherapy medication errors
  - patient morbidity, mortality and financial burden

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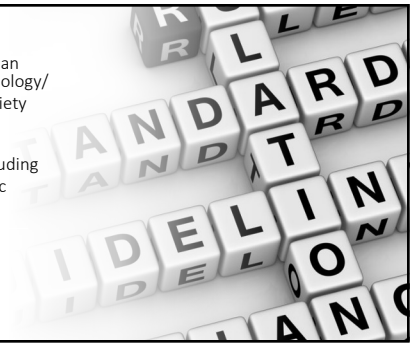
2016 Updated American Society of Clinical Oncology/ Oncology Nursing Society Chemotherapy Administration Safety Standards, Including Standards for Pediatric Oncology



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Domain 1: Creating a Safe Environment—Staffing and General Policy

Qualifications of clinical staff who order, prepare, and administer chemotherapy	**Education program** for initial and ongoing educational requirements for staff who prepare and administer chemotherapy	At least one clinical staff member **basic life support** is present during chemotherapy administration	A licensed independent **practitioner is on-site and available** to staff who administer chemotherapy	**Chart is available** before the first administration of a new chemotherapy regimen,
Patient assessment and appropriate action on each clinical encounter	**Provides information** and financial resources and/or refers patients to psychosocial and other cancer support services	The **patient's medications** are updated at every visit and reviewed when a change occurs	Documentation and **follow-up for patients** who miss or cancel scheduled visits and/or chemotherapy treatments	Policy that addresses mandates and processes for pediatric patients that account for legal requirements
Identify a process to provide **24/7 triage for toxicities and emergencies**	Standardized **documentation and communication of toxicities, modifications in dose or schedule, or discontinuation of treatment**	**Standardized** systems to promote a safe handoff between all sites of care	Policy for reporting of adverse events	

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Domain 2: Treatment Planning, Patient Consent, and Education

- Standardized process for obtaining and documenting chemotherapy **consent or assent**
- Documented informed consent and assent for chemotherapy treatment before initiation of a chemotherapy regimen
- Provided patients **verbal and written or electronic information** as part of an education process before the first administration of treatment of each treatment plan
- Education **includes family, caregivers, or others** based on the patient's ability to assume responsibility for managing therapy.

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Domain 3: Ordering, Preparing, Dispensing, and Administering Chemotherapy

- Defines standard chemotherapy regimens by diagnosis
- Verifies institutional review board approval of research regimens
- Orders for chemotherapy are signed
- Policy for managing nonstandard regimens chemotherapy orders
- Policy for chemotherapy orders
- Standardized, regimen level, preprinted or electronic forms for parenteral chemotherapy
- Chemotherapy orders
- Prescriptions for oral chemotherapy
- Chemotherapy is prepared by a licensed pharmacist, pharmacy technician, physician, or registered nurse with documented chemotherapy preparation education, training, and annual competency validation

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Domain 3: Ordering, Preparing, Dispensing, and Administering Chemotherapy

A licensed pharmacist verifies all orders for pediatric patients under the age of 18 years	A second person performs three independent verifications	Before preparation, a second person independently verifies	Upon preparation, a second person verifies	Before each chemotherapy administration two practitioners verify and document the accuracy
Chemotherapy drugs are labeled immediately upon preparation	Sequencing of drug administration	A warning or precautionary label or sticker, as applicable, to storage and handling	Administration schedule, including number of times per day and days on and off treatment	Administration instructions related to food ingestion and other medications.
	A warning or precaution statement, as applicable, to storage and handling.	Caution statement label attached to the prepared product, for example, "Caution: chemotherapy" or "HAZARDOUS DRUG."	Intrathecal medication maintains policy that specifies that intrathecal medication preparation	

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Domain 3: Ordering, Preparing, Dispensing, and Administering Chemotherapy

Intrathecal chemotherapy has policy that specifies that intravenous vinca alkaloids are administered only by infusion, for example, mini-bags	Prepared chemotherapy policy for quality control of that chemotherapy	Policy for own pharmacy safe storage of chemotherapy	Chemotherapy is administered by a qualified physician, physician assistant, registered nurse, or advanced practice nurse as defined in standard
Before initiation of each chemotherapy administration cycle, confirm the treatment with the patient	At least two individuals, in the presence of the patient, verify the patient identification by using at least two identifiers.	When chemotherapy is administered in a nonhealthy care setting by a health care provider, a second identifier	Documentation of chemotherapy administration confirms the verification of the eight elements of standard
	Extravasation management procedures are defined and align with current literature and guidelines		

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Domain 4: Monitoring After Chemotherapy is Administered, Including Adherence, Toxicity and Complications

- The health care setting uses standard, disease specific processes to monitor treatment response and has policy that determines the appropriate time interval for regimen-specific laboratory and organ function tests that are based on evidence and national guidelines when available.
- Policy for emergent treatment of patients
- Policy outlines the procedure to monitor an initial assessment of patients' adherence to chemotherapy that is administered outside of the health care setting
- Assessment of each patient's ongoing chemotherapy adherence and toxicity at each clinical encounter to address any issues identified.
- The health care setting has policy that requires evaluation and documentation of treatment-related toxicities, dose modification related to toxicities, and how these are communicated before subsequent administration.
- Cumulative doses of chemotherapy are tracked for agents associated with cumulative toxicity

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- Overview of American Society of Clinical Oncology and Oncology Nursing Society standards
- Training and staffing
- Planning and documentation
- Patient consent and documentation
- Ordering
- Mixing standards
- Administration
- Intrathecal administration
- Intraperitoneal administration
- Intrahepatic administration
- Hemodialysis fistula administration
- Management of hypersensitivity anaphylactic reaction to antineoplastic agents
- Management of antineoplastic extravasation
- Monitoring and assessment
- Safe handling
- Spills, exposure, and medical surveillance

FIGURE 2. Standards of Practice for Chemotherapy and Targeted Therapy

Vioral AN & Kennihan HK (2012)

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