Good Clinical Practice (GCP)

an outline

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Coverage

- What GCP is
- The history & need for GCP (a mention)
- Guidelines /principles for GCP
- Players (an outline)
- Key documents
- References

Why are ethical guidelines important?
Why is ethics oversight important?

Common principles in Guidelines: Science & Ethics are linked

- A clinical trial is not justified ethically unless capable of producing scientifically reliable results

- A clinical trial is not justified scientifically unless executed ethically – i.e. protects trial participants from exploitation and harm

NB: Poor ethics oversight invalidates trial results

GCP?

An international ethical & scientific quality standard for designing, conducting, recording & reporting human clinical studies

- Assurance that data and reported results are credible and accurate
- rights, integrity and confidentiality of trial subjects are protected

Objectives of GCP Guidelines

- Are mainly focused on the protection of human rights in clinical trials
- Provide assurance of the safety of newly developed compounds.
- Provide standards on how clinical trials should be conducted.
- Define the roles and responsibilities of key players (*clinical sponsors, clinical research investigators, Clinical Research Associates, and monitors).*

History of Good Clinical Practice

- Prior to an actual set of guidelines to follow for good clinical practice, clinical studies were dangerous and could result in serious disease, or possibly death
- *The Nuremberg Code of 1947: response to Nazi experiments!*
  - Experiments performed in Germany during WWII opened the eyes of the world for guidance for clinical testing on humans.
  - The code did set ethical guidelines, **but it lacked legislation to back it up**.
- *Declaration of Helsinki (1964-2000, 2008) six revisions*
  - In 1964, the World Medical Association established recommendations guiding medical doctors in biomedical research involving human subjects.
  - **These guidelines influenced national legislation, but there was no set standard between nations**
- *The Belmont Report (1979)*
- *CIOMS/WHO* International Guidelines (1993, 2002)
- *ICH:* The formation of the International Conference on Harmonization led to the creation of the Consolidated Guidance on GCP
  - The ICH consisted of the governments of the United States, EU and Japan coming together to develop common set of regulations for the pharmaceutical markets among member countries

DoH

- 1964 - Declaration of Helsinki - set ethical standards for human research; 6 revisions to 2008

Requirements in 2008 Dec. of Helsinki, absent in ICH-GCP

1. **Investigators to disclose funding, sponsors, other potential conflicts of interest to both Ethics review committees & study participants**
2. **Study design to be disclosed publicly - eg clinical trial registries**
3. **Research, especially in developing countries, to benefit and be responsive to health needs of populations in which it is done**
4. **Restricted use of placebo controls in approval process for new drugs and in research done in developing countries**
5. **Post-trial access to treatment**
6. **Authors to report results accurately, and publish or make public negative findings**

Council for Int. Organizations of Medical Sciences

CIOMS Ethics Guidelines differs from Declaration of Helsinki on **placebos: ...**

" ... it may be ethically acceptable to use an alternative comparator - placebo or no treatment" - when:

1. There is no established effective intervention

2. Withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in symptom relief /placebo would not add any risk of serious or irreversible harm

3. Using an established intervention as comparator would not yield reliable results

DECLARATION OF HELSINKI 2000, #29

The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods.

This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

CIOMS (2002)GUIDELINE 11

Guideline 11: Choice of control in clinical trials

- As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention.

- **In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or "no treatment".**

Placebo may be used:

1. when there is no established effective intervention;

2. when withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms

3. when use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects.

CONCERNS AND CONTROVERSIES

- Following the adoption by the World Medical Association Assembly in October 2000 of a substantially revised version of the *Declaration of Helsinki* (DoH), concerns were voiced about a few of its provisions, especially paragraph 29 dealing with the use of placebos in clinical trials
- Para. 29 was addressed in a note of clarification adopted by the Assembly in October 2002.

NOTE OF CLARIFICATION #29

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

1. Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

2. Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebos will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

Thirteen principles of GCP Guidance

1 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 requirements

2 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

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

Thirteen principles of GCP Guidance

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

5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol

6 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

7 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

Thirteen principles of GCP Guidance

8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective tasks

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

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

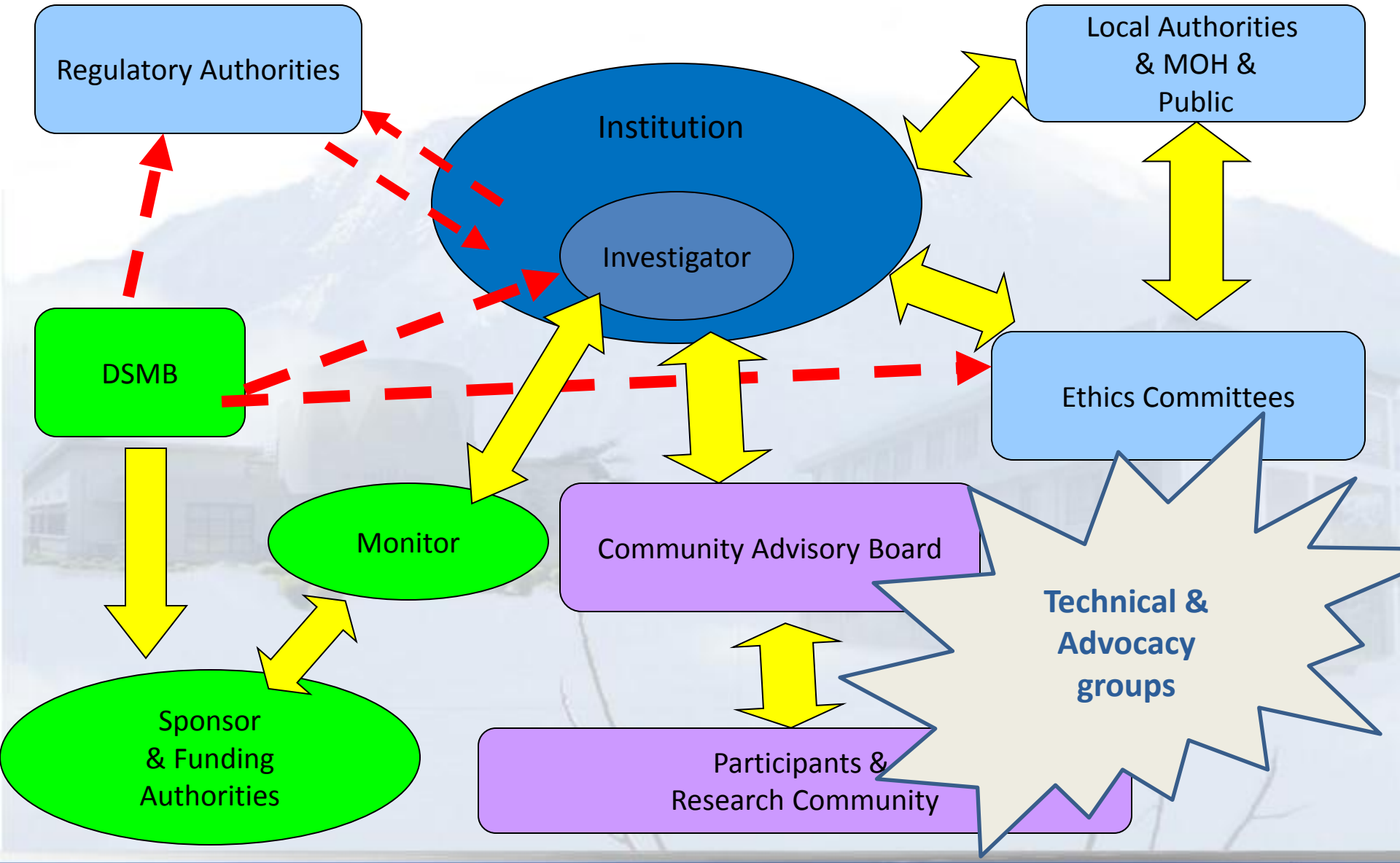
11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements

Thirteen principles of GCP Guidance

12 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

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

Requires Multiple/ Multidisciplinary Players



GCP: Participating Parties

- IRB/Ethics Committee
- Investigators
- Sponsor
- Regulatory Authorities

IRB/EC: Roles & Responsibilities

To safeguard study subjects' rights & welfare by:

- Evaluation/disposition of study proposal
- Evaluation of proposed subject consent materials
- Evaluation of emergency use consent methodology
- Evaluation of investigator qualifications
- Ongoing review of study progress (at least yearly)
- Evaluation of proposed subject compensation plans

Investigator: Roles & Responsibilities

- Qualified to conduct study
- Have adequate resources to conduct study
- Provide medical care to study subjects
- Regular communication with IRB/EC reviewing study
- Compliance with study protocol
- Compliance with study randomization & unmasking procedures
- Provide informed consent to study subjects

Sponsor: Roles & Responsibilities

- Study quality assurance
- Appropriately qualified medical personnel to advise on study
- Utilization of qualified personnel in study design & operations
- Study management, data handling & record keeping
- Investigator selection & training
- Definition/allocation of study responsibilities

GCP: Key Documents

- Investigator Brochure
- Study Protocol
- Informed Consent Document

Investigator Brochure: *What IS IT??*

A compilation of clinical & non-clinical data on the product that is relevant to the product's study in humans

Necessary for Investigator & IRB/EC review to assess the risks/benefits associated with study

Investigator Brochure: Components

Product formulation summary

Introduction/background info regarding product & investigational plan

- Investigational product physical, chemical & pharmaceutical properties & formulation
- Non-clinical studies
- Human clinical studies
- Summary of data & guidance for Investigator

Study Protocol: Components

- General administrative info
- Background
- Study purpose & objectives
- Study design
- Subject eligibility requirements
- How subjects will be treated
- How safety & efficacy will be assessed
- Sample size justification & statistical analysis methods

Study Protocol: Components

- How data will be captured & maintained
- Monitoring procedures
- Proposed informed consent document

Informed Consent Document: Components

- Statement that study involves “research” & product “experimental” (if applicable)
- Study purpose
- Number of expected study subjects to be enrolled
- Study treatment(s) & probability for random assignment
- Study exams & procedures for duration of trial
- Subject’s responsibilities
- Foreseeable risks to subject (embryo, fetus, nursing infant)

Informed Consent Document: Components

- Expected benefits
- Alternatives procedures or therapies & associated risk/benefit
- Compensation available in event of study-related injury or sickness
- Anticipated ‘payments’ to subject for study participation
- Anticipated expenses to subject for study participation
- Statement that participation is voluntary

Informed Consent Document: Components

- Description of extent to which confidentiality can be assured
- Commitment to keep subject apprised on new information that may affect subject's willingness to participate in study
- Contact info for questions re: subject rights; trial-related adverse events
- Circumstances under which subject's participation may be terminated

Reference Documents & Links

1. ICH - E6: Guideline for Good Clinical Practice
2. 21 CFR 50 - Informed Consent
3. 21 CFR 56 - Institutional Review Board
4. http://www.ich.org/cache/compo/276-254-1.html
5. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm