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# Conforming to GCP/GLP standards in resource-poor settings: can we meet the challenge ?

MSF Symposium - Overcoming Gaps in TB drug  
Research and Development

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# What is GCP?

- ICH Guideline for Good Clinical Practice:

*“GCP is an international **ethical and scientific** quality **standard** for designing, conducting, recording, and reporting trial that involve the participation of human subjects.*

*Compliance with this standard provides public assurance that the **rights, safety and well-being of trial subjects are protected**, consistent with the principles that have their origin in the Declaration of Helsinki, and that the **clinical trial data are credible.**”*

# What is GCP?

*“A **standard** by which clinical trials are designed, implemented and reported so that there is public assurance that the **data are credible** and that the **rights, integrity and confidentiality of subjects are protected**”*

Hutchinson D: *Dictionary of Clinical Research*

# Where did GCP come from?

- Human rights abuses
  - WW II crimes
  - prison populations for «medical» experiences
  - mentally ill
- Unsafe medicines/poor testing (Thalidomide disaster)
- Poor quality/fraudulent data
- Declaration of Helsinki (1964):
  - "It is the duty of the physician in medical research to protect the life, health, privacy and dignity of the human subject".*

***Why bother with GCP ?***

*Mainly to avoid this...*



...and this...



# A V I S



## GUÉRISON DE LA TUBERCULOSE



J'informe les personnes atteintes de *Phtysie* ou de *Bronchite chronique*, que nous sommes arrivés à les guérir par un traitement spécial.

La guérison sera obtenue rapidement si la maladie est traitée dès son début et avant l'apparition des fièvres.

Les malades désirant suivre ce traitement SERONT SOIGNÉS GRATUITEMENT PENDANT LE PREMIER MOIS et cela afin de leur montrer l'amélioration obtenue pendant ce peu de temps.

D<sup>r</sup> MÉLOTTE.

# Why bother with GCP?

- Legal obligation
- Ensures protection of human subjects
- Ensures generation of quality and credible data
- Sets obligations of sponsor(s) and investigator(s)
- Increases chances of regulatory success
  - *GCP is here to stay*
  - *It is here to help all of us*

# GCP guidelines

- Describe in detail:
  - responsibilities of the Institutional Review Boards / Independent Ethics Committees (IRB/IEC)
  - responsibilities of the investigator(s) and the sponsor(s) of the trial
  - main documents to be produced for the conduct of the trial (trial protocol, investigator's brochure, CRFs, informed consent, SOPs, ...) and their archiving for trail checking
  - guidance for the monitoring of the trial

# Main aspects of GCP guidelines

1. Institutional Review Boards / Independent Ethics Committees:
  - describe responsibilities of the IRB/IEC re. safeguard of rights, safety and well being of trial subjects
  - give indications on procedures for the assessment of protocols
2. Informed Consent:
  - participation must be voluntary
  - patients' right to refuse or withdraw from the trial without interference with their treatment.
  - details on content

# Main aspects of GCP guidelines

3. Responsibilities of the Investigator:  
study conduct, staffing, ethical requirements, reporting AEs & SAEs, archiving source data, auditing
4. Responsibilities of the Sponsor:  
protocol design, information on IMP, trial monitoring, safety, data collection & analysis, report, compensation
5. Trial monitoring: ensures that:
  - the rights and well-being of human subjects are protected;
  - reported trial data are accurate, complete, and verifiable from source documents;
  - conduct of the trial is in compliance with the approved protocol and GCP requirements.

# Good Laboratory Practice (GLP)

- Apply **laboratory quality standards** in drug research development and testing;
- Defined as *“a quality system concerned with the organisational process and conditions under which studies are planned, performed, monitored, recorded, archived and reported”*;
- Indispensable for regulatory purposes;
- Guidelines ensure that all laboratory data can be verified and are of adequate quality;

*GCP / GLP provide standards of operation  
in the conduct of clinical research*

- Conducting clinical trials under GCP and GLP requirements is a **legal obligation** made to the sponsors and the investigators to ensure that the best possible clinical research is conducted, ensuring together the **protection of patient's rights** and the collection of **high quality data**
- Conforming with these increase the chances of **regulatory success.**

# Challenges of conducting trials in high burden settings

- Drastic differences seen between industrialized and low-income countries:
    - large variability of structure and role of IRB/IECs
    - difficulties with informed consent
    - variability in understanding and applying GCP and GLP
    - difficulties in monitoring
    - variability of laboratory infrastructure and QA procedures
    - problems in practical aspects of trial conduct
- *All resolvable, but need to be properly addressed*

## Review of nine Bioethics journals 1990-2003

	High income countries (n=54)	Low-income countries (n=154)
Research articles published	382/4029 (96%)	156/4029 (4%)
Countries represented in publications	28/54 (52%)	31/154 (20%)
Top 5 countries contributing articles	USA (62%) UK (14%) Canada (4%) Australia (4%) Netherland (3%)	China (15%) Turkey (11%) South Africa (11%) Hungary (7%) Philippines (6%)

*Borry et al, NEJM 2005*

# 1. IRBs/IECs

- Large variability of IRBs/IECs in terms of :
  - structure / composition
  - terms of reference
  - requirements
  - review process
  - recommendations
  - frequency of meetings
- *Reinforce the role of Ethics committees*
- *Need to standardize structures and TOR*

## 2. Informed Consent (IC)

- High complexity of some IC forms !
  - Language issue
  - Cultural issues
  - Pb of Misunderstanding
  - Doubts from health staff on necessity to "explain everything" - fear that the patient refuses participation
  - Problems with HIV infected subjects
- 
- *translation in colloquial languages*
  - *consult with health workers and patients*
  - *advocacy groups*
  - *alternative means (illustrations, stories, radio)*
  - *staff training*

# 3. Complying with GCPs

- A "top-down" approach ?
- Mainly needed for quality of data (licensing trials) ?
- Gaps can be observed between GCP concept and reality in the field:
  - lack of understanding of the necessity of GCP
  - SAE reports (although SAEs clinically addressed)
  - confidentiality
  - documenting and archiving data
- reasons are mainly historical or cultural / socio-economic
- dealing with clinicians – not with scientists

→ *training* +++

## 4. Practicalities in trial conduct

- recording patients' addresses
- respecting appointments (patients' follow-up)
- concomittent treatment
- lack of reliable equipment
- power cuts (problems with electrical equipment, storage of samples, etc...)
- difficult internet access
- transfer of specimens from sites to references laboratory
- under-staffing
  - *training*
  - *appropriate resources*
  - *regular monitoring*

## *Meeting the challenge ?*

1. TB trials conducted in countries where the greatest needs are → multi-centre collaboration
2. Develop clinical trial capacities in these countries → upgrade sites and laboratories to suitable standards (resources +++)
3. Role of IRB/IECs to reinforce
4. Importance of training
5. Availability of and access to drugs/interventions to local populations (if efficacy demonstrated)

# Importance of training

- Clinical trials methodology
- GCPs and GLPs
- Clinical monitoring
- New laboratory techniques
- Data management + statistics
- Research ethics
  
- *Training should be on-going*

# Trials of new drugs/regimens for the treatment of TB

- Large numbers of patients required to demonstrate *at least equivalence* with a regimen of known efficacy
- Primary end-point for efficacy trial is the *rate of relapse during a 2-year period following treatment*
- Role of new drugs/regimens to be assessed in HIV infected patients treated with ARVs
  - *Multinational multicentre trials most likely to be the rule for development of new drugs/regimens for the treatment of TB*

# Trials of new drugs/regimens for the treatment of TB

- Sophisticated laboratory methods needed:
  - respective bactericidal activity of the drugs included in the combined regimens
  - role of each drug in these regimens
  - relapse vs reinfection for definition of end-point (finger-print method)
  - evaluation of drug resistance (DST)

→ ***importance of addressing the challenge of GCP and GLP***

# ***No time to wait ....***

.... to meet the challenge...

- *not insurmountable*
  - *matter of channeling appropriate resources for capacity development*
  - *ensure training*
  - *willingness*
  - *team work*
- *Platform for GCP/GLP enhancement ?*

