Massachusetts Institute of Technology
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# SUMMARY OF FEDERAL REGULATORY ISSUES AND CLINICAL TRIALS

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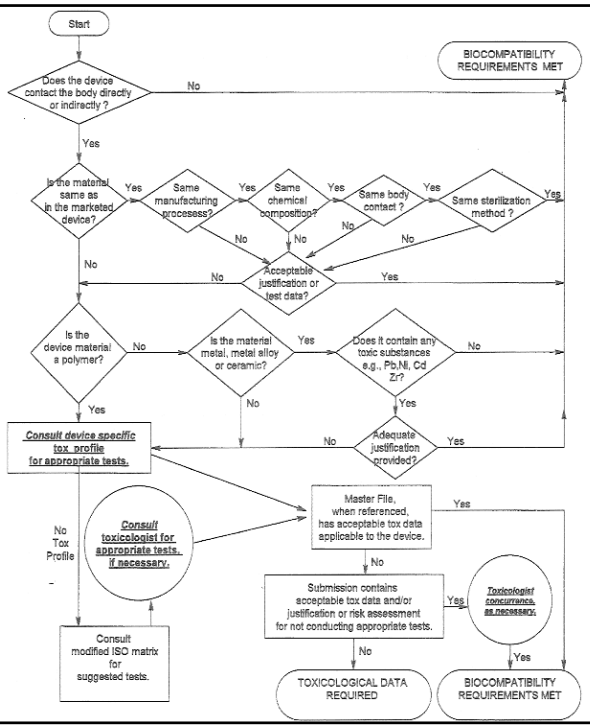
## FDA

- Name of device
- Description of device
  - Indication and intended use
  - Performance claims
- FDA classification
- Preclinical testing: functional and biological testing
  - Tests
  - Which components of the device to be evaluated by each test method
  - Form of the component to be tested
- IDE protocol
  - Inclusion criteria for patients to be enrolled in the study
  - Controls?
  - Number of patients; statistics-power calculation (http://calculators.stat.ucla.edu/)
  - Outcome variables
  - Informed consent form
- Benefit/risk ratio

**Biocompatibility Flow Chart for the Section of Toxicity Tests for 510(k)s**




# Guidance for Industry

## E6 Good Clinical Practice: Consolidated Guidance

Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials 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.

Source: U.S. FDA

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CLINICAL TRIAL PROTOCOL AND PROTOCOL . .



# Guidance for Industry

## E 10 Choice of Control Group and Related Issues in Clinical Trials


**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**
**Center for Biologics Evaluation and Research (CBER)**
**May 2001**




Source: U.S. FDA

## FDA CLINICAL TRIAL GUIDANCE

### Purpose of Control Group

Control groups have one major purpose: to allow discrimination of patient outcomes (for example, changes in symptoms, signs, or other morbidity) caused by the test treatment from outcomes caused by other factors, such as the natural progression of the disease, observer or patient expectations, or other treatment. The control group experience tells us what would have happened to patients if they had not received the test treatment or if they had received a different treatment known to be effective.

## FDA CLINICAL TRIAL GUIDANCE

- Purpose of Control Group
  - Randomization
  - Blinding
- Types of Control
  - Placebo Concurrent Control
  - No-treatment Concurrent Control
  - Dose-response Concurrent Control
  - Active (Positive) Concurrent Control
  - External Control (Including Historical Control)
  - Multiple Control Groups

## FDA CLINICAL TRIAL GUIDANCE

**Purposes of Clinical Trials and Related Issues**

- Evidence of Efficacy
- Comparative Efficacy and Safety
- Fairness of Comparisons
  - Dose
  - Patient Population
  - Selection and Timing of Endpoints

## FDA CLINICAL TRIAL GUIDANCE

**Guidance for Industry**
**E6 Good Clinical Practice:Consolidated Guidance**

- Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.
- Compliance with this standard provides public assurance that the rights, safety, and wellbeing 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.
- The objective of this ICH GCP guidance is to provide a unified standard for the European Union (EU), Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

# POWER CALCULATION
# SAMPLE SIZE DETERMINATION

**Type I Error (False Positive)**

- Alpha ($\alpha$) is the probability that the test will lead to the rejection of the hypothesis tested when that hypothesis is true.
  - Hypothesis: The medical device results in an improved outcome. $\alpha$=0.05 means that there is only a 5% probability that this is wrong; *i.e.*, low chance of a false positive.
  - There could be dire consequences if we are wrong because the new device would be used even though it is no better than the control. Therefore, we have to be confident that we are right (*i.e.*, a 95% probability that the new device is better than the control).

**Type II Error (False Negative)**

- Beta ($\beta$) is the probability that the test will reject the hypothesis tested when a specific alternative hypothesis is true; 1-$\beta$ is the "power."
  - Hypothesis: The medical device results in no improvement in outcome. $\beta$=0.2 means that there is a 20% probability that the new device is shown by the study to be the same as the control, when it is actually better; *i.e.*, a 20% chance of a false negative.
  - Not as much a problem if we are wrong, because the new device would just not be used. Therefore we can accept only an 80% probability (*i.e.*, power) that there is no difference between the device and control.
- In meeting the criterion of $\alpha \leq 0.05$ it is shown that there is a high probability (95%) that the new device is better than the control. The study should have a sufficient number of patients in each group (*i.e.*, a sufficient power; 80% is enough) such that if there were no difference it would have been detected.