Clinical Trials Management Policies & Procedures

Pre- and Post-Award Management

Clinical trials are research studies to determine whether new drugs or treatments are safe and effective. These research programs are conducted with patients to evaluate a new medical treatment, drug or device, and their purpose is to find new and improved methods of treating different diseases and special conditions. Private companies such as pharmaceutical companies sponsor such trials. The scope of work known as the "Protocol" may be solely formulated by the sponsoring company or it may be designed by the principal investigator. In either case, clinical trials are considered sponsored projects and must be reviewed and approved as such.

The review of clinical trial differs from other research projects because their proposals are different. The below sections provide definitions related to clinical trials, and information about the review process of clinical trials, the pre- and post-award procedures for managing clinical trials, as well as define the responsibilities of principal investigators and OGC.

1. Definitions

2. Types and Phases of Clinical Trials

3. Pre-Award Procedures for the Conduct of Clinical Trials

4. Post-Award Procedures for the Management of Clinical Trials

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Clinical Trials Management - Definitions

**Clinical Trials** are research studies that involve human subjects and which are conducted under conditions controlled by a medical doctor and/or scientist referred to as Principal Investigator (PI). Clinical Trials should be designed, conducted and analyzed according to sound scientific and ethical principles, such as the Helsinki Declaration, to achieve the desired objectives.

Clinical Trials are designed to determine whether new drugs or treatments are safe and effective and/or evaluate a new medical treatment, a drug or a medical device. Their purpose is to find new and improved methods of treating diseases and special conditions. In most cases private companies (referred to as Sponsors), mainly pharmaceutical companies, sponsor such trials.

Clinical Trials are designed either as a “Single Center” or “Multi-Center” trials, with, in the latter case; AUB becomes one of the sites among other national and/or international sites participating in the conduct of the trial.

**Principal Investigator (PI):** The PI is the project director and assumes full responsibility for the research project or Clinical Trial conduct. The PI is in charge of preparing the Clinical Trial proposal, securing internal approval for the conduct of the Clinical Trial including institutional ethical committee approval, and overseeing the scientific and technical aspects of the Study. The PIs are responsible for the management of Clinical Trials including patient recruitment, and submission of original case report forms ("CRFs") for each patient or subject participating in the Study (“Study Subject”) and, if applicable, regular narrative reports to the Sponsor.

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**Clinical Trial Protocol:** A Clinical Trial Protocol is a document that describes the objective(s), design, methodology, statistical considerations, and the organization of a Clinical Trial. The protocol should contain a study plan on which the Clinical Trial is based. The plan is designed to safeguard the health of the participants (while limiting their financial liability) as well as answer specific research questions. It should also describe what types of people may participate in the trial; the schedule of tests, procedures, medications, and dosages; and the timeline of the study. It is expected that during a Clinical Trial, study participants are seen regularly by the research staff (usually medical doctors and/or nurses) to monitor their health and to determine the safety and effectiveness of the treatment(s) they are receiving.

The Clinical Trial Protocol could be solely formulated by the sponsoring company; or by the Principal Investigator (PI). In either case, Clinical Trials are considered sponsored projects and are reviewed and approved as such.

**Approved Clinical Research Protocol:** This is a sponsor-supplied protocol that has been approved by the Institutional Ethical Committee, in AUB’s case the “Institutional Research Board (IRB) and the PI.

**Institutional Review Board (IRB):** IRB is an administrative body established to protect the rights, safety and wellbeing of all human subjects recruited to participate in research activities conducted by members of AUB Faculty, regardless of the funding source. IRB pays special attention to studies that may include vulnerable subjects.

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**Declaration of Helsinki Protocol:** The Declaration of Helsinki Protocol is a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. The Declaration includes principles on safeguarding research subjects, informed consent, minimizing risk, and adherence to an approved research plan/protocol.

**Good Clinical Practice:** Good Clinical Practice is an international quality standard that is provided by the International Conference on Harmonization (ICH); an international body that defines standards, which governments can transpose into regulations for clinical trials involving human subjects. Good Clinical Practice guidelines include protection of human rights as a subject in clinical trial. It also provides assurance of the safety and efficacy of the newly developed compounds. Good Clinical Practice Guidelines include standards on how clinical trials should be conducted; define the roles and responsibilities of clinical trial sponsors, clinical research investigators, and monitors.

**Adverse Event/Reaction:** An adverse event is any occurrence that a person in a Clinical Trial is subjected to during and/or after drug administration. Such event could be directly related to the drug administered to a patient or to the dose. A serious adverse event (SAE) is an event that occurs during the Clinical Trial and which is deemed life threatening, such as illness requiring hospitalization, or involving cancer or fetal exposure or even death, and must be reported to the regulatory authorities immediately, whether the SAE is thought to be directly or indirectly related to the Clinical Trial.
Liability / Malpractice Insurance: This insurance is coverage for a professional practitioner against liability in the case of malpractice and is not related to the drug, its administration or dosage.

Indemnification: This is a contractual obligation by which one person or organization agrees to secure another against loss or damage from specified liabilities. Compensation is usually made to a victim of a loss by the repayment, repair, or replacement in whole or in part.

Agreement: This is a document made between two parties or more for the purpose of defining their business relationship and responsibilities. Agreements address issues such as time line for patient recruitment, responsibilities of the PI and the Sponsor, publication rights and restriction, ownership of intellectual property, confidentiality of information, payment and payment schedules, record keeping, termination, warranty, liability, indemnification, assignment and subcontracting, amendment, notices, relationship of parties, governing law and governing priorities.

Clinical Research Associate (CRA): A CRA is an agent/employee of the Sponsor, whose main function is to monitor clinical trials. He or she may work directly with the Sponsor, as an independent freelancer or for a Contract Research Organization (CRO). A CRA ensures compliance with the clinical trial protocol, checks clinical site activities, makes on-site visits, reviews Case Report Forms (CRFs) and communicates with the Principal Investigators.
Types and Phases of Clinical Trials

Types of Clinical Trials

Clinical Trials belong to one of the following types:

A. Company Sponsored Trials: The Company takes the ultimate responsibility for the initiation, management and financing of the study.

B. Investigator-Initiated Trials: Investigator-initiated Clinical Trials are studies whereby the Principal Investigator designs the trial protocol and is, legally, the owner of the study. Investigator-initiated trials are usually submitted as proposals to pharmaceutical companies for soliciting financial support.

C. Observational-Study Trials: Observational studies report associations (correlations) between treatments already used by participants and their health status or diseases.

Phases of Clinical Trials

Below are the description of four phases of clinical trials as defined by the International Conference on Harmonization (ICH), Health Canada, and the U.S. Food and Drug Administration (FDA).

Phase 1

The Phase 1 of clinical research studies constitute the first set of testing of a new drug into humans. They typically include studies grouped under Human Pharmacology. Phase 1 clinical research has non-therapeutic objectives and is therefore not usually used for treatment of a disease. They are conducted on a small group of healthy volunteer subjects or on certain types of patients (such as patients with mild hypertension). The participants often need to stay overnight at the trial center to be closely monitored and observed. However, drugs that are
known to have a high potential of toxicity (such as cytotoxic drugs used in chemotherapy in cancer) are usually studied in patients.

The phase 1 of clinical trial design can be open, meaning that both researcher and subject may know the details of the treatment. Phase 1 studies can also be baseline controlled: there is an assessment of the volunteer before and after treatment. Randomization and blinding may also be used. In this case, there is a random allocation of the treatment, without the researcher and/or the subject knowing what treatment is being administered, which lead to more accurate results. The clinical trial design Phase 1 can involve:

(a) Estimation of Initial Safety and Tolerability is used to determine the tolerability of the dose range expected to be needed for later clinical studies and to determine the nature of adverse reactions that can be expected.

(b) Pharmacokinetics information is used to characterize the profile of the new drug about its absorption, distribution, metabolism, and excretion by the human body. Although predominant in Phase 1 of clinical trials, PK are studies throughout the trial, and other PK studies are carried during Phase 2, Phase 3 and even Phase 4.

(c) Assessment of Pharmacodynamics, to provide an early idea of the activity and the potential efficacy of the new drug. PD can also guide the dosage of the drugs in later studies.

(d) Early Measurements of Drug Activity. Although usually done in later phases, it is possible to carry preliminary studies about drug potential therapeutic benefit in Phase 1 of a clinical trial, as a secondary objective.
Phase II

Clinical research studies Phase 2 can be initiated after enough information has been collected from phase 1 and safety been confirmed. Their primary objectives are to explore therapeutic efficacy in patients. Phase 2 studies are used to evaluate how well the drug works, and also to collect additional safety data in a larger group of volunteers and patients. While early studies of Phase 2 may include baseline controlled, later studies of Phase 2 are usually randomized with a placebo control, to evaluate the efficacy of the new drug and its safety under specific conditions or indications.

In Phase 2, the therapy or the drug is usually administered on a relatively uniform patient population, and groups are larger than those of Phase 1. Subjects are closely monitored and information collected is important to determine the dose and treatment indications that will be used during Phase 3. More studies under Phase 2 may be used to assess potential study endpoints, therapeutic restrictions (such as simultaneous or concomitant medications) or target populations (such as mild versus severe disease) for further studies.

Phase III

Phase 3 studies in clinical trials complete the information needed for the actual drug marketing approval, and give the official product information. For a drug to be approved, it typically has to undergo at least two successful Phase 3 trials, showing that the drug is safe for humans use and its efficacy in the targeted population.

Phase 3 studies aim to confirm the therapeutic benefits of the new drug on the targeted population, and also to confirm previously collected evidence about drug safety. Additional Phase 3 studies may be used to research the dose-response relationship or the drug's use in wider populations, in different stages of disease, or in combination with another drug.

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Phase 3 studies are done on large group patients and are randomized controlled multi-center trials. The size and the relatively lengthy duration of Phase 3 trials make them notably expensive and time-consuming. Phase 3 trials can be difficult to design and run, especially in therapies for chronic medical conditions. Trials involving extended exposure to the drug may be started in Phase 2 of the clinical trial.

**Phase IV**

Phase 4 studies are post-approval studies and include therapeutic use type of studies. Clinical research studies Phase 4 are not mandatory for drugs and therapies approval, but can be important to optimize their use. Clinical trials Phase 4 can be used to refine the dosing recommendation of a drug or to identify rare side effects. Mortality and morbidity or epidemiological studies are other examples of clinical trial Phase 4 studies. Some Phase 4 studies have led to the finding of harmful side effects, and the discontinuation or restriction of some drugs.

**Pre-Award Procedures for The Conduct of Clinical Trials**

OGC provides administrative support for all clinical and/or basic medical research projects performed by faculty members and staff at AUB.

The set procedures are designed to ensure sound management and execution of Clinical Trial (CT) Agreements and to ensure compliance.

This section will describe the responsibilities of the Principal Investigators (PI) and the Office of Grants and Contracts (OGC) in pre-award management of clinical trials.

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I. Principal Investigator Responsibilities

PIs participating in CTs are requested to obtain approval for and submit all of the items, listed below, that forms a complete “Clinical documentation File” before any negotiation with the pharmaceutical company can be initiated at OGC.

The “Clinical Documentation File” consists of these documents:

1. The Clinical Research Protocol/and or Proposal submitted or to be submitted to the sponsor for review and evaluation.

2. OGC Proposal Transmittal & Approval Form: The proposed Clinical Trial must be approved by the Chair of the Department and the Dean/ or Dean Designee before it is sent to OGC for review and approval and to the provost for final approval. The form can be found on http://www.aub.edu.lb/ogc/Pages/forms.aspx.

3. The Draft Agreement between the sponsor and the University if available.

4. The Estimated Budget: The PI must ensure that sufficient funds are requested to cover the proposed tasks. The PI should submit a budget breakdown of the direct and indirect costs needed for the implementation of the proposed CT. Direct costs shall include costs such as investigator fees, laboratory tests, materials and supplies, cost of medication (if applicable), transportation costs, record storage fees, IRB annual renewal fees (if applicable) and other similar costs, in addition to AUB’s indirect costs of 20% applied to total budget. Usually, a cost per patient is negotiated between OGC and the Sponsor. Once the Sponsor approves the Budget it becomes an integral part of the Agreement.

For pharmaceutical initiated trials, it is the responsibility of the PI to inform the company that IRB fees should be paid directly to the IRB office prior to the CT agreement signature.

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5. **Details of the Insurance** offered by the Sponsor to cover the patient against any adverse effects that might occur during the course of the Clinical Trial.

6. **Patient Consent Forms:** The PI should make sure that the full and informed consent forms, of participating human subjects, as approved by IRB, are included.

7. **Copy of IRB Approval Letter:** All research involving human subjects conducted at AUB must be reviewed by IRB. A detailed description of the rules governing IRB functions and the responsibilities of a Principal Investigator (PI) can be found in the section entitled: "Principles and Policies" under the Faculty of Medicine Research. IRB reviews and approvals must be obtained either before the proposal is submitted or before a deadline set by the sponsoring agency. CT agreements will be not be negotiated with the sponsoring company before IRB approval is issued.

8. **Information about the Sponsor Company:** The Sponsor contact name, phone number, and e-mail address.

9. **Contract Research Organization:** If sponsor has delegated authority to a "Contract Research Organization" (CRO), to coordinate research work with AUB, OGC requests a copy of the letter of delegation, which should include the agreed-upon activities and responsibilities of the CRO. The agreement should also specify the required quality and safety program provided by the CRO on behalf of the sponsor.

10. All other Sponsor-supplied information about the proposed clinical research not detailed in (A) through (H).

**II. OGC Responsibilities**

1. **Receipt and Review of Clinical Documentation File**

   Upon receipt of the Clinical Documentation File, OGC shall review it and if approved, forwards the file to the Provost for final approval.

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To ensure the smooth administration of the planned trial, it is important to inform OGC at an early stage of discussion between the PI and Sponsor regarding a specific trial. Upon receipt of the Clinical Documentation File from the PI, OGC checks that all documents are in order and will then proceed with the agreement negotiation process with the Sponsor.

2. Review of Clinical Trial Agreements

The PI is not authorized to enter into an agreement with a Sponsor or to commit AUB into an agreement and a budget. OGC is responsible for verifying that the agreement appropriately addresses legal issues, including indemnification and patient insurance provisions and checks whether the agreement clearly defines the responsibilities of the PI and AUB, as well as that of the Sponsor. OGC also reviews and negotiates with the Sponsor, if needed, the final requested budget and payment schedule.

3. Negotiation of Clinical Trial Agreements

The Sponsor and OGC work together to ensure that arrangements are in place for the research team to access resources and support and to implement the Study. OGC and the Sponsor will negotiate an agreement, which defines responsibilities for managing, monitoring and reporting of research, as well as define the procedures to record, report and review significant developments as the Study progresses. The agreement shall also include procedures particularly those related to the safety of individuals at risk and to improve modifications to the design.

Budget Negotiation: OGC requires and will request from sponsor companies a 3 months advance payment for the time effort of research fellow coordinators or assistants and subsequently will request advances on three months basis until completion of the trial.

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AUB requests that all Clinical Trial agreements shall include the following clauses:

- **Indemnification** - AUB requests that the Sponsor always defends, indemnifies and holds harmless the PI and the University and its employees from any and all liabilities, claims, actions or suits for personal injury or death, including reasonable attorneys' fees directly arising out of or in connection with the administration or use of the Study Drug given by the PI in accordance with the Study Protocol.

- **Intellectual Property** - The Sponsor may be granted a certain range of rights to intellectual property such as copyright, made in the direct performance of the Clinical Trial protocol. However, patent rights are reviewed on a case-by-case basis depending on the type of Clinical Trial and the scope of work.

- **Publication** - Timely publication and dissemination of research/study results are important principles behind the academic freedom afforded to faculty members. OGC will only negotiate the time needed for the Sponsor to review a proposed publication ONLY to secure that none of the Sponsor's confidential information is included.

- **Insurance** - AUB usually requests that the Sponsor covers all subjects participating in a Clinical Trial for all medical costs in diagnosing and treating research-related injury.

- **Professional Ability and Research Competence** - OGC requests that in the signed agreement, the sponsor is assured that the principal investigator, his/her sub investigators and research team is trained, qualified and have the ability and professional competence to carry out the research work.

- If Sponsor has **Delegated Authority to a Contract Research organization (CRO)**, the letter of delegation must be submitted to OGC. Duties and functions of the CRO must be specified and must be included in the letter of delegation. The letter of delegation becomes an integral part of the Agreement between AUB and Sponsor (or CRO).

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• The agreement shall include the **Required Quality and Safety Program** provided by the sponsor. OGC requests that the sponsor is responsible for monitoring the contract and the quality and integrity of the research.

4. **Signature of Agreement**

Once negotiation with Sponsor is completed and the agreement is finalized and agreed upon, OGC sends the agreement to the PI for his/her final approval before signature.

Any agreement between funding company and AUB is only binding when approved and signed through the Office of Grants and Contracts. AUB's policies prohibit PIs from conducting a study before an agreement is signed by both AUB and the Sponsor, therefore, PIs must not begin clinical trial implementation until they have confirmation from OGC that the agreement has been signed.

The time required to finalize and sign on an agreement varies depending upon several factors, so PIs are encouraged to submit the Clinical Documentation File material well in advance of the anticipated study start date.

**Post Award Procedures**

OGC is responsible for all administrative and financial management of Clinical Trials, to ensure the smooth conduct of the studies, and acts as the official liaison between AUB (the PI) and the Sponsor on administrative and financial queries. OGC also monitors sponsored Clinical Trials for compliance with Sponsor terms and conditions and University policies, and handles financial and administrative queries and matters including budget modifications, budget re-allocations, no-cost extensions, renewals, and reporting.

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I. Responsibilities of the Principal Investigator (PI)

1. Clinical Trial Implementation

Upon signature of the Agreement, the PI may start the Clinical Trial implementation. The PI should abide by all clauses of the Agreement, and will be responsible for the performance of the scientific, technical, financial and administrative duties normally associated with the Clinical Trial including the submission of CRFs as required by the Sponsor. The PI is responsible for administering the trial in accordance with the signed Agreement terms and conditions and the approved clinical research protocol as well as in compliance with University policies.

2. Submission of Reports

The PI is responsible for cooperating with the Sponsor’s CRA responsible for the Study, who will have regular site visits, and is responsible for providing the sponsor agency with reports detailing the trial administration process, patient recruitment, screening failures, drug administration among other requested information as agreed with the Sponsor.

3. Budget Expenditures

The budget included in a Clinical Trial Agreement is an integral part of the Agreement, and thus PIs should adhere to the budget for needed expenditures to successfully implement the CT. The PI must ensure compliance with the budget ceiling and line items as defined in the Agreement.

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II. Responsibilities of OGC

Administrative and financial management of the trial is regularly performed to ensure that AUB and the PI are adequately compensated for in terms of resources used during the investigation, including personnel, supplies, hospital services, and administrative and indirect costs.

1. Account Set up

Upon the signature of the clinical trial Agreement, OGC opens the account (cost center) for the clinical trial under the PI's name and the PI's faculty, and requests the first payment from the Sponsor as agreed upon in the Agreement. OGC will give specific directives on the account and budget details.

If cost share is committed on the clinical trial, OGC will follow up with the PI and the Office of the Comptroller to ensure its recording, documentation and reporting.

2. Monitor Patient Recruitment and Expenditures

Throughout the duration of a Clinical Trial, OGC follows up with the PI to monitor the number of patients recruited to ensure that expenditures on account are charged in accordance with the approved budget. This will ensure expenditures are made in line with the actual number of recruited patients.

3. Relations with Sponsor Agencies

OGC develops and maintains positive and effective contacts with Sponsor and the Sponsors' CRAs, and handles correspondence with them on various administrative aspects of the Clinical Trial. It is the Sponsor's responsibility to ensure the reliability and validity of the research data and the statistical and ethical correctness of the results through site audits, inspections and investigator's reports.

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4. Follow-up and Submission of Reports

OGC will follow-up and ensure the timely submission of final report on Clinical Trials to Sponsors. Reports submitted to sponsors are made, while safeguarding and protecting confidentiality and excluding any personal identifiable information.

Signed & Approved by:

Dr. Fadia Homeidan
Director Office of Grants & Contracts

Dr. Muhamad Harajli
Provost

Signature:

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