A Primer on Clinical Trials Issues

Aim

To give background to the CRIT team on the fundamentals of clinical trials practice and relevant regulations.

A Note on Sources

General information in this primer comes primarily from three sources: *Food and Drug Law,* 4th ed. (ed. Hutt, Merrill, Grossman); *A Practical Guide to FDA's Food and Drug Law and Regulation*, 5th ed. (ed. Piña and Pines); and materials from the FDA's Clinical Investigator Training Course (http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/SpotlightonCPIProjects/ucm201459.htm).

When other texts are heavily referenced, a source list will appear at the end of the section.

Contents

Clinical Trials 101

A clinical trial can be defined as a research study in which human volunteers are prospectively assigned by an investigator to interventions based on a pre-specified protocol, then evaluated for effects on biomedical or health outcomes.

Phases

Drugs/Biologics

Phase 0	*"Very limited human exposure" x 7 days* An new exploratory phase (designated by FDA in 2005), designed to confirm a product's mechanism of action in humans, provide preliminary pharmacokinetics information, explore biodistribution, and allow companies to select the most promising lead product from a class.
Phase 1	**Toxicity and Dosage** *20-80 healthy subjects, <1 year* Generally, the first introduction of an investigational medical product into humans (excepting Phase 0). Gathers information on pharmacokinetics (what the body does to the drug - absorption, distribution, metabolism, excretion) of a drug and establishes a safe dose range for the drug, including maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs).
Phase 2	**Safety and Efficacy** *100-300 subjects, 2-3 years* Controlled clinical studies to detect major adverse reactions and obtain preliminary data on efficacy, which provides planning information for Phase III.
Phase 3	**Efficacy** *1000-3000 subjects, several years* Clinical studies to gather the additional data on efficacy and safety necessary to determine the overall benefit-risk ratio for the drug.
Phase 4	*1000s of subjects x unrestricted* Postmarketing studies, which obtain long-term, large-scale information on morbidity/mortality and the rate of adverse events.

Devices

Feasibility	**Basic Safety** *10-40 patients* Often required by the FDA prior to a pivotal study, focused on the safety on the device and whether the potential benefit justifies risk of continued study. Design is generally not statistically driven; not intended to be primary support on marketing application.

Pivotal	**Safety and Efficacy** Intended as the primary clinical support on a marketing application, with a design that is statistically driven.

Trial Design

Designs

Randomized Controlled Trial (RCT)	Participants are randomly assigned to receive one of multiple interventions. This is considered to be the "gold standard" for generating clinical evidence because randomization, blinding, and controls are intended to minimize bias. However, differences in randomization and blinding procedures, and the use of different kinds of controls, may influence the internal validity of the study.
Parallel	Participants are assigned to treatment and control groups, which run simultaneously.
Crossover	Participants are assigned to treatment and control groups, then "cross-over" to the opposite arm. All receive treatment but non-simultaneously.
Randomized Withdrawal	All participants are started on the treatment, then randomized to continue receiving the treatment, or switching to placebo (withdrawal).
Factorial Design	The effect of more than one treatment at a time is tested by crossing different doses of the treatments with each other.
Adaptive Design	Participants are assigned to a treatment, but patient groups and characteristics of the treatment may be modified throughout the trial according to a pre-determined protocol.

Controls

Active	The treatment is compared with a known effective therapy.
Placebo	The treatment is compared with an inactive preparation designed to resemble the test treatment.
Dose-Response	At least two doses of the treatment are compared, with or without a placebo and/or active control group.
No Treatment Concurrent	The treatment is compared with the natural history of the disease.
Historical	The treatment is compared with a historical group with well-documented natural history (sometimes the participant themselves). This is considered less rigorous than the above designs because of issues with selection bias, and usually reserved for diseases with high mortality (e.g. cancer), or for which the treatment effect is apparent (e.g. anesthetics).

Endpoints

Primary Endpoint	The endpoint which is designed to capture the treatment's therapeutic effect, and for which the trial is powered and randomization conducted. This is ideally a clinical endpoint, but may be a well-characterized surrogate endpoint.
Secondary Endpoint	Other endpoints which may capture information about the treatment's effects but are analyzed post-hoc. The trial may or may not be powered to support these analyses.
Clinical Endpoints	A direct measure of effect on how a participant "feels, functions, or survives." These include endpoints like survival, improvement in symptoms, or decreased risk of developing a complication.
Surrogate Endpoints	A biological or laboratory measurement that does not directly measure clinical outcomes, but is intended to predict them. These include endpoints like LDL levels, blood pressure, or HbA1c levels. These are faster and easier to study (and therefore cheaper). However, even well-characterized surrogates have been found to inadequately predict clinical outcomes.
Composite Endpoint	A single measure of effect measuring a combination of individual endpoints. A common example is MACE (major adverse cardiac events), including cardiovascular death, non-fatal MI, and non-fatal stroke. Although composites may be useful in highlighting wide-ranging benefits that may otherwise appear infrequent as individual events, they may also use positive results on less meaningful components to mask ambivalent or negative results on more meaningful components.

Analysis

Superiority	Analysis tests the hypothesis that the treatment shows superiority to a control, showing that the treatment has the intended effect.
Non-Inferiority	Analysis tests the hypothesis that the treatment is not worse than a known active comparator by a defined amount (the "non-inferiority margin"). This does not demonstrate "equivalence" to the alternative treatment, only some measurable effect within the margin. A finding of non-inferiority can also be problematic because it may imply either that both treatments studied were effective, or that neither was effective.
Intent-To-Treat (ITT)	Analysis is performed according to which treatment was initially assigned to participants, regardless of later violations, dropouts, and crossovers. These attempt to provide an estimate of real-world effectiveness (where dropouts and non-adherence are common),

	and minimize false positives; however, there will be more heterogeneity introduced.
Per-Protocol	Analysis is limited to those patients who adhere completely to the clinical trial protocol. This is subject to selection bias.
As-Treated	Analysis is performed according to which treatment participants received, regardless of which treatment they were initially assigned to. This is subject to confounding.

Ethics

Informed Consent

Informed consent may be defined as the act of the provider disclosing information to the patient/participant consisting of the relevant information required to make a voluntary choice to accept or refuse treatment/participation. Informed consent has three components:

1. Threshold – including the ability to give consent (competence) and the circumstances surrounding consent (e.g. diversion, coercion)
2. Information – what the participant needs to know about the study, including but not limited to:
    a. The nature of the study/treatment/decision
    b. Alternatives (i.e. in this case, the option of *not* participating in the trial)
    c. Risks, benefits, and alternatives
    d. Assessment of patient understanding
3. Agreement

Most states have legal/legislative precedents that determine the required standard for informed consent in terms of what information is disclosed.

Monitoring

Clinical trial monitoring and oversight takes place at several levels to ensure that clinical trials are conducted ethically and produce valid results by reducing bias.

Institutional Review Board (IRB)

Institutional Review Boards (IRB) are formally designated groups whose purpose it is to review and monitor biomedical research, with the authority to approve, disapprove, or request modification of research protocols. The purpose of these groups is to protect the rights and welfare of participants in the research, and assure that risks are minimized and reasonable in relation to anticipated benefits.

IRBs participate in review of the study protocol and related materials prior to approval of the trial, and are responsible for the continued acceptability of the trial at a particular study site as the trial is ongoing.

Data Monitoring Committee (DMC)

Data Monitoring Committees (DMC), sometimes called Data Safety Monitoring Boards (DSMB), are independent committees that review accumulating data from ongoing clinical trials on a regular basis. These bodies are responsible for advising the sponsor as to the continuing safety of trial participants and the continued validity and merit to the entire trial.

DMCs have more access to data than an IRB during the trial, including data concerning enrollment, safety, and achievement of endpoints, as well as analyses of data quality and trial conduct. Unlike an IRB, the recommendations given by the DMC apply to the entire trial and are not site-specific. In order to maintain independence, DMC members are separate from the investigators and not involved in the final analysis. Some sponsors may also appoint a clinical trial steering committee composed of investigators, independent experts, and sponsor representatives, to which the DMC reports, rather than reporting to the sponsor directly.

Current FDA regulations impose no requirements for the use of DMCs in clinical trials except in emergency settings where informed consent is waived; however, a number of government agencies sponsoring research require the use of DMCs in certain trials.

Adjudication Committee

An independent endpoint assessment/adjudication committee, sometimes called a clinical events committee, may be called to review endpoints identified by investigators to determine whether they meet protocol criteria. The adjudication committee is considered particularly valuable for reducing bias when endpoints are subjective and/or complex, because it is blinded to study arm assignment during the process of reviewing laboratory data, imaging data, autopsy reports, among other types of data.

Site/Clinical Monitoring

The sponsor conducts site monitoring of the clinical trial to ensure adherence to the pre-specified protocol among other quality control measures. Monitors are blinded to study arm assignment.

Individual Monitoring

Individual study investigators monitor individual adverse event reports as they occur, adjusting the treatment as necessary and reporting such events to the sponsor.

Sources:

- FDA. *Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees*. 2006. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127073.pdf

Regulation

Drugs

The FDA was first given regulatory oversight over drugs with the Pure Food and Drugs Act of 1906, which prohibited the interstate trade of misbranded drugs. Modern standards requiring evidence of safety and effectiveness prior to the approval of new drugs were established by the Food, Drug & Cosmetics Act (FDCA) of 1939 and the Kefauver-Harris Amendments to FDCA, respectively.

The Kefauver-Harris Amendments (1962) set a standard for the quality of evidence supporting such claims, requiring "substantial evidence" of effectiveness supported by "adequate and well-controlled investigations." (Note: the agency has interpreted this as requiring more than one controlled trial in the past, although this was modified by FDAMA in 1997 to allow one study in some cases.) This effect must be "clinically meaningful" (Warner-Lambert v. Heckler 1986), although there is no requirement for relative efficacy (i.e. superiority compared to other existing drugs on the market).

FDA Review

Investigational New Drug Application (IND)

The IND is the regulatory filing that governs whether sponsors are permitted to ship the investigational drug or biologic across state lines and to initiate a clinical trial. The filing contains information about the investigational drug as well as the proposed protocol to evaluate it. The IND process is designed to ensure that studies are safe and ethical, likely to produce meaningful results, and have adequate safety monitoring and reporting safeguards in place. If the FDA does not object to the IND within 30 days, it is automatically permitted and clinical trials can begin.

New Drug Application

The NDA is the regulatory filing required to place the investigational drug on the market. This filing must include all data from non-clinical studies (including chemistry, in vitro, and animal studies), as well as efficacy and safety results from clinical studies performed under the IND.

Special Designations/Pathways

There are several special designations/pathways that sponsors may seek from the FDA in order to gain special consultations or expedited reviews:

Program	Reference	Qualifying Criteria	Features
Orphan Drug	21 CFR 316 via Orphan Drug Act of 1982.	Drugs intended to treat a rare disease (prevalence <200,000 patients in the US).	Submit prior to BLA, NDA, or supplement. Qualifies for development incentives including tax credits for clinical testing, waiver of the

			prescription drug user fee, and 7-year market exclusivity; does not change regulatory standards.
Accelerated Approval	21 CFR 314 Subpart H, 21 CFR 601 Subpart E, Section 506(c) of FD&C, as amended by FDASIA 2012.	Drugs intended to treat a serious condition AND provide a meaningful advantage over available therapies AND demonstrate an effect on a surrogate endpoint.	Discuss throughout development process. Enables approval on basis of surrogate or intermediate endpoint, but requires post-marketing trial to prove effect of drug on subsequent clinical endpoint.
Priority Review	PDUFA 1992	Drugs intended to treat a serious condition AND provide a significant improvement in safety or effectiveness, OR a supplement proposing a labeling change following a pediatric study, OR qualified infectious disease products, OR products submitted with a priority review voucher.	Submit with BLA, NDA, or supplement. Enables shorter clock for application review (6 months vs. 10 months).
Fast Track	Section 506(b) of FD&C, as added and amended by FDAMA 1997 and FDASIA 2012.	Drugs intended to treat a serious condition AND data that demonstrate the potential to address unmet medical need, OR qualified infectious disease products.	Submit with IND or soon after. Enables actions to expedite development and rolling review.
Breakthrough Therapy	Section 506(a) of FD&C, as added by FDASIA 2012.	Drugs intended to treat a serious condition AND preliminary clinical evidence of substantial improvement on a "clinically-significant endpoint" over available therapies	Submit with IND or soon after. Enables intensive guidance on efficient development, actions to expedite review, and rolling review.

Biologics

The federal government was given regulatory oversight over biologics under the Biologics Control Act of 1902, which marked the first time that a class of products required premarket approval. As opposed to drugs, which are generally synthetic small molecules, biologics are complex and typically derived from living organisms. These can include products such as vaccines, cellular and tissue products, blood products, and gene therapies.

FDA Review

Investigational New Drug Application (IND)
Biologics License Application (BLA)
Equivalent to the NDA for drugs; see description above.

Devices

Devices are defined by Section 201(h) of the FD&C as any product that does not achieve its principle intended purpose by chemical action or by being metabolized. The FDA was given regulatory oversight over the safety and effectiveness of medical devices with the Medical Device Amendments in 1976. Devices are grouped into three classes by risk level:

- **Class I** represents low-risk devices (e.g. cotton swabs), typically exempt from any kind of pre-market submission.
- **Class II** represents intermediate-risk devices (e.g. lab tests, most devices), which require Premarket Notification under the 510(k) pathway.
- **Class III** represents high-risk devices (e.g. defibrillators), which require a full Premarket Application (PMA) and approval by the FDA before they can be marketed.

FDA Review

Investigational Device Exemption (IDE)
The IDE functions as the equivalent of the IND for drugs and biologics, and is a regulatory submission that permits clinical investigation of high-risk devices (including in vitro diagnostics) while ensuring the protection of human subjects in those clinical trials. Similarly to an IND, the FDA has 30 days to review the IDE before it is automatically approved.

These device trials are typically smaller than drug trials, less likely to be randomized or blinded, and more likely to be subject to differences in physician technique. They may be in the form of a small feasibility study, which is required by the FDA to assess basic safety signals, followed by a pivotal study to demonstrate a "reasonable assurance of safety and effectiveness" in order to support a marketing application.

There are three pathways by which devices may be cleared or approved if they require premarket submission (Class II or Class III devices):

510(k)
The 510(k) pathway requires demonstration of "substantial equivalence" to a predicate device on the market – usually involving only confirmatory performance testing (only 10-15% require clinical data). These have a 90-day review cycle and are cleared, not "approved."

De Novo
The De Novo pathway exists to approve devices for which a predicate device does not exist. Entirely new devices are typically automatically classified as Class III devices. However, if a device is filed through the De Novo pathway, the FDA may choose to reclassify it as Class I or II and clear it for immediate marketing, at which point the device would serve as the new predicate device for similar products.

Premarket Approval (PMA)
The PMA pathway requires demonstration of safety and effectiveness to approve Class III devices and new devices where risk cannot be mitigated by special controls. This evidence is usually in the form of a single pivotal trial. These have a 120-day review cycle and additional FDA oversight before approval.

Special Designations/Pathways
A **Humanitarian Device Exemption (HDE)** may be granted to a medical device, exempting it from meeting effectiveness requirements for approval. Devices eligible for HDEs must:

- treat a disease/condition affecting fewer than 4,000 individuals per year;
- not be available otherwise, or have no comparable device to treat that disease;
- not expose a patient to significant risk;
- have benefits that outweigh the risks.

Sources:

- FDA. *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*. 2014. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf.

Other Issues
Special Populations
Certain statutes have provisions to encourage the study of medical products in pediatric populations.

- The **FDA Modernization Act of 1997 (FDAMA)** incentivized clinical trials conducted in pediatric populations, granting an additional 6 months of exclusivity to the manufacturer's entire product line containing the active pharmaceutical ingredient tested.
- The **Best Pharmaceuticals for Children Act of 2002 (BPCA)** granted priority review status for all supplements contingent on a pediatric study report. This was made permanent by the **FDA Safety and Innovation Act of 2012 (FDASIA).**
- The **Pediatric Research Equity Act of 2003 (PREA)** required that applications for all new drugs and biologics include a pediatric assessment, including an evaluation of efficacy/safety within all relevant pediatric subpopulations, as well

as dosing and administration information. This requirement may in certain circumstances be deferred or waived (such as if the necessary studies are impossible/impractical, there is existing evidence that the product would be unsafe for children, or if the product is not expected to be used by children). The FDA also gained the authority to require a pediatric assessment of existing drugs on the market. This was made permanent by FDASIA in 2012.
- The **FDA Amendments Act of 2007 (FDAAA)** incentivizing medical device manufacturers to design products for pediatric populations.

Postmarket Oversight

The FDA's oversight of medical products continues after premarket approval. As a condition of approval, it has the power to mandate postmarket studies to continue the evaluation of a medical product's safety and/or effectiveness.

- In 2007, **FDAAA** expanded regulatory authority to evaluate postmarket safety of drugs, establishing a new program for imposing risk evaluation and mitigation strategies (REMS), permitting postmarket requirements rather than voluntary commitments as a condition for approval, and establishing the Sentinel Initiative for proactive monitoring of the safety of medical products.
- The **Safe Medical Devices Act of 1990 (SMDA)** enabled the FDA to order postmarket surveillance (PMS) requirements as a condition of clearance/approval for Class II and Class III devices. This was further reinforced by the **Medical Device Amendments of 1992 (MDA)**, which made manufacturers subject to criminal and civil penalties for failure to comply, and the relevant medical products subject to seizure.

Outside of formal postmarket studies, the FDA requires that any serious and unexpected adverse events for approved medical products be reported to the FDA within 15 days of the sponsor's receipt of information, and that any other adverse events be reported to the FDA quarterly or annually afterward.

In response to the information collected through postmarket studies or surveillance, the FDA has the power to compel a sponsor to make safety-related changes to drug labeling after approval. If the FDA deems there to be a serious risk, it may notify the sponsor, which has 30 days to issue a labeling supplement reflecting safety information or challenge the request. The FDA may also invoke its authority to withdraw medical products, although this occurs rarely.

Supplements

Changes to approved drugs and biologics can be made through supplements to the NDA, which may or may not require prior approval by the FDA. These can include:

- changes in labeling, including **efficacy supplements** that describe new indications, dosing regimens, or populations (requiring prior approval);

- changes in manufacturing that with high potential to affect the drug's action (requiring prior approval);
- changes with moderate potential to affect the drug's performance ("changes being effected" without requiring prior approval);
- changes unlikely to affect the drug's performance, including minor changes in labeling, changes in inactive ingredients that impact the product's color only, and changes in container design that exclude the closure system (do not actually require a supplement, only an annual summary of changes sent to the FDA).

Changes to approved devices can similarly be made through PMA supplements, include those for new indications or changes in manufacturing.

Generics/Biosimilars

The Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch-Waxman Act, streamlined generic drug approvals by allowing the FDA to approve generic drugs on the basis of "bioequivalence" studies rather than clinical trials – lowering the barrier to market entry by reducing the time and cost of development, and allowing generic manufacturers to pass on the savings to consumers by offering the generic product at a lower price. Applications for generic approval on the basis of bioequivalence are known as **Abbreviated New Drug Applications (ANDA).**

In return for expediting generic approval, the Hatch-Waxman Act granted brand-name manufacturers an extended patent term to cover for development and FDA review times, as well as 5 years of market exclusivity before the FDA approves an ANDA for new products, and 3 years of exclusivity for new uses of previously-approved products (such as those requiring a new full NDA or efficacy supplement).

Within the Patient Protection and Affordable Care Act of 2010 (ACA), the Biologics Price Competition and Innovation Act (BPCIA) similarly created an abbreviated licensure pathway for biologic products deemed to be "biosimilar" or "interchangeable" with an existing licensed biologic product. Unlike for generics, however, biosimilars and interchangeable products must demonstrate both analytic similarity and clinical similarity, and must be submitted through the full BLA process. This licensure pathway is under active development as the FDA continues to release guidance on definitions and requirements for meeting "biosimilar" or "interchangeable" status.

Source:

- FDA. *FDA's Overview of the Regulatory Guidance for the Development and Approval of Biosimilar Products in the US*. 2016. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM428732.pdf.