New Initiatives to Promote Clinical Research
Clinical Research is a Priority at Upstate Medical University

- Resources
  - Clinical Research Unit
  - Clinical Trials Office
  - Availability of inpatient beds for Phase I trials
Clinical Research Unit

- Located in the IHP
- Staffed by experienced research nurses
  - Can be trained to perform study specific evaluations
- 12 beds
- Charges are very modest
- The CRU is underutilized and wants your trials
Clinical Trials Office

Clinical Trials Officer- Jennifer Rudes

Services

- Budget evaluation and negotiation
- Access to newly developed Hospital Research Charge Master List

NEW SERVICES

- Starting April 15, the CTO will have the services of an experienced CRA who will prepare IRB submissions
  - $1500 charge, included in Clinical Trials Agreement
We are recruiting a nurse coordinator who will be available to work on trials for any funded investigator without access to a trained coordinator.

Coordinator time will be charged against the trials on which he/she works.

Plan is to expand this service as needed.
Principal Investigator: The Responsibilities Behind the Title

Jeremy M. Shefner, MD, PhD
The PI fills many roles

- Initial decisions
  - is study worth doing?
  - Does the budget make sense?
  - Do I have the patients?
  - Do I have the staff resources?
  - Where will I do the study?
  - Do I have the personal resources?
Is the study worth doing?

- Is there a clinical need?
- Does study fit into accepted drug development paradigm?
  - I.e., is this a research study or a marketing study?
- Will the study answer an important clinical question?
Is the Budget Adequate?

- Is funding for personnel adequate?
- Funding for laboratory procedures or tests
  - CTO can help with research charges, can negotiate on your behalf with sponsor
  - Hospital has established a research charge master list, with research charges set at 45%
- Studies need to be paid for
Budgeting for your time

- Being a site investigator takes time - how to pay for it?
  - Will vary department to department
    - Some departments allocated monetary credit for research expenditures
    - The Research Foundation can be invoiced for physician time, according to site budget
Do I have the patients?

- Recruitment
  - From existing patients
  - From new referrals
  - From community
Recruitment Issues

- The prime determinant is investigator passion

NEALS

- 92 member sites, all committed to ALS research, all pay annual membership fee
  - Recruitment rates from 5/month- .2/month within same study
  - At SUNY, 37% of all patients seen enter study

Recruitment outside of personal patient base

- Fliers, talks, interviews on radio, etc.
- Need to be cleared with IRB
Resources

- Staff
  - Clinical
    - Research nurse, clinical evaluator
  - Coordinator
  - For new investigators, resources will be available from CTO

- Space
  - Consider the CRU!!!
  - Phase 1 studies require inpatient admissions
Investigator’s Agreements

- Provide evidence of staff qualifications
  - CV for all personnel
  - 1572
- Know the study drug
- Understand and comply with the protocol, GCP and applicable regulatory requirements
- Allow monitoring, auditing & regulatory inspections
- Maintain adequate records for each subject involved in the study
Informed Consent

- A primary duty of the PI
  - Process for meaningful exchange of study information between the investigator and subject
  - Must be signed by all parties before any study procedures begin
  - Documentation in source should reflect that the subject met all eligibility criteria
  - Changes to the I/C need to be signed by active study participants – all changes must be discussed in detail with study subjects
Ongoing Involvement

- PI must demonstrate involvement with every patient visit
  - Personal attendance at visit
  - Documentation of communication with study staff if not personally present
  - Must demonstrate involvement in decisions regarding AE management, stopping medication, withdrawing subject from study
- This is a major issue when studies are audited
Adequate Involvement

- Need active participation of Investigators
  - Although investigator does not have to perform all study procedures, should be informed of status, AEs of all subjects
  - Meet with monitor(s)
  - Keep staff informed about all study related matters
  - Know protocol and amendments
Compliance With Protocol

- The principal investigator’s signature on the protocol and all amendments confirms agreement
- Any deviation from the protocol must be agreed to by Sponsor
- All protocol deviations must be adequately documented
Ongoing Involvement

- PI is responsible for all data entered onto CRFs
- PI is responsible for up to date maintenance of regulatory binder
- PI is responsible for all ongoing consent issues
  - New consent required with every protocol amendment
Regulations in Clinical Trials:
Communication with IRB

- Written documentation from IRB that “it is organized and operating according to GCP…”
- Do not start the trial without written IRB approval
- This includes approval for protocol and all related documents including informed consent and advertisements
- Do not implement amendments before written IRB approval
Communication with IRB

As trial progresses, provide IRB with:

- Updated Investigator Brochure & safety information
- Amendments
- Safety Reports
- Site Specific SAEs
- Revised Consents
- Protocol violations violations-if required
- Annual reports
Source Documentation

- Original records should be separate from the CRF workbook
- Should document the existence of and the qualification for enrollment of each subject
- Should be available to support the accuracy & completeness of data reported on the eCRF or CRF
Drug Accountability

- Provide adequate storage conditions
- Assure medication dispensed according to Protocol
- Drug records must be dated/signed by the Principal Investigator or designee
- Records of delivery of study medication to site
  - Individual dispensing records
  - Records of return or destruction of unused medication
Maintenance of Records

- Maintain trial documents (source docs/CRFs) securely for the time period required by regulations
Joint sponsor/site responsibilities

- Investigator may delegate specific roles to study staff, but still retains ultimate responsibility for study conduct.
- Sponsor also delegates responsibilities to site, but is ultimately responsible to FDA.
Regulatory Submissions and Maintenance

- Investigational New Drug (IND) Application
- Clinical Trial Application
- IRB Submission
- Review of GCP Responsibilities
IND Application Process

- FDA Definition
- IND vs. non-IND study
- Pre-IND Meeting
- IND Content and Format
- IND Submission and Review
An Investigational New Drug (IND) application is a request for FDA authorization to administer an investigational drug to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug that is not the subject of an approved new drug application (NDA).
In general a study requires an IND if it is intended to support a new:
- Drug (or biologic)
- Indication (or population)
- Route of administration or dosage level

IND exemption can be requested if:
- Study drug is lawfully marketed in US
- Study not intended to be reported to FDA as well-controlled study for label extension
- Study not to involve dosage, route of administration, patient population or other factor that significantly increases risk
Non-IND Studies

- Must have IRB review and approval
- Study must be conducted in accordance with GCP guidelines
- System for safety reporting needs to be clearly defined prior to study start
Protocol Amendments

- Protocol amendments can be implemented after submission to FDA for review and IRB approval (good idea to get FDA feedback if changes are major or could impact patient safety)

- Types of Protocol Amendments
  - New protocol
  - Protocol changes that could significantly effect safety, scope of investigation or scientific quality of study
    - Submit list of changes and rationale for each
  - New investigator: FDA must be notified within 30 days of adding new investigator (submit 1572 and CVs)
Types of Information Amendments:

- New toxicology, chemistry or other technical information should be submitted as it becomes available
- Notification by the sponsor that they are terminating the clinical investigation
ICH GCP: Definitions

- **Adverse Event (AE):** Any untoward medical occurrence, regardless of causality

- **Serious Adverse Event (SAE):** Any untoward medical occurrence that at any dose is; fatal, life threatening, requires or prolongs hospitalization, results in permanent or significant disability/ incapacity, or a congenital anomaly/ birth defect

- **SAEs requiring expedited reporting:** Any SAE that is both serious and unexpected
Safety

- Sponsor must notify FDA by phone or fax, of any unexpected fatal or life-threatening experiences associated with the use of the investigational drug within 7 days of initial notification.
- Sponsor must notify FDA of any adverse event associated with the drug that is both serious and unexpected, and any finding in lab animals that suggest significant risk for human subjects, within 15 days of initial notification.
- Sponsor should further investigate each report and submit follow up information as it becomes available.
- It is the responsibility of the site to submit any SAEs to local IRBs.
Safety at the site level

- Serious AEs must be reported to sponsor within 24 hours
- Follow up reports as soon as possible
- Irb notification should also occur

-The Northeast ALS Consortium-
Withdrawal of IND

- Sponsor can withdraw an IND at anytime
- If IND is withdrawn due to a safety concern, the sponsor must inform the FDA, participating investigators, IRBs, and inform them of the reasons for such withdrawal
ICH GCP: Definitions

**Sponsor-Investigator:** An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.
ICH GCP: Sponsor/Investigator Responsibilities

**Monitoring**

- Ensures that trial data are accurate, complete and verifiable
- Ensures trial conducted in compliance with protocol, GCP and other applicable regulatory requirements
- Investigator must make him/herself available, provide necessary resources for efficient monitoring.
ICH GCP: Sponsor/Investigator Responsibilities

- **Audit**
  - Sponsor selects independent, qualified auditors to evaluate trial conduct and compliance
  - Notice is given to sites
  - Investigator must make all data available to auditor, be available for consultation as well

- **Noncompliance**
  - It is the sponsor responsibility to act quickly in situations of noncompliance
  - Sponsor may terminate investigator’s participation in cases of persistent noncompliance
Clinical trials are partnerships between sponsor, local review boards, site investigators, and staff.

Attention to detail and close adherence to study procedures are essential to success.

At the site level, success or failure of a trial is in the hands of the investigator.

When done with sufficient resources and training, clinical trials can be rewarding experiences for investigators and patients.