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What is an Academic Research Organization and How to Get Organized to Conduct RCTs

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Phases in Drug Development

- Phase 1: Feasibility, Tolerability, PK, PD
- Phase 2: Safety
  - Identify safe dose of drug
  - Evaluate efficacy event rates to power Phase 3
  - Predict probability of success in Phase 3 by studying relationship of surrogate endpoints to outcomes
- Phase 3: Pivotal Efficacy Trial

Drug Development

- Overarching Strategy
  - What disease(s) does the drug potentially work in? (STEMI vs NSTEMI vs UA vs stable CAD etc)
  - How many patients have that disease
  - What is the incidence of adverse outcomes at different timepoints?
  - How modifiable are those adverse outcomes
  - Can you identify patients at a higher risk of MODIFIABLE adverse outcomes
  - Very different considerations for IV acute therapy vs PO chronic therapy

Pre-Clinical Issues

- Must drug be refrigerated? (Can it be outside central pharmacy like in ER or cath lab?)
- How long is the drug stable for? How often will drug need to be supplied at sites.
- Can you redistribute it to sites that are not enrolling?
- Vigorously shake to reconstitute (careful, some drugs break down) or gentle swirl?
- How hard is it to make a matching placebo (is it yellow & foamy like Apo A, will you need to create yellow tubing to blind)
- Can it be infused in the same line with other drugs without crystalizing? (Heparin crystalized rPA)
- What is its pH? How do you buffer it? (buffer IC eptifibatide with blood)
- Can you inject drug in a coronary artery (do dog or pig studies in each artery)
- Can it be given PO, SQ, IV, by patch or inhaled? Good to plan pharmacokinetic studies around this

Phase 1

- Is the drug tolerated
- Phase 1A Healthy volunteer PK (drug levels) and PD data (impact on biomarkers of disease activity)
- Phase 1B may involve patients with the disease
- Dose escalation study in patients with the disease (increase dose after q 6-10 patients), halt between doses to assess safety by DSMB & FDA

ARO Role in Phase 1

- Write protocol (100 to 200 page document)
- Design statistical analysis plan (SAP)
- Go to FDA and represent sponsor in presenting protocol and investigational plan
- Sometimes hold the IND and submit all regulatory correspondence to the FDA
- Write informed consent form
- Create case report forms
- Report Serious Adverse Events to FDA
- Design database

Identify Sites & Assess Quality / Timelines with Feasibility Questionnaire

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- Use Survey Monkey to design questionnaire & store site responses
- What trials have you done in this space before?
- How many patients does your site see each month with this disease?
- How many days a week does your site have nurses screening? 5 vs 7 days/week, 9 to 5 vs 24 hours per day screening?
- How many other trials are you doing? Are you doing competing trials?
- How many patients are there in your clinic that could be enrolled right away (lipid trials)
- Can your site collect blood night and day for PK/PD? Do you have freezers with appropriate QA process to store samples?
- Can site assess surrogate endpoint: high end imaging like MRI, PET, platelet function testing, intracoronary pharmacotherapy etc.
- How long does it take your IRB to approve studies or do you use a central IRB?
- Can the contract be negotiated at the same time as the IRB is reviewing the protocol or must the protocol be approved first?

Constituting a Data Safety Monitoring Board

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- Unsung heroes of clinical trials
- Want an experienced DSMB (elder statesmen, former or active trialists, FDA/regulatory experience helpful, experienced statisticians)
- DSMB reports to you as the study chairman, not to the sponsor
- Must indemnify them against lawsuits with guarantee of independent counsel (not provided by sponsor since sponsor / shareholders may sue them)
- Must have no financial or intellectual conflicts of interest

Constituting a Data Safety Monitoring Board

- ARO must prepare 20-30 page charter describing activities:
  - Qualifications of and number of individuals (odd number for voting purposes)
  - Firewall of independent unblinded statistician who is not connected to the study
  - Frequency of meeting (not quarterly but after X no of enrolled patients, more frequent assessment by the chair, after each ICH or stent thrombosis by chair)
  - Define endpoints of particular interest (ICH, stent thrombosis, death)
  - Stopping rules; balance of safety and efficacy before stopping a trial, sequential probability testing for infrequent catastrophic endpoints
  - Lines of communication
  - Written documentation you must receive from them & timeline
  - Archiving of information
  - Procedure if conflict of interest arises
- DSMB Should review protocol and SAP before the trial begins & provide feedback

Getting The Phase 1 Trial Up and Running

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- Track IRB and contract execution
- Develop and negotiate budget with each site, may vary by country
- Collect confidential disclosure agreement
- Create study aids (when to draw bloods, how to do angio or MRI)
- Develop screening tools: paper vs an app
- Create FedEx shipping accounts
- Register trial at www.clinicaltrials.gov website
- Conduct start up meeting
- Write design paper describing study

Randomization

- Two general methods to randomize:
  - Envelope randomization: You print out the code and put it in an envelope
  - Interactive voice response system: IVRS is a computerized system that you use to call into to randomize the patient
    - Assures inclusion / exclusion criteria met
    - Linked to drug re-supply chain
    - You must review all of the code
- Sites/countries have different practice patterns so at each site randomization is done in blocks of say 6 (e.g. you would not want all the patients in one strategy treated at one site)

Data Entry

- Data entry system must be independently audited and validated as being CFR (Code of Federal Regulations) 21 part 11 compliant
- Key card entry to track who enters room and when they enter room
- Security camera
- Computer not connected to internet
- Dual authentication required: you must have password to log in but must also wear a device that the computer recognizes to verify your identity
- If you walk away from the computer it shuts down

Data Entry

- Atomic clock on computer, time cannot be changed (you can't go back in time and change data)
- Audit trail required to know who entered what on what date
- Dual data entry: two people enter data, entries must match exactly
- Range checks to clean data on the fly (every data point must fit within a range of valid entries)
- Backed up locally in case of fire, backed up remotely in case of local disaster such as hurricane, earthquake, natural disaster.

Once The Phase 1 Trial Up and Running

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- Report Serious Adverse Events (SAEs) to FDA
- Make sure there are no protocol violations
- Track enrollment
- Send weekly emails
- Conduct investigator meetings at AHA, ESC, ACC, TCT etc.
- Communicate with DSMB
- Weekly operational meetings with sponsor

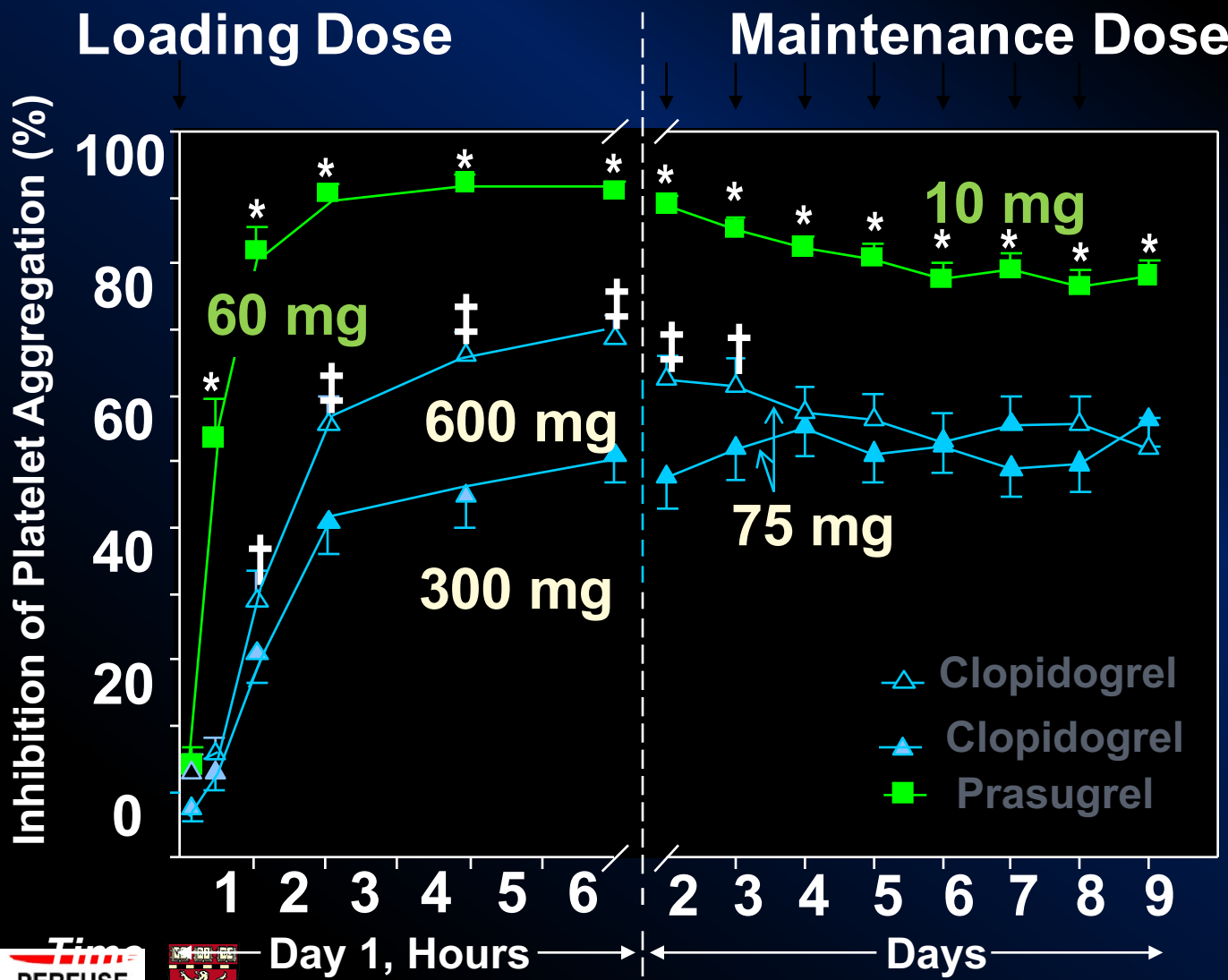
Once The Phase 1 Trial is Complete

- Clean the database
- Lock database once pre-defined criteria met
- Analyze data
- Present data
- Create Clinical Study Report (200-300 page single spaced document) for FDA
- Update www.clinicaltrialresults.gov

What Are You Looking for in Phase 1

- PK/PD dose response curve
- Rule out dose dependent rise in LFTs, QTc prolongation, immune responses (allergic and antidrug antibody response, characterize them as either neutralizing or non-neutralizing) Cr rise, neutropenia, thrombocytopenia
- Collect SAEs to detect unforeseen side effects like myositis

Inhibition of Platelet Aggregation (Mean ± SEM, 20 μM ADP)



*P<.001 vs Clop 300 mg 600 mg and 75 mg

†P <.05 vs Clop 300 mg/75 mg

‡P <.001 vs Clop 300 mg/75 mg

ADP=adenosine diphosphate
Clop=clopidogrel
Pras=prasugrel

The 600 mg LD of clopidogrel is an off-label dosage

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Jakubowski et al. Cardiovasc Drug Rev 2007;25:357-374.