

Multi-Site Clinical Trials In The Community

Models and Methods:
What Works,
What Doesn't
and Why

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Why Do Research ?

Strategically Critical

- May be the best care for the patient
- Physician engagement & retention
- Patient retention and local marketing
- Proactive role in drug development
- Exposure for the group: “fame factor”

Revenue ?

Key Insights

- High fixed costs, but low capital investment.

Fixed costs are staff salaries and benefits.




Capacity of research operations is poorly distributed and unbalanced

Potential areas of excess capacity coexist with capacity constrained operations at both central and local level.

Enhancing the information technology supporting research.

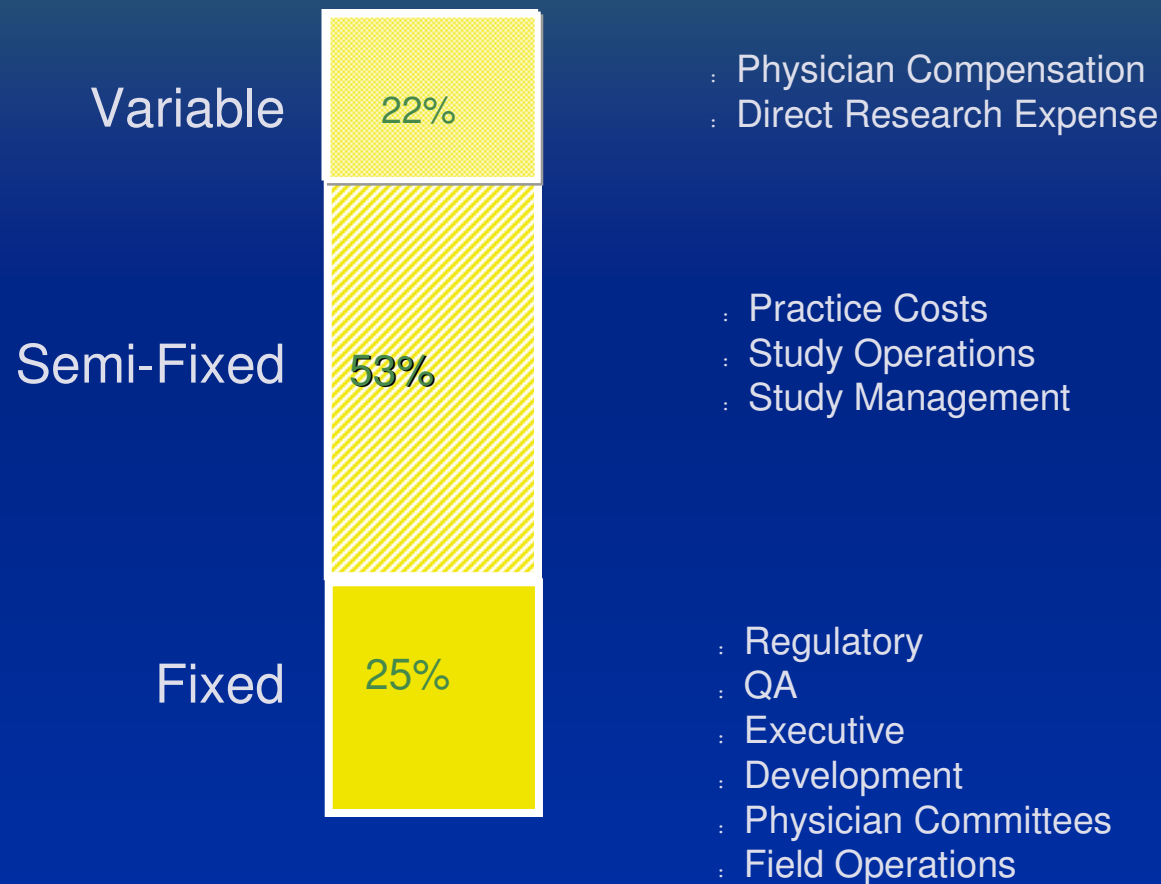
Should improve the efficiency & cost of research operations

Economics of Each Type of Trial

	<u>Avg. Rev/Accrual</u>	<u>Avg. Gross Margin Accrual</u>
1. Registration		58%
2. Inv. Initiated		46%
3. Phase I		12%

Research Cost Structure

KEY COST ITEMS



Models

- Private Network
 - Multiple Disease Types
 - New: Single Disease
- Academic/Community Network
- Industry-drug focused
 - Direct
 - SMO/CRO
- Sometimes a Mixture of all above

Multi-site Trials: Private Group/Network

- Infrastructure
 - Leadership group
 - Committees
 - Monthly teleconferences
 - Meetings with industry
 - Administrative Staff
 - Protocol writing
 - IRB submissions/reporting
 - Central Data management (Invest. Initiated)
 - DSMB
 - Finance/budget
 - Statistical support
 - Technical report writing
 - Field support/audits/quality control
 - Office space
 - Pharmacy/lab kits
- Funding
- Phase III Registration trials more labor intensive by a factor of 3-5 compared to Investigator initiated but with a better margin

A very
Substantial
Investment

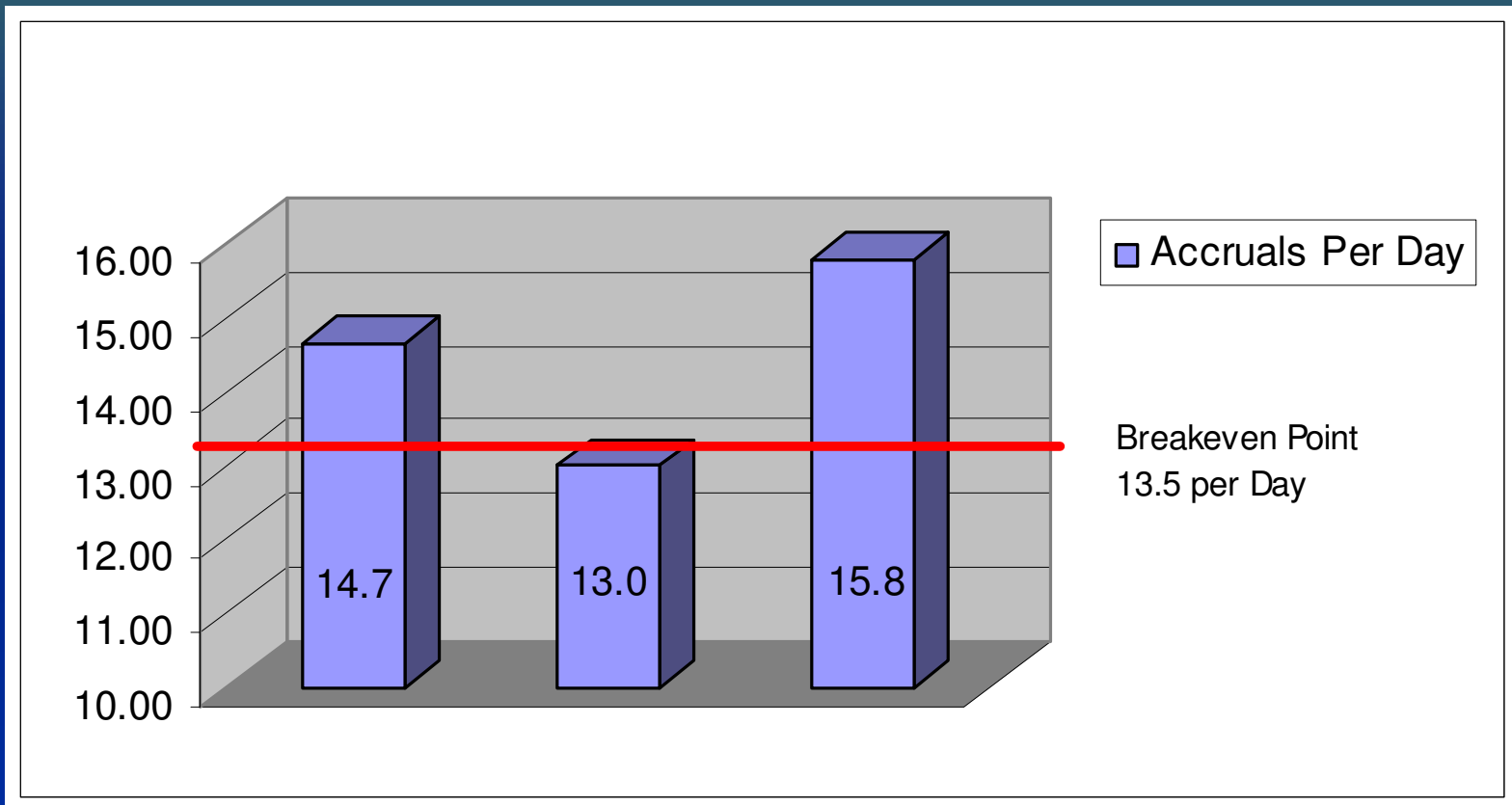
Investigational Pharmacy

- Central drug management
- Central lab kit distribution
- Regional pharmacies to handle trial material
- Drug logs maintained centrally and at site for tracking, administration and final disposition of drug

What Works?

- Pre-study involvement
 - When it happens
- Initiation Meetings
 - If they are local or by teleconference
- Central IRB
 - Frequency
 - Efficiencies and economics
- Funding
 - At least break-even
- Audits
 - In moderation
 - Frequent feedback, correction of queries

Break Even Analysis



Risk Factors

- High fixed cost infrastructure
- Lack of control over practice behavior: physicians accrual rates, hiring practices
- Regulatory compliance
- Operations stability and staff attrition
- Gaps in study pipeline

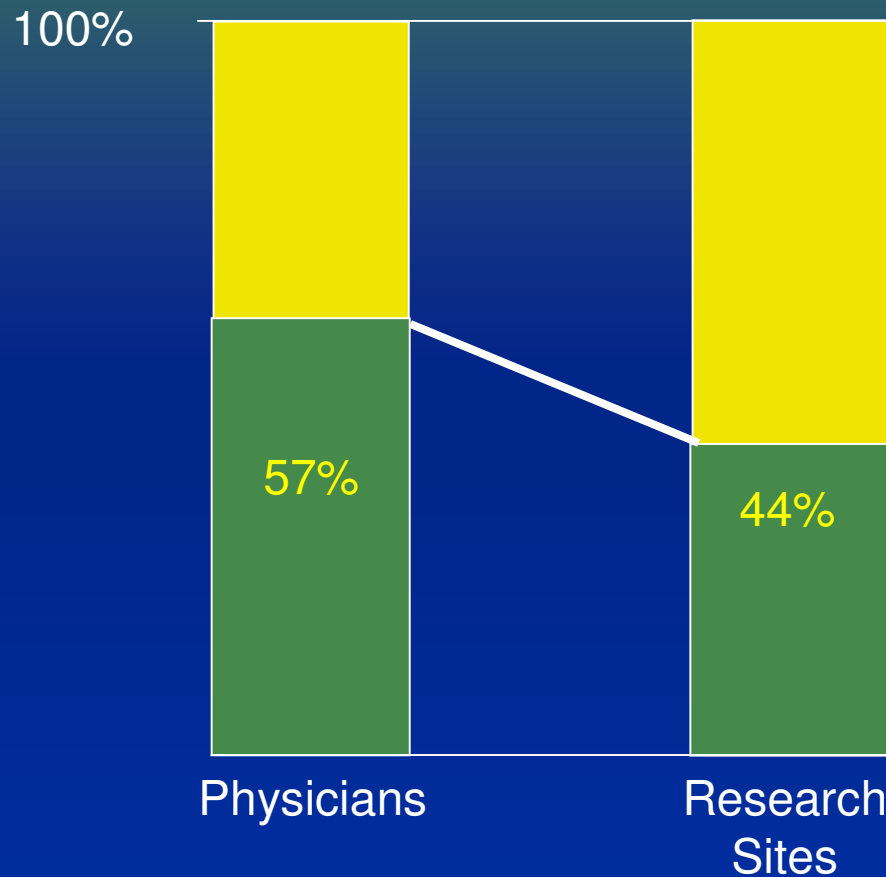
What Does Not Work?

- Initiation Meetings
 - If travel involved
- Local IRBs
- FDA
 - How many 1572's and CV's does the FDA really need?
- Audits
 - Trouble when number of appointments with auditors exceed those of your patients
- SAE's
 - Piecemeal, no context, multiple submissions, worldwide reporting.
- Long follow-up burden
- Storage of records
- Danger of double billing
 - Defining standard of care (tests)

What Does Not Work?




- Non-Accruing Sites
- Low or non accruing physicians
- Cherry-picking sites by sponsor

Physicians and Sites with <1 Accrual



Willingness to close those sites

Assuring Quality and Ethics Oversight

- Unlikely that a single investigator can accrue enough patients to affect study results
- Industry sponsored trials:
 - More frequently audited
 - Audits dependent on accrual
 - Performance Based:
 - Poor quality  not invited back
 - Poor accrual  poor data
 - Poor accrual  huge financial drag
- For investigator initiated trials, internal audits.

Opening a Trial:

Not Always an Easy Decision

- Perceived benefit
 - patient care
 - scientific importance
- Patient population
- Can you recruit
- Total costs before the first patient accrued
- Timeliness of accrual

Finally, do you open the trial?

Small Phase II

- New Drug
 - Could fill a needed gap
 - Only 45 patients to be accrued nationwide
- Patients generally available to recruit, but
 - Narrow eligibility criteria
 - “Degree of difficulty” 10/10
 - Tissue specimens, central lab, Recist criteria, frequent tests and scans, self-reporting questionnaires, many data points per visit, queries
 - But you can do all of that

Small Phase II

The Work Ahead:

- IRB application
- Re-write consent
- Present at IRB
- Annual reports
- SAE's that you sign
- SAE reports to IRB even when no patients accrued locally
- Amendments to IRB
- Annual reviews

Time to decide-is it really worth the effort ?

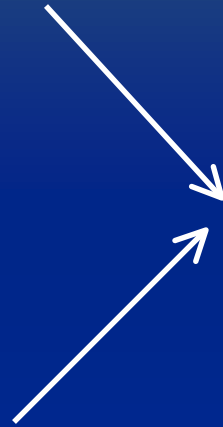
What can be done?

- Central IRB with No Local Review
 - Remove roadblocks
 - Let's re-look at “Local Context”
- Simplify Financial Disclosures
- Investigator Approval/Accreditation

Central IRB

- Reduces:
 - Redundancy
 - Costs
 - Variability
 - Time

- Increases
 - Oversight
 - Safety



All of these items have been cited as reasons for high costs and poor safety/quality in delivering medical care

Central IRB: Roadblocks

- Institutional
 - Fear
 - Provincialism
- Local review of central process just another layer
 - Perpetuated in order to accomplish what?
 - Get buy-in locally
 - Protect the Central IRB
 - Based on the “Local Context”

Local Context

“Local Context” is a sacred cow

- We are a Monolithic Nation of:
 - Treatment guidelines
 - FDA approvals
 - Medicare “approved” coding
 - National payer reimbursement approvals and decisions
 - Judging standard of care
 - And NCI “directs” certain wording in informed consents already
 - So who decides if local context applies?
 - (having it both ways, i.e., overriding local context)
 - Yes, it is arbitrary

Furthermore, when has an approved drug for an indication been disapproved by any regulatory body because of geographic, political, cultural, religious or ethnic differences ?

Never !

Recommendation:

Get rid of the “local context”
requirement

Re-tooling Regulatory: IRB

- We have a Central IRB for NCI-sponsored studies
 - Help us use it !
 - Institutions that receive federal funds must use Central IRB
 - Institution then has the option to open or not open the study
- Efficiency, safety, oversight, and increase in accrual

Financial Disclosures

- Disclosure is doing the right thing
 - Should go farther in some instances
 - Physician owns the product/device
- More often disclosure is a solution that is not needed:
 - Double-blind studies
 - Where an individual Investigator does not manage study data
 - Or Investigator contributes <10% cases
 - And Investigator cannot block publication of negative data

Retooling Financial Disclosure

- Financial Disclosure IF:
 - Greater than 10% accrual
 - and non-blinded study
 - DSMB
 - unless blinded
 - Own 5% of company stock
 - Probably should not accrue patients
 - Author

NCI Sponsored Investigator Approval Process

- Done at the Time of Grant Application:
 - 1572
 - PI, Sub-investigators, ? Ancillary staff
 - CV's
 - Financial disclosure if pharmaceutical sponsor
 - Also on file with IRB (maybe more than one)
 - Renewed Yearly

FDA

Investigator Approval Process:

- 1572
 - Principal Investigator, sub-investigator, location
- CV's
- Financial disclosures
- Lab CLIA's
- IRB filings

And repeated every time for every study!

If we can cross-file drug INDs why not cross-file investigators?

Retooling Investigator Participation

- National Investigator and CLIA Database
 - NCI and FDA sponsored trials
 - Pharmaceutical sponsor access to database that matches investigators for particular trial
- Investigator PIN
- Web-based
- Follows investigator, not location
- email reminder for updates q 2 years
- NCI trials open to any qualified, registered investigator

Private Network Trials Do Not Lower Costs

- Budgets are better than NCI
- Costs are still high
- Low/no margin business
- Sustainability ?

Pressures Being Felt Now

- Oncology workforce
 - Nurses, Physicians, Trained Staff
- Aging population
 - More cancer at more advanced age
- Going from cancer phenotype to genotype
 - Smaller pools of specific cancer
- Cost Inflation
- Victim of “success”
 - More effective drugs for second and third line indications

Add One New Huge Pressure

- Reimbursement-Medicare
 - Medicare 10% reduction
 - All drugs given at a loss unless patient able to pay co-pay or has supplemental insurance
 - Medicare's "80% allowable" an anachronism in our current world of unbelievable drug costs

Clinical Trial System Under Threat in the Community

- We have cost-shifted for the last time
 - Nothing left to shift

Community Response

- Last Week Our group Voted to :
 1. Stop accruing Medicare patients to NCI sponsored trials
 2. Medicare patients unable to pay co-pays (most U.S. citizens) or without co-insurance will be treated at the hospital
 3. Limit number of new Medicare patients

This Threat is Real

- Unless fixed, all of the preceding may render improvements to the clinical trial system moot

Oncologists are Optimists

Keep working for improvements

“Its Not About the Bike”

It is about the patients

Thanks !

“Make it Easy”

Harry Hines, MD

The winds of change
are blowing

But sometimes known as a
tornado in Oklahoma

54 year old female

- 1990, “low grade” sarcoma of the small bowel-resected
- 1994. Intra-abdominal recurrence, resected
- 2001. Recurrence, partially resected
 - path recognized as Gastrointestinal Stromal Tumor (GIST), CD 117 positive

ECOG trial was available, but not opened at our site.

Why ?