Overview

- This will be a highly interactive session
- We will introduce you to new ways of thinking about the study feasibility / acceptance process
- Please share and contribute (and keep an open mind!)

Note: Our discussion will focus primarily on industry sponsored trials but many of the principles and concepts apply to any type of trial.
When we ponder whether a protocol is “feasible” what are we really trying to ascertain?

What is the sponsor or CRO trying to ascertain?

Are these in alignment?

Predictable Enrollment Targets

Site Selection

The “Typical” Process

What % of Time (or How Many Hours) Do You Spend on...

Protocol Synopsis

Final Protocol, Budget, CTA

All Manuals, Job Aids, Etc.

XX% Completing questionnaires / internal assessment process?

Yes

No

Selected as Site?

Feasibility Questionnaire

~4-6 months

~4-6 months

~1 month

~1-3 months

3-6+ months

Per Protocol

XX% Study start up activities?

No

Yes

IRB and other committee approval?

Budget and Contract Approval

Site Initiation visit

First Patient In

Last Patient In

Last Patient Out

XX% Creating Operational and Recruitment / Retention Plan?
Discussion

- How many of you have ever encountered an “unfeasible” protocol?
- What made it unfeasible?
- When did you determine that it was unfeasible?
Discussion

- How many of you have ever experienced a “failed” or unsuccessful trial?
- What made it unsuccessful?
- When did you determine it was going to be, or was, unsuccessful?

Hindsight is 20/20

Is there anything you could have found out earlier in the process that would have predicted failure?
- If so, what information would have helped and when would you like to have received it?
Discussion

- Every study is “feasible” given enough time, money and resources
- When studies fail it is primarily because of...
- The impact of a failed study is...
- Instead of asking the feasibility question, what if we started asking “is it worth the time, money, resources (and precious patients!) to take on this study”?
  - How would this change your decision making process?
- What would it take to “fail fast” and quickly reject studies that will be unsuccessful?

"Reverse Engineering" the Process

Step 1
- Interest and enrollability assessment

Step 2
- Just Ask / Just Tell

Step 3
- Confirm Commitment and Recruitment Resource Plan

Step 4
- Formalize operational and recruitment action plan
### Step 1A

**Investigator Interest**

<table>
<thead>
<tr>
<th></th>
<th>Hi</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hi</td>
<td>![Green-star]</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>![Red-x]</td>
<td></td>
</tr>
</tbody>
</table>

Higher likelihood of success – pursue further information and maximize enrollment potential

May be able to support with training, resources, recruitment assistance, etc. – pursue more information and validate realistic enrollment potential

Likely not worth investing more effort as it will be difficult to engage PI and sustain study enthusiasm even if a lot of potential patients

Not worth pursuing – quickly fail the study opportunity and provide rationale

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### Step 1A Decision Making

**Site Protocol Acceptance Decision Algorithm and Process Flow**

**Interest Assessment**

- **Stop**
  - **No**
  - **Yes**
    - Does the Study Ask a Legitimate Scientific or Medically Important Question?
      - **Yes**
        - Yes (assumes that opportunity to provide input to modify the study design is limited or non-existent)
      - **No**
    - Am I Comfortable with the Research Question Being Answered and the Way the Study is Designed?
      - **Yes**
        - Yes (based on known information)
      - **No**
    - Does the Study Place the Subject at a Level of Risk that is Unreasonable?
      - **Yes**
        - Yes (based on known information)
      - **No**
    - Am I Likely to Get the Study Approved by my Scientific & Ethics Committee?
      - **Yes**
        - Yes (based on known information)
      - **No**

**What else would influence the investigator’s interest?**

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Step 1 B
Decision Making Process

Enrollment Estimation

High Level Funnel Analysis

Past Performance Evaluation
Recruitment Funnel Calculator

Per Site Estimates (approximate)

<table>
<thead>
<tr>
<th>Overall Targets</th>
<th>Monthly Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td># That Will Need to Be Identified</td>
<td>100.0</td>
</tr>
<tr>
<td># That Will Need to Be Pre-Screened</td>
<td>31.0</td>
</tr>
<tr>
<td># That Will Need to Be Consented</td>
<td>13.0</td>
</tr>
<tr>
<td># That Will Need to Be Randomized</td>
<td>8.9</td>
</tr>
</tbody>
</table>

Available: Randomized Ratio = 1:3

Historical Performance Report Card Example

On Average we get our 1st patient in within 24 days

And

On Average we achieve 76% of our enrollment targets

Discussion:
- What metrics do you capture?
- Are they value-added to your decision making? The sponsors?
- Challenges /opportunities with collecting this information (e.g., Research Resonance Network)
Protocol Feasibility and Operationalization Framework

Estimated Enrollment Contribution

- XX from outside sources
- XX from our own database
- XX from referrals

Total Enrollment Contribution = XX within XX Month
(Estimate will be validated upon site selection decision and availability of detailed protocol)

Step 2: “Just Ask / Just Tell”

Typical process “pain points”:
- Not enough information / evidence
- Not enough time
- Restricted questionnaire formats
- Perceived “non value added” information
- Not enough CONVERSATIONS!

Potential solutions:
- Provide EVIDENCE
- “Reverse feasibility” questionnaires and site profiles
- Determine must haves for site selection
- Discuss and negotiate timelines, expectations, interest and information needs

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Critique of “Reverse Feasibility” Questionnaires

Discussion:
• Has anyone used something similar? What was the outcome?
• What would you change?
• How might the process work?

Step 4: “Confirm Commitment”
Enrollment Validation – An Ideal Process

Now that you have a more detailed protocol

- High Level Funnel Analysis
- Database Estimate
- Sample Chart Review
- Estimate the Remaining Funnel Loss Ratios
- Identify Gaps

Step 1

- Set up the “leaky pipe” calculations to estimate loss ratios
- Use benchmark data or past historical performance data

Recruitment Funnel Calculations

"Top Down" Funnel Calculations

<table>
<thead>
<tr>
<th>Funnel Parameters and Stages</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment Period (months)</td>
<td>12</td>
</tr>
<tr>
<td># of Sites</td>
<td>1</td>
</tr>
<tr>
<td># Patients at a Given Site with Diagnosis Seen in 1 Year</td>
<td>120</td>
</tr>
<tr>
<td>% Lost During Pre-Screening</td>
<td>0.69</td>
</tr>
<tr>
<td>% Decline to Participate</td>
<td>0.58</td>
</tr>
<tr>
<td>% Lost During Screening</td>
<td>0.32</td>
</tr>
<tr>
<td>% Drop-out Post Randomization</td>
<td>0.18</td>
</tr>
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"guesstimate the #: and confirm with the database query"
Step 2a Database Estimate

100 subjects in 1 year

Run Query with primary diagnostic code only

Run query with remaining codes / characteristics to determine % loss due to e-Pre-screening criteria

Can be determined at Pre-Screening

Can only be determined at Screening*

EMR-queriable criteria

Chart review criteria

Define query parameters (e.g., ICD-9 Codes)

UC Criteria

*After obtaining informed consent

100 subjects in 1 year e.g., 35% e-Pre-screening Loss

Step 2b Update Calculator

Recruitment Funnel Calculations

"Top Down" Funnel Calculations

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</tr>
<tr>
<td># of Sites</td>
<td>1</td>
</tr>
<tr>
<td># Patients at a Given Site with Diagnosis Seen in 1 Year</td>
<td>100</td>
</tr>
<tr>
<td>% Lost During Pre-Screening</td>
<td>0.35%</td>
</tr>
<tr>
<td>% Decline to Participate</td>
<td>0.38%</td>
</tr>
<tr>
<td>% Lost During Screening</td>
<td>0.92%</td>
</tr>
<tr>
<td>% Drop out Post Randomization</td>
<td>0.18%</td>
</tr>
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</table>

Confirm the starting # based on your database query of the # of patients with diagnosis

Adjust for e-Pre-screening loss ratio
Step 3a Sample Chart Review

- Further segment and prioritize the remaining pre-screen criteria
- Out of the above group pull 10-20 random charts to review against all protocol criteria and document what percent of those patients meet the pre-screen criteria
- If no patients qualify out of the 20, pull an additional 10-20 charts
- Use this to determine the remaining pre-screening loss ratio
- Combine with the e-pre-screening ratio to determine the full pre-screening loss ratio

Step 3b Update Calculator

Recruitment Funnel Calculations

*Top Down* Funnel Calculations

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<tbody>
<tr>
<td>Enrolment Period (months)</td>
<td>1</td>
</tr>
<tr>
<td># of Sites</td>
<td>100</td>
</tr>
<tr>
<td>% Patients at a Given Site with Diagnosis Seen in 1 Year</td>
<td>0.6</td>
</tr>
<tr>
<td>% Lost During Pre-Screening</td>
<td>0.32</td>
</tr>
<tr>
<td>% Decline to Participate</td>
<td>0.18</td>
</tr>
<tr>
<td>% Lost During Screening</td>
<td>0.64</td>
</tr>
<tr>
<td>% Drop-out Post Randomization</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Confirm the starting # based on your database query of the # of patients with diagnosis

Adjust for Total Pre-Screening Loss Ratio
Step 4 Estimate Remaining Loss Ratios

- Estimate the loss ratios across the full recruitment funnel.
- For consent declines, consider distance, age range (work hours/school hours), and other study burdens to estimate the consent refusal ratio.
- Estimate screen:fail and post randomization losses based on prior site/sponsor experience.

The Enrollment Validation Results

These fields are auto-calculated showing the realistic # of patients you can enroll, randomize and complete in 1 year from within your own internal pool of patients.

And the overall conversion ratio.
Recruitment Resource Plan

- Provides justification for budget and demonstrates clear proactive thinking about recruitment tactics, resources and materials!

Step 4 – Start Up and Implementation Plans

- Proceed with Study Start Up Activities as per Institutional SOPs
- Conduct Mock Patient Simulation and Identify Key Challenge Areas/Questions
- Create Study Implementation and Recruitment Action Plan
- 1st Approves OIB (RA) prior to initiative (Tech / Inv Mgt)
- Site Initiation

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Protocol Feasibility and Operationalization Framework

DILO: Day In the Life of a Patient Mock Protocol Simulation Exercise

Study XXX: Optimized Patient Process Flow and Study Support Materials

Recruitment Action Plan

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Study Implementation Plans

Pulling it All Together

If we follow this “optimized” process...
• How many of the typical study failures and pain points could we eliminate?
• Could our resources be better utilized?
• Could we make quicker “reject” decisions?
• Could we improve our likelihood of success?
• Why or why not?

Become friends with your CTMS / Excel / Visio!
Reflection

- Please answer the following...
  - The one or two things I really like about this approach is (are)...
  - The key concerns I have about the proposed process and/or tools are...
  - One or two things I would recommend to change or adapt the process for our site would be...

- Remaining thoughts, questions, comments?

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