The Importance and Impact of Effective Clinical Trial Feasibility Assessment

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Presentation Objectives

• Discuss how feasibility assessment works “both” ways.

• Examine the reasons why Sponsors, Clinicians, and Institutions often undervalue the research vetting process.

• Detail various approaches taken by Sponsors to formalize their assessment program.

• Outline proven methodologies used by provider organizations to institutionalize feasibility assessment procedures.

• Identify the key roles and necessary stakeholders who should be engaged early on during research project preparation.

• Questions and Discussion.

…but first
Why Should You Care?

Financial Realities
Nurturing Clinical Research Assumes a Fundamental Understanding

<table>
<thead>
<tr>
<th>Costs</th>
<th>Revenue</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Administrative Staff</td>
<td>• Indirect Cost recovery</td>
</tr>
<tr>
<td>• Laboratory Staff</td>
<td>• Per patient payments from Sponsors</td>
</tr>
<tr>
<td>• Coordinators</td>
<td>• Grants</td>
</tr>
<tr>
<td>• Office Space, utilities, overhead</td>
<td>• Contracts</td>
</tr>
<tr>
<td>• Laboratory Space</td>
<td>• Sub-contracts</td>
</tr>
<tr>
<td>• Coordinator Space</td>
<td>• Sub-awards</td>
</tr>
<tr>
<td>• Technology (billing, patient reg., acct, db mgmt.)</td>
<td>• Donations</td>
</tr>
<tr>
<td>• Compliance Oversight</td>
<td>• Many of the revenues are based on recouping expenses budgeted at cost or with only marginal premiums.</td>
</tr>
<tr>
<td>• Policy development / enforcement</td>
<td>• Many institutions negotiate IDC at levels below actual overhead.</td>
</tr>
<tr>
<td>• Regulatory</td>
<td>• Few organizations proactively deploy advancement professionals to raise money for research endeavors.</td>
</tr>
<tr>
<td>• Marketing / Patient Recruitment</td>
<td>• An institution's ability to just break even with research, is difficult.</td>
</tr>
<tr>
<td>• Training</td>
<td></td>
</tr>
<tr>
<td>• Continuing Education</td>
<td></td>
</tr>
<tr>
<td>• Institutional Review Board</td>
<td></td>
</tr>
<tr>
<td>• Tracking AEs, SAEs, protocol deviations, amendments</td>
<td></td>
</tr>
<tr>
<td>• Investigator Recruitment</td>
<td></td>
</tr>
<tr>
<td>• Seed funding</td>
<td></td>
</tr>
<tr>
<td>• Outreach</td>
<td></td>
</tr>
<tr>
<td>• Unbudgeted screen failures</td>
<td></td>
</tr>
<tr>
<td>• Lost Clinical Revenues</td>
<td></td>
</tr>
<tr>
<td>• Research Discounts</td>
<td></td>
</tr>
<tr>
<td>• Strategic planning and time taken away from other ventures</td>
<td></td>
</tr>
</tbody>
</table>
Shifting Landscape

The decision to engage in research and build a program is being made in a much different environment than just five years ago. Or, as the case may be, a few months ago!

<table>
<thead>
<tr>
<th>Issue</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conflict of Interest scrutiny</td>
<td>↑</td>
</tr>
<tr>
<td>International collaboration</td>
<td>↑</td>
</tr>
<tr>
<td>Competing institutions sinking more into strategic growth of clinical research increases challenge of landing funding</td>
<td>↑</td>
</tr>
<tr>
<td>Sub-recipient monitoring</td>
<td>↑</td>
</tr>
<tr>
<td>Fraud and abuse, heightened enforcement agendas, Stark, etc.</td>
<td>↑</td>
</tr>
<tr>
<td>Stem cells and other scientific controversy</td>
<td>↑</td>
</tr>
<tr>
<td>Effort reporting, unique employment terms / appointments, consulting arrangements and other comp-related complexities</td>
<td>↑</td>
</tr>
<tr>
<td>Clinical Trials billing</td>
<td>↑</td>
</tr>
<tr>
<td>HIPAA issues</td>
<td>↑</td>
</tr>
<tr>
<td>Compliance requirements with clinicaltrials.gov</td>
<td>↑</td>
</tr>
<tr>
<td>Patent protections / Intellectual property / tech transfer</td>
<td>↑</td>
</tr>
<tr>
<td>Funding levels (already trending down and then the Sequester)</td>
<td>↓</td>
</tr>
</tbody>
</table>

But, the Challenges Don't Stop There...

- Reduction in financial margin from clinical activities has made it difficult to fund research.
- No measurable outcomes and no accountability.
- Understanding about the mission, vision, direction, or interest in research by institutional leadership has become muddled.
- Absence of engagement by leadership. Uncertainty about where they need to invest.
- Dramatic increase (in some cases decrease) in the size and capability of research administration.
- Increased importance in cross-functional, inter-disciplinary translational research by the government has challenged programs that have not evolved.
- Need for more integration of research administrative departments.
- For anything interdisciplinary with a translational component, almost always, another institution will have to be involved.
Why Is This Process Difficult to Get Right?

Feasibility Works Both Ways

<table>
<thead>
<tr>
<th>Sponsors / CROs</th>
<th>Patients</th>
<th>Research Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key Factors:</td>
<td>Key Factors:</td>
<td>Key Factors:</td>
</tr>
<tr>
<td>- High enrollment.</td>
<td>- Past participation</td>
<td>- Alignment with mission</td>
</tr>
<tr>
<td>- Medical usage</td>
<td>- Comprehensive evaluation of the disease</td>
<td>- Reputable sponsor / easy to work with</td>
</tr>
<tr>
<td>- Patient interest</td>
<td>- Study medication</td>
<td>- Complementary to the portfolio</td>
</tr>
<tr>
<td>- Investigator interest</td>
<td>- Reimbursement</td>
<td>- Valuable to patients</td>
</tr>
<tr>
<td>- Reimbursement patterns</td>
<td>- Helping others</td>
<td>- Willingness of physicians</td>
</tr>
<tr>
<td>- Timeliness</td>
<td>- Duration of visits</td>
<td>- Patient interest</td>
</tr>
<tr>
<td>- Competing trials</td>
<td>- Distance to travel</td>
<td>- Scientifically meritorious</td>
</tr>
<tr>
<td>- Track record</td>
<td>- Likelihood that a research project will improve their health</td>
<td>- Capability of clinicians</td>
</tr>
<tr>
<td>- Patient demographics</td>
<td>- Ability to provide feedback</td>
<td>- Logistically realistic</td>
</tr>
<tr>
<td>- Access to site data / analytics</td>
<td>- Comfort level with research team</td>
<td>- Financial solvency</td>
</tr>
<tr>
<td>- Ease of use</td>
<td></td>
<td>- Consistent with risk profile</td>
</tr>
<tr>
<td>- Professional</td>
<td></td>
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</tbody>
</table>

Failure to appreciate how your interests may or may not align with the other key participants in a research study, can hinder success.
Feasibility Assessment
Process Overview - Sponsors

Sponsor IDs Investigator List

External (25%)
• Clinicaltrials.gov
• Clinical Research Investigator Directory
• SMOs

Internal (75%)
• PIs from prior trials with good history
• Prospecting (i.e., clinical development liaisons)
• Investigators who call in
• Referrals

What is missing?

Questionnaire

Can Site Conduct the study?

<table>
<thead>
<tr>
<th>Experience</th>
<th>Time / Resources</th>
<th>Logistics</th>
</tr>
</thead>
<tbody>
<tr>
<td># of trials, access to good CRC, e-CRF system, etc.</td>
<td>Current studies, competing studies</td>
<td>Db, monitoring space, rooms, etc.?</td>
</tr>
</tbody>
</table>

Sponsor Challenges

Good Sponsors / CROs:

• Maintain site prospective worksheets and databases.
• Confirm the training and experience of staff
• Request an advertising strategy.
• Study feedback from CRAs, vendors, and others.
• Review site metrics from past studies.
• Analyze data about a site's catchment area, patient mix, and other information provided by the site.

Reality: Significant reliance on the Questionnaire.
## Sponsor Challenges

- Some information is captured after signing the CDA.
- Investigator often must affirm interest having only limited information about the respective study.
  - Limited inclusion and exclusion are disclosed as are basic study schema.
  - Willingness to participate is made prior to the investigator having access to the complete study protocol and budget.
  - Coordinator time and the impact on personnel resources is a wild card.
- It is a common scenario that sites are identified and investigator ‘sign-on’ occurs prior to investigator review of a full protocol; in fact, oftentimes the protocol has not been finalized by the Sponsor.

## Sponsor Challenges

- Information provided may or may not be backed up by facts because these are often completed by the PI, a CRC or a department-based resource who may not have a full appreciation of a site’s infrastructure characteristics.
  - Experience of PI.
  - Size of human subject pool.
  - Research ethics training.
  - Information on the clinical research staff.
  - Willingness to defer to or use a CIRB.
  - Presence of a Scientific Review Committee.
  - Ability of the site to carry out contract negotiations and IRB review in tandem.

While sponsor-driven feasibility assessments can helpful, to an extent, the true risks, opportunities, logistical concerns, and financial realities that a proposed study may have on a specific site should be determined by the site itself.
Feasibility Assessment
Process Overview - Sites

Study Opportunity Presented

Review Committee (25%)
• Alignment with Mission
• Portfolio considerations
• Internal feasibility assessment form
• I/E review
• Database review
• Impact on various depts. / service areas

PI Review (75%)
• Time
• Interest
• Financial Opportunity
• Ability
• Benefit

What is missing?

Sign-Off

Can Site Conduct the study?

Ancillary Dept. Investigator

Site Challenges

• Administrative Support Structures
  – Reactive, transaction focused, and not routinely asked to contribute to the strategic direction of the research program.
  – Decentralized.
  – Measured by and pressured to be fast.
  – Limited policies, documented procedures
  – Oversight authority either lacking or ineffective:
    ▪ Underrepresentation of stakeholders directly affected by the proposed research activity
    ▪ Operate with loose rules, guidelines, charters, scoring systems, review methodologies, etc.
    ▪ May operate with a sort of quid pro quo
    ▪ Saying "no" seldom occurs for fear of reprisals
Site Challenges

- **Clinical Support Structures**
  - Overburdened clinical research coordinators.
  - Absence of laboratory or pharmacy specialists.
  - Often not "seated at the table" as new project opportunities are considered (e.g., pathology department needs to be engaged in oncology studies should they be asked to judge the effects of a particular drug on cancer tissue even if the study design uses the results for a tertiary endpoint).

Site Challenges

- **Investigators**
  - In many settings, they wield considerable influence and power.
  - Limited visibility into the financial realities. Will it break even?
  - Underestimate impact of a study's management (i.e., recruitment, screening, consenting, etc.).
  - No thoughtful consideration of how inclusion/exclusion criteria may or may not align with existing patient mix.
  - Armed with a signed CDA, may will proceed without documented analysis or input from the administrative or clinical departments that will need to be involved.
Where Do You Start?

Taking Stock of Your Circumstances

- Is there a strategic plan for research?
  - Is it still relevant?
  - Is it still feasible?

- What research is important to your institution’s brand?
  - If research activity disappeared, what would be the impact on clinical services, reputation, patient satisfaction, physician engagement?

- What are the core pressures that your institution faces?
  - When was the last research risk assessment?
  - Do you have a research audit plan?

- If you were to self diagnose what your institution does well, and subsequently what it doesn’t do well, what would you identify?

It is vital to consider your environment and your governance structure to confirm that your program is ‘right-sized’ and that financial expectations are aligned with structural realities.
Take the Time to Plan
Eyes Wide Open

- The pathway to financial solvency depends upon many things:
  - Expectations
  - Resources
  - Governance / Leadership
  - Patient engagement
  - Physician engagement
  - Process optimization
  - Partnerships

Understand who you are, why you are in it, what kind of research matters, and embrace the investments necessary to support the current state and BUILD toward a desired future state.

Before initiating clinical research, define the institutional breadth and depth of commitment. Realistically assess the feasibility of your accrual goals. Furthermore, make certain that the proposed clinical trial is in alignment with the mission and vision of the institutional research program.

What Should You Do?
Understand the State of the Protocol

- Protocols are frequently not in final form during the Sponsor’s site identification process because precedent studies are usually still ongoing.

**Investigators**
- Produce projected accrual numbers
- Keep CRCs funded

Even so….there is PRESSURE on all parties to get studies initiated quickly. But, don't rush!

**Institutions**
- Fulfill strategic plans
- Confirm studies match mission/vision
- Avoid overburdening resources

**Sponsor / Designated CRO**
- Identify sites….some of which will inevitably fall short of their project expectations.

Institutions Must Set the Rules and Establish the Culture

- Take the time to carefully define the institutional breadth and depth of commitment.
  - What is the institutional risk tolerance?
  - What are the implications of the study on institutional resources?
  - Does the necessary patient population align with the institution's catchment area?
  - Is the study is aligned with the mission and vision of the institutional research program?
  - DON'T DABBLE!

- Formalize policies and procedures for clinical study evaluation and vetting.
- Make sure that research compliance is seated at the table.
Feasibility Assessment
Getting It Right

Install Accountable Decision Makers

• Who will say "no"?

• Establish a committee (institutional, departmental, or both) that is charged with assessing feasibility.
  – Carefully evaluate the make up of these groups.
  – Don't under-represent stakeholders directly affected by the proposed research activity.

• Consider requiring departmental sign off.

Establish Research Credentialing Process

• Require minimum training level for Investigators

• Disengaged Investigators are the enemy of a thriving research program.

Feasibility Assessment
Getting It Right

Ensure that the Investigator is Involved, Aware and Engaged

• The ability to easily navigate questions does NOT mean that the study is right for your institution.

• Without a complete study protocol or a draft budget, good decision making is impossible.

WHAT GETS OVERLOOKED MOST OFTEN?

  – Specialized tests
  – Specialized training
  – Time for subject screening
  – Costs associated with screen failures
  – Completing questionnaires, CRFs, etc.
  – Expectations that CRCs to place calls to patients before/after visits.

Checklists and internally developed Feasibility Assessment Forms are critical.
Invest in Patient Registries, Databases, and Other Tools to Track Trends

- Investigators should work with coordinators to examine historical data through an electronic medical record as much as possible.
  - Before submission of the completed questionnaire, the patient population can be prescreened in real time to get the most accurate projections.
  - EHRs should help in this area.
  - Don't rely on memory.

Be sure you have a sense of likely patient accrual.
Don't let the CRO pressure you into a decision.

Financial Viability
Operational Factors

Other Key Considerations

- Ask questions….make sure that you are not the only ones.
  - Are there safety or human research protections issues
  - Avoid high risk studies or badly designed studies from private sponsors.
- Make the process appropriately rigorous. Weed out dabblers.
- Are the financial incentives too high? Maybe there is a reason!
- Confirm buy-in by every department the protocol touches (radiology, pathology, nurses, physical therapy….everyone).
- Can you use a CIRB? Is your IRB's backlog, speed a limiting factor?
- If there are study assessments that fall outside of what is normally done in clinic, do a mock set up.
  - Run them as if the protocol was up and running.
  - Assess what space is needed and for how long, how does patient flow work?
Efficient Research Participant Billing Processes and Oversight are a Must

From the standpoint of optimizing process, it is vital to spend time early on to plan for potentially challenging billing issues.

- Oversight, tools, IT, and dedicated personnel at each step in the process continuum are essential.
- Organizations dedicate inadequate resources to confirm that this process is efficient and that all dollars are being captured through the billing process.
- Ensure that there is mechanism in place to flag visits, suspend charges, review bills, scrub, and then accurately bill payors for routine care AND debit study accounts for non-billable non-standard of care items and services.

What About Coordinators?
Factoring in Coordinator Capacity

Operational Factors

- The best laid plans and the most thoughtful analysis of feasibility can fail if there is not a careful evaluation of whether or not your Research Nurses and/or Clinical Research Coordinators have enough time.

- Develop a plan for measuring coordinator time and modeling what it will take to carry out a clinical trial based on a review of the available draft protocol.
- Data drives the decision.
- Avoid approximating a CRC’s time estimate by using a percentage (i.e., 20%-30%).
- Avoid costing a visit by calculating other factors (i.e., tissue collection, time needed to use a room, bandage, etc.). None of that captures CRC time.
- If possible, limit a single CRC to three clinical trials.

Factoring in Coordinator Capacity

Let's Get Technical

- Document everything and come up with the actual number of hours needed to complete a task.
- Establish a reference list that includes a set amount of hours needed for common tasks. Tailor them slightly for each study. Example, interventional oncology trials are complicated and take longer.

<table>
<thead>
<tr>
<th>Study Start Up Tasks (in hours)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>IRB Submission</td>
<td>6</td>
</tr>
<tr>
<td>Scientific Review (if applicable)</td>
<td>4</td>
</tr>
<tr>
<td>Other committee approvals (if applicable)</td>
<td>1</td>
</tr>
<tr>
<td>Initiation meeting</td>
<td>8</td>
</tr>
<tr>
<td>Other administrative (year 1 only)</td>
<td>20</td>
</tr>
<tr>
<td>Monitoring visits (expect two 8 hour meeting in year 1)</td>
<td>16</td>
</tr>
<tr>
<td>Research meetings (half hour per meeting each week)</td>
<td>26</td>
</tr>
<tr>
<td>TOTAL (Equates to about 4% of a 2000 hour work year)</td>
<td>81</td>
</tr>
</tbody>
</table>
Factoring in Coordinator Capacity
Let's Get Technical

• In Year 1 many tasks (i.e., setting up patient visits, administration of the ICF, etc.) will only occur once
• In Year 1, you should forecast more visits, CRFs.

<table>
<thead>
<tr>
<th>Year 1 (in hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admin of Informed Consent</td>
</tr>
<tr>
<td>Setting up a patient visit (half hour per visit)</td>
</tr>
<tr>
<td>Patient Visit (2 hours per visit)</td>
</tr>
<tr>
<td>Coord. of tissue collection and transfer</td>
</tr>
<tr>
<td>Blood draw</td>
</tr>
<tr>
<td>CRF (per time point) - 5 in year 1</td>
</tr>
<tr>
<td>Other administrative duties</td>
</tr>
<tr>
<td>Amendments (assume 2 per year)</td>
</tr>
<tr>
<td>AEs (assume 5 per year)</td>
</tr>
<tr>
<td><strong>TOTAL (Equates to about 3% of a 2000 hour work year per patient)</strong></td>
</tr>
</tbody>
</table>

Factoring in Coordinator Capacity
Let's Get Technical

• Not totally complete, but you get the idea.
• Don't forget about screening time
  – Keep track, keep a log
  – Could take up to two hours per patient depending upon complexity of the eligibility criteria and/or how data is stored at a particular center.
  – What is anticipated yield? Will you have to screen 100 to get 2?
• What percentage of patients will have to be replaced?
• Why?
  – Prove that you are doing what you said you would do with respect to screening so lack of accrual is not due to lack of effort;
  – Help you understand your own population of patients which will save you feasibility screening time for studies in similar groups; and
  – Help the Sponsor figure out why sites are not accruing so you can help propose solutions.
Summary and Wrap Up

Conclusion and Take Home Message

Seek transparent communication and strong relationships among all stakeholders.

**Sponsors:**
- betters tools for assessment may cost more but the results may decrease costs by picking better sites.
- Proven track record, demonstrated metrics, data driven decision making.

**Investigators:**
- Require more accountability.
- Understand role.

**Sites:**
- Mission / vision / strategy / expectations / risk tolerance
- Committees
- FAFs / Policies / procedures
- Build up data repositories. Understand what sites are looking for.
Questions and Discussion