Protocol Feasibility Analysis

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LEARNING OBJECTIVES

- **At the end of the class attendees should know:**
  - The importance of conducting study feasibility analysis
  - The importance of feasibility for industry sponsored trials and investigator-initiated research
  - How to conduct a feasibility analysis (best practices)
  - How to track successful and unsuccessful studies for better analysis in the future

IMPORTANCE OF FEASIBILITY ANALYSIS

Prediction is very difficult, especially if it's about the future. - Niels Bohr

- **Feasibility assessments cost time and money but they are a good investment and can proactively identify risk factors**
  - Prevent wasting resources
  - Prevent wasting money
  - Preserve the PI/Site's reputation

WHY COMPLETE A FEASIBILITY ANALYSIS?

2011 paper published about research at OHSU found that 31% of studies at OHSU enroll 0 or 1 subject

- Cost to institution = $1 Million annually
- Underperforming studies slow down the entire research system
- Increase the risk of bad science

Source*: Kitterman, D.R., Cheng, S.K., Dilts, D.M., & Orwoll, E.S (2011) The Prevalence and Economic Impact of Low-Enrolling Clinical Studies at an Academic Medical Center. Academic Medicine, Vol. 86(11), pp.1-7*

MORE REASONS

- 48% of clinical sites under-enroll participants (*Tufts, 2013*)
- 46% of investigators report being “generally unsatisfied” with finance related issues for conducting clinical trials (*Corneli, et al, 2017*)
- High rate of turnover in clinical investigator community
  - 50% of PIs completing a 1572 chose not to file again (*Tufts CSDD, 2017*)
  - Nearly have of PIs were new to the job (*Tufts CSDD, 2013*)

FEASIBILITY ANALYSIS FOR SPONSORED TRIALS

- **Agreeing to the wrong studies can:**
  - Drain resources
  - Damage reputation with Sponsor/CRO/Coordinating Center

- **Agreeing to the right studies can:**
  - Build PI/site experience
  - Provide research opportunities to patients
  - Provide revenue
  - Contribute to PI/Departmental goals

FEASIBILITY ANALYSIS FOR INVESTIGATOR-INITIATED TRIALS

- **Without a thorough feasibility analysis:**
  - PI may find it takes longer to enroll than funding allows
  - PI may need to get NIH approval (and other funders) approval for a change in scope of the research
  - PI may not be able to complete the study
    - Looks bad for future funding

- **Feasibility Analysis = Successful Study**
  - More funding and publications

So, what is a protocol feasibility analysis?

- **An initial step in the clinical trial start-up process, includes assessment of protocol components:**
  - Study design and objectives
  - Site resources and capabilities
  - Patient population

STUDY DESIGN AND OBJECTIVES

- **Is the study question important to the PI at OHSU?**
- **Is the protocol well designed and clear?**
  - Is it the final version of the protocol?
- **Can the protocol be adequately integrated with routine standard of care?**
  - Do the study procedures/treatments match OHSU standard of care? If not, are there research funds to pay for research procedures?
- **Is there an impact on institutional reputation or academic interest in our specialty related to this research? Positive/Negative?**

STUDY DESIGN AND OBJECTIVES

- **Is there a clinical impact on patient treatment or need for therapy?**
- **Post Marketing/Registry Trials**
  - Is there a research question?
    - Is it mandated by FDA?
    - Is it solely for marketing purposes?

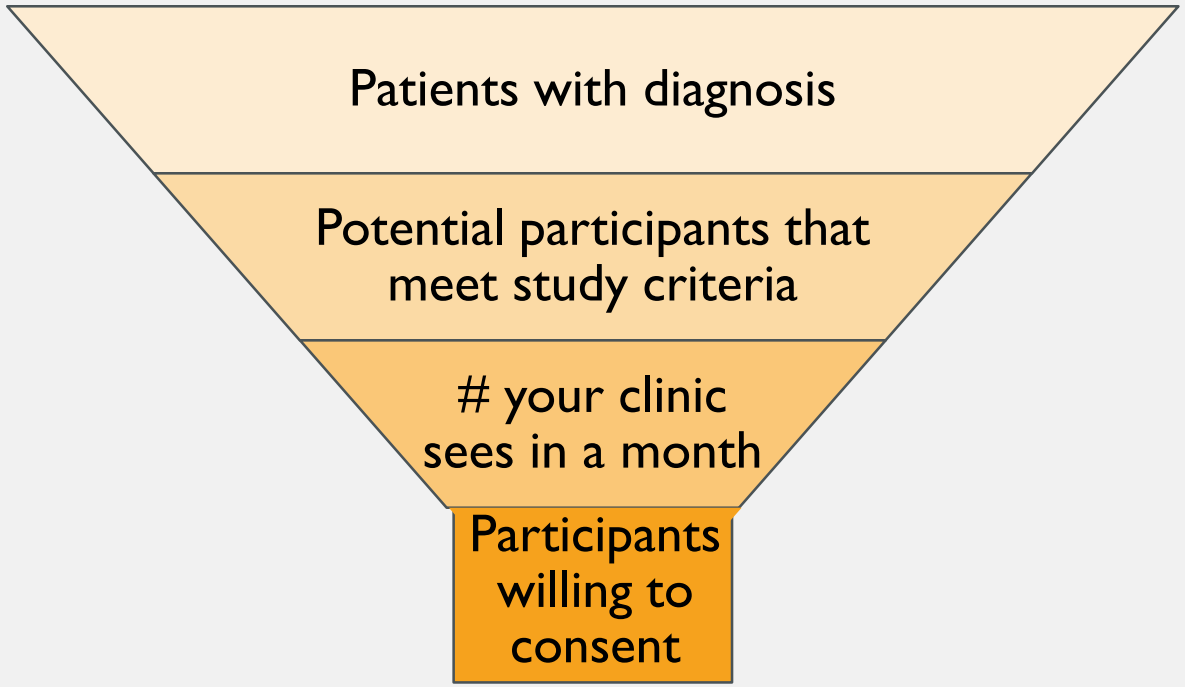
SITE RESOURCES AND CAPABILITIES

- **Principal Investigators (PI) Time**
  - Clinic time to accommodate study visits
  - Time to oversee/complete regulatory and contractual obligations
- **Coordinator/study staff Time**
  - Staff time to conduct the study and complete study regulatory and institutional requirements
  - Appropriate training/credentials
- **Ancillary/support staff**
  - After hours coverage (if needed)
  - Capacity for additional research procedures
- **Equipment/Facilities**
  - Space
  - Protocol required equipment (e.g. freezers, specific equipment)
  - Access to the equipment at the protocol required time points

PATIENT POPULATION

- **Can you enroll the required # of participants in the specified timeframe? Consider:**
  - **Funding Period**
  - **Sponsor recruitment timeline**
    - Competitive enrollment
  - **How will you identify participants?**
  - **Do you have competing studies?**
  - **Is the protocol attractive to potential study participants?**
    - Participant burden
    - Potential benefits to the participant
    - Are there other treatment options available?

ESTIMATING YOUR POTENTIAL PARTICIPANT POPULATION



- Need to have pool of patients that have the diagnosis
- AND meet the inclusion/exclusion criteria
- Consider how many can you reasonably screen in a month at regular/study specific visits
- Participant Burden? Are the study procedures/ visits reasonable

Don't over estimate! 48% of clinical sites under-enroll participants (Tufts, 2013)
Don't Guess! Tools are available

FINANCIAL CONSIDERATIONS

- **46% of investigators report being generally unsatisfied with finance-related issues for conducting clinical trials (Corneli, et al., 2017)**

- **A CenterWatch Focus Group Study (2014) found that Sites say Sponsors/CROs are asking sites to do more but are not covering the costs**
  - More staff trainings
  - Studies are more complicated
  - Consent forms are longer
  - Push for quicker start up
  - Multiple amendments before studies start

- **Administrative costs are rising but budgets have been flat**

EXAMPLE FEASIBILITY CHECKLIST

Study Population	Yes	No	Unk
Does OHSU have the patient population described in the inclusion/exclusion criteria?			
Do you see these patients in your clinic at OHSU?			

See OCTRI Website – Policies, Forms and Templates - Protocol Feasibility Checklist

CASE STUDY - BACKGROUND

- **OHSU Dermatology Clinical Trials Unit profile:**
  - 10 active Principal Investigators
  - 8 person study team

- **Trial portfolio covers all age ranges and many indications (including rare diseases)**
  - Primarily industry trials, but also NIH-sponsored and IIT's

CASE STUDY

- **Earlier this year, we decided to pursue a particular industry sponsored clinical trial:**
  - Study population included **adolescents and adults with mild to severe atopic dermatitis (AD)**

- **We thought we were playing it smart:**
  - Trials for **mild** AD are more of a rarity
  - We anticipated rapid and easy enrollment to that cohort
  - Trial involved a different drug and route of administration (topical) from other studies

CASE STUDY

By the time we opened, there were only two months left to enroll

Despite best efforts, we only consented one subject before enrollment closed…

…and that subject screen failed

What went wrong?

Unanticipated changes to enrollment

- *Mild AD cohort enrolled rapidly study-wide and closed early*
- *Enrollment communications from Sponsor were infrequent*

Unappealing to population

- *Patients preferred oral or injectable treatments over topicals*
- *Topicals viewed as potentially less effective*

No clear recruitment strategy

- *Overly confident that enrollment would be easy*
- *Did not adequately identify resources upfront*
- *No preparation for potential complications*

WHAT SHOULD WE HAVE DONE DIFFERENTLY?

Effective protocol feasibility would have helped us to avoid these issues

Unanticipated changes to enrollment

Established and maintained **effective communication** between all parties for study-wide **enrollment updates**

Unappealing to population

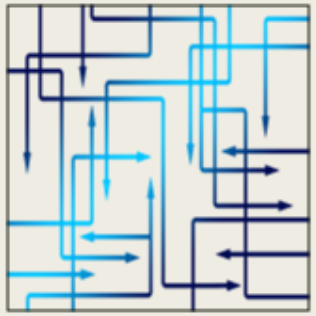
Held **upfront discussions** with Investigators about the **selling points of the study treatment**

No clear recruitment strategy

Exercised caution and properly **established a recruitment strategy** to **identify resources** and prepare for potential complications

WHY IS PROTOCOL FEASIBILITY SO DIFFICULT?

There are many factors you need to take into consideration in order to effectively determine whether or not a study is right for your site



Logistics

- Site infrastructure
- Resources
- Study timing

Population

- Subject recruitment and retention
- Study portfolio

Finances

- Study budget
- Staff and site costs

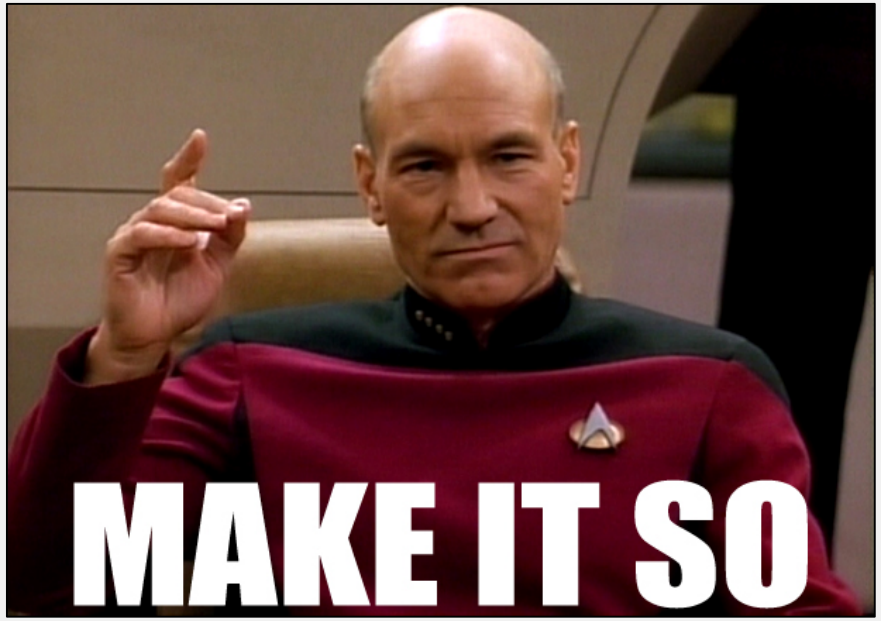
Purpose/Merit

- Protocol design and objectives
- PI education
- Impact

If we open this trial at our site, will it be successful?

Success defined as:

- ***Completion of study objectives***
- ***Meeting enrollment goals***
- ***Effectively covering all study costs***



- ***And making a difference in the world ☺***

STANDARD FEASIBILITY PROCESS

Sponsor/CRO sends feasibility questionnaire to site

Site completes questionnaire

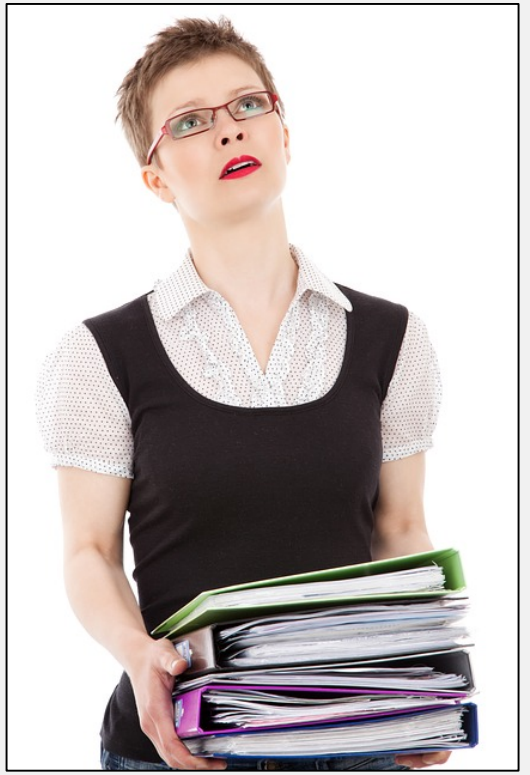
Site qualification visit takes place

Site selected

- **Site demographics** – previous experience, staff/investigator qualifications, site equipment and resources
- **Study recruitment potential** – patient population and frequency, referral systems

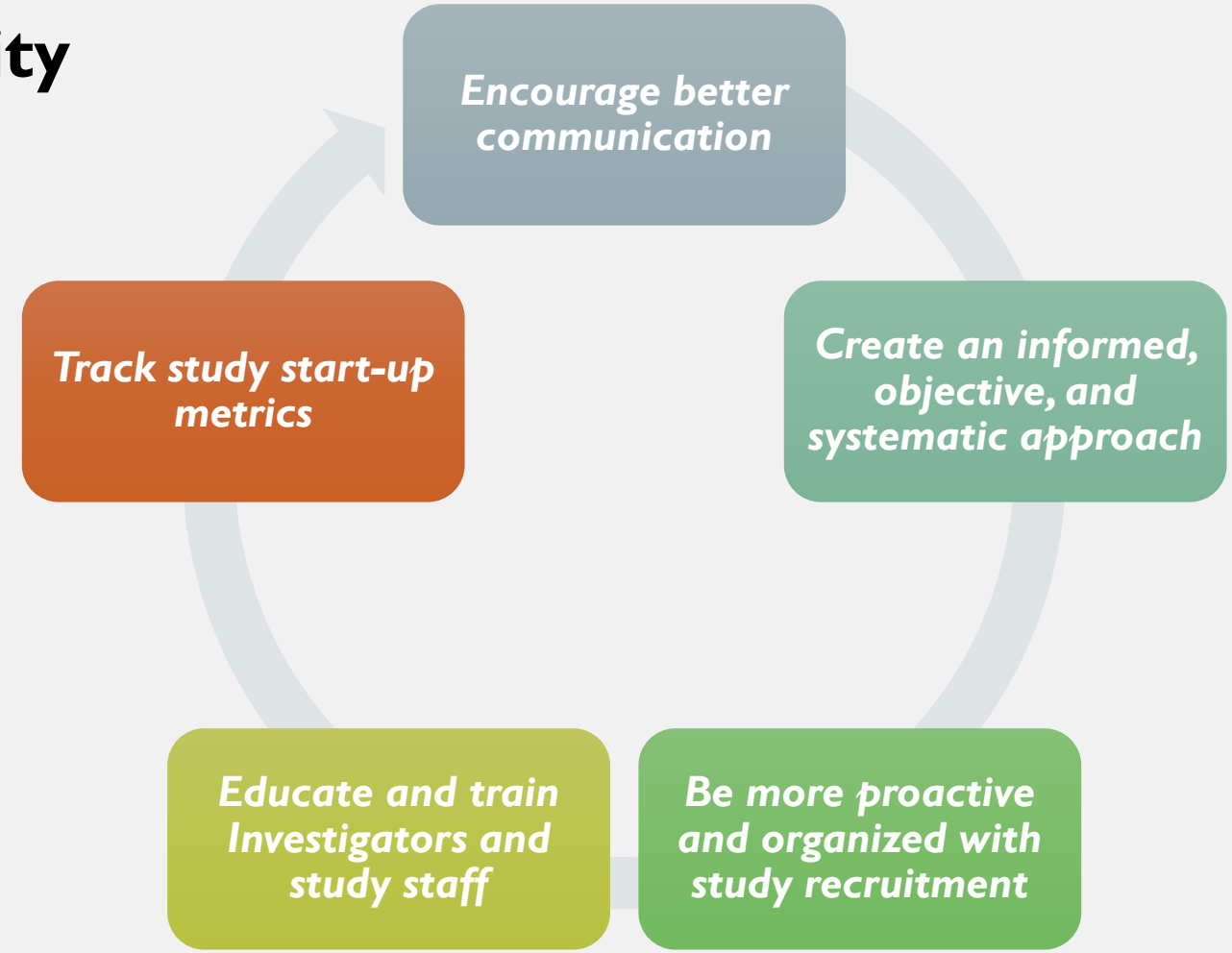
What isn't great about this?

- **Industry sponsored site questionnaires all tend to be the same, which can lead to a cut-and-paste job**
- **Site qualification visits can feel worthless**
  - **Uninformed CRA's**
  - **Limited time with PI**
- **Site selection isn't an informed decision**



Refining our protocol feasibility process became a priority:

- Communication
- Approach
- Organization
- Education
- Tracking



- And these are the lessons we learned…

ENCOURAGE BETTER COMMUNICATION

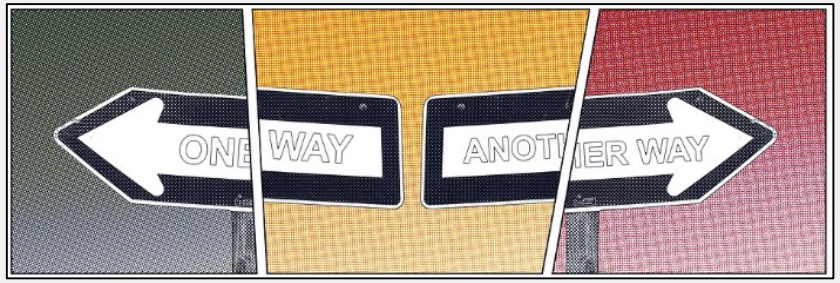
- **Familiarize yourself with rules, policies, and operations (and make friends!)**
  - Many essential departments and processes involved
- **Focus on your team**
  - Connections between Investigators and study team builds rapport and allows for all perspectives to be heard
- **Know your contacts and history**
  - CRO, Sponsor, Medical Monitor
  - Have you worked with this company before? How did that go?
- **Reverse Feasibility Form**

REVERSE FEASIBILITY FORM

Start-up feasibility process can feel like a one-way street of assessment and approval, but it's not!

- **Study status**
  - Where is Sponsor at with site selection? Are other sites already enrolling?
  - Planned duration of enrollment, significant dates

- **Study components**
  - Description of study, if not already provided
  - What are the optional portions of the study?



CREATE INFORMED AND OBJECTIVE APPROACH

- **Ensure that you have a fair process for study selection**
  - Multiple Investigators = Multiple interests and priorities

- **Have a system/reference in place to prioritize start-up with transparency**
  - Essential when there many trials being considered or are already in start-up
  - Hold meetings to ensure PI's and study team are aware of the priority rationale

- **Trial Feasibility Matrix and Study Timeline Tracker**

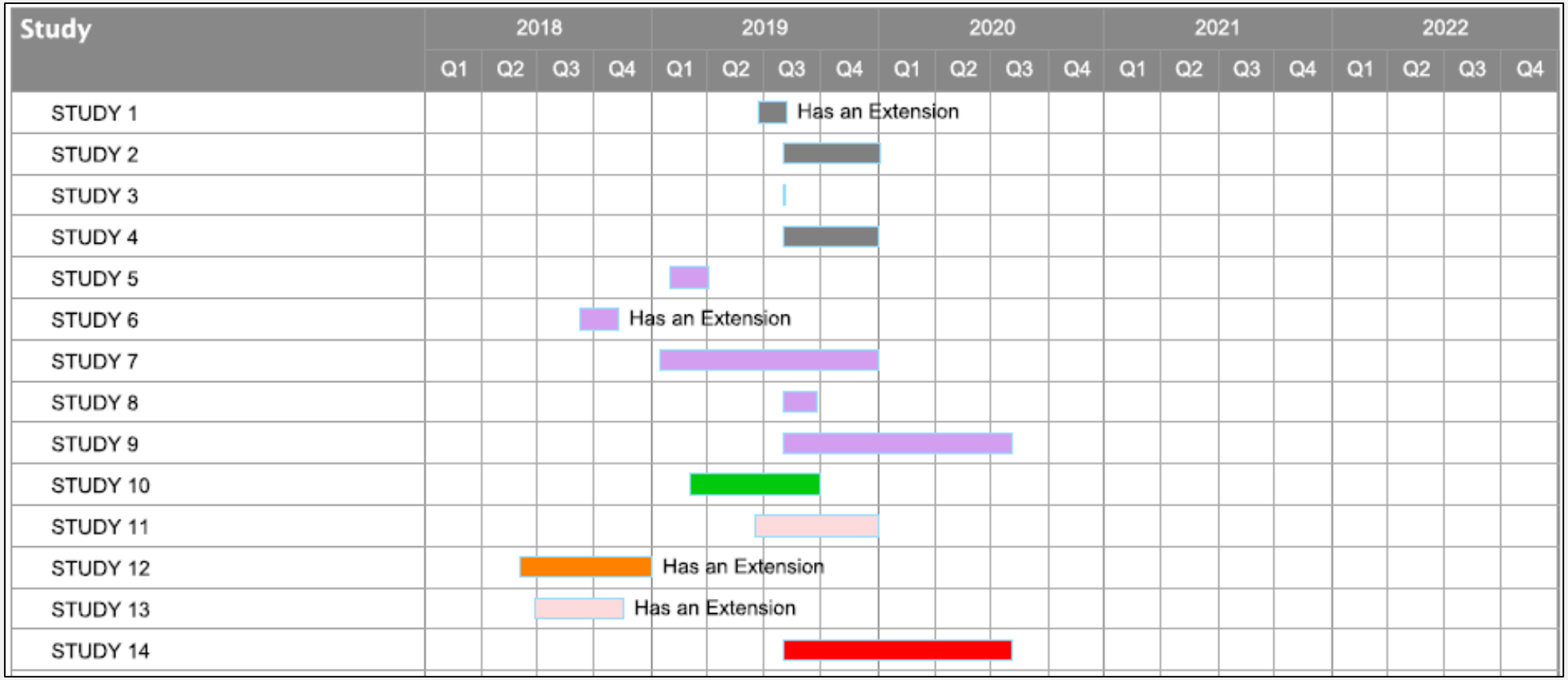
TRIAL FEASIBILITY MATRIX

Name of Study: **PI:** **Date Evaluated:**

Area of Determination	0 points	1 point	2 points	3 points	Points
Science and PI Importance	Little to no impact to science; past study data does not show favorable results	Minimal scientific importance; PI somewhat motivated to participate	Moderate scientific importance; PI motivated to participate	Would significantly contribute to science and/or PI is very motivated to participate	
Financial Impact	No funding and would require a significant amount of Admin/CRC time	No funding and require very little time from Admin/CRC (ex: registries)	Is funded with a small budget	Is funded with a large budget	
When was Regulatory Packet Received	< 1 month	1-3 months	3-6 months	>6 months	
Duration until Enrollment Closes	>12 months	8 - 12 months	4-8 months	3-4 months	
Competing Studies	≥3	2	1	none	
				Total (out of possible 15)	
				Priority	

Priority Scoring:
0-4 Points = Low **5-10 Points = Moderate** **11-15 Points = High**

STUDY TIMELINE TRACKER



- **Provides high-level review of open enrollment timelines and projections**
- **Colors representative of different disease groups/indications**

ORGANIZE STUDY RECRUITMENT

Internal

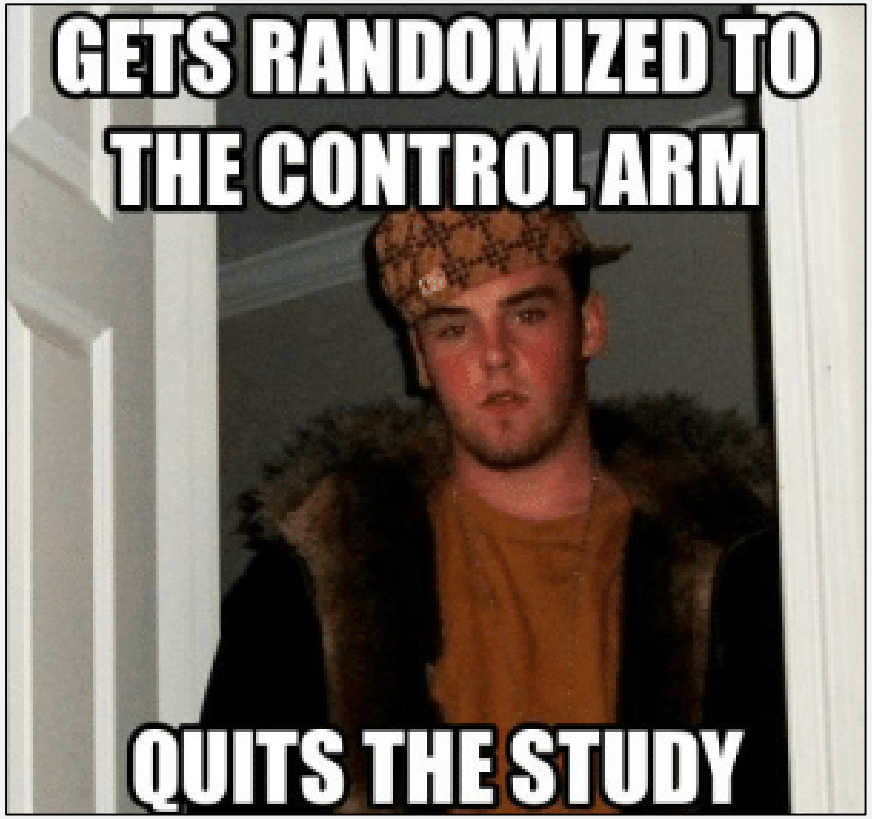
- Chart reviews
- Screening calls
- Study update distributions (emails, meeting presentations)
- Clinic discussions
- Flyers

External

- Websites, Social media, Google Ads
- Printed materials, Radio/TV spots
- Patient advocacy groups
- Central Ad services

RECRUITMENT PLAN

- **Bring PI's and study team together to develop recruitment strategy**
  - Determine enrollment goal and timeline
  - Identify unique trial characteristics and selling points
  - Troubleshoot potential snags
  - Review study-specific recruitment materials
  - Plan to re-visit throughout the study to track progress
  - Check the study budget for advertising funds

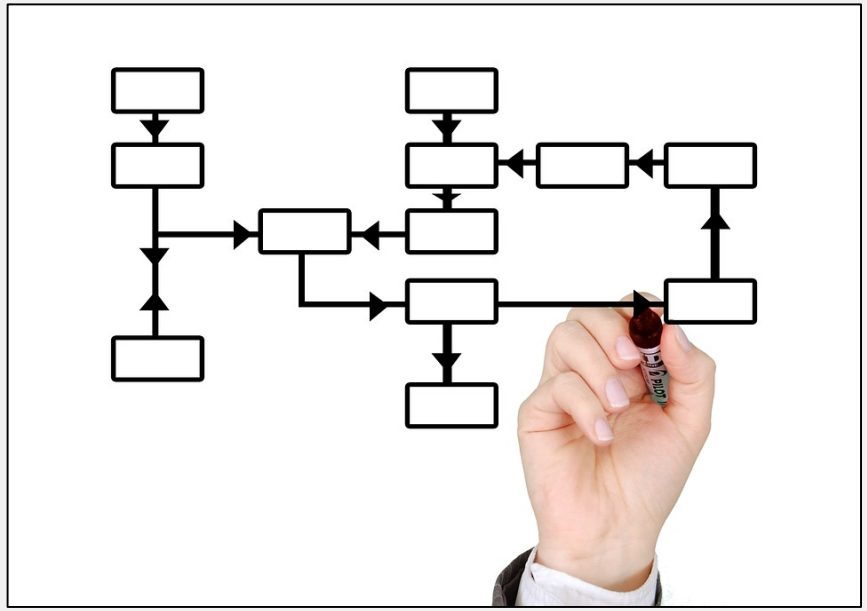


FOCUS ON INVESTIGATOR AND STAFF EDUCATION

- **Confirm that PI/Sub-I and study teams have received adequate training to understand their study roles and responsibilities**
    - CITI and GCP ain't cutting it
    - Important items to discuss with prospective Investigators and team:
        - Time commitment
        - Consequences of non-compliance
- **Investigator and study team training, includes relevant topics:**
    - Proper regulatory practices
    - Roles and responsibilities
    - Study start-up process

STUDY START-UP METRICS

- **Know your capabilities for start-up timeline**
  - Big ticket items: Receipt of study materials, decision to pursue, IRB approval, contract execution, open to enrollment



- **Using a high-level and detailed tracking system will provide a more accurate representation of your process**
  - Will lead to more informed decisions during feasibility

Clinical Research Internal Project Plan

IRB: 20208

PI: Bob Ross

Primary CRC: Steve Ross

Sponsor: Happy Trees, Inc.

Reg Tasks	Completed Date	Days (approx)	Comments/Delays
Site Selected	**6/5/2019**	0	
Reg Packet Received from Sponsor	**6/7/2019**	2	
Reg PM ICF Drafting (Draft ICF Sent to Sponsor)	7/11/2019	34	
Sponsor Reviewing ICF (ICF Finalized by Sponsor)	7/11/2019	0	
IRQ Prep	7/11/2019	9	
Initial CRRC/IRB Submission Date	**8/8/2019**	28	
IRB Scheduling (Initial IRB Review Date)	8/9/2019	1	
IRB Comments (Clarification Memo Received)	8/15/2019	6	
RPM addressing comments (IRB Clarifications Sent to Sponsor)	8/15/2019	0	
Sponsor addressing comments (IRB Clarifications Finalized by Sponsor)	8/26/2019	11	
Finalized for resubmission (Resubmission Date)	8/28/2019	2	
IRB Re-review	9/4/2019	7	
IRB Approval Date	9/17/2019	13	
CTA Finalized		-43725	
SIV		0	
Green Light from Sponsor		0	
Open to Enrollment		0	

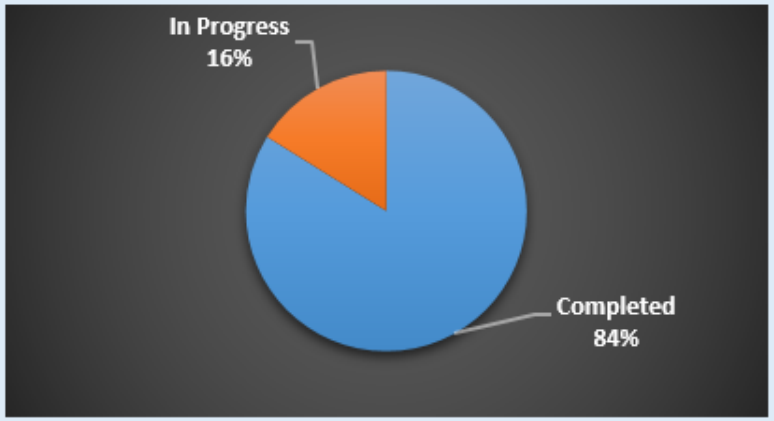
Budget Tasks	Completed Date	Days	Comments/Delays
Budget Received	6/5/2019	0	
Negotiate budget/payment terms -Round 1	6/20/2019	15	
Negotiate budget/payment terms -Round 2	7/12/2019	21	
Negotiate budget/payment terms -Round 3	7/20/2019	8	
Final Budget Review/Approval	8/1/2019	57	

STUDY START-UP TRACKER

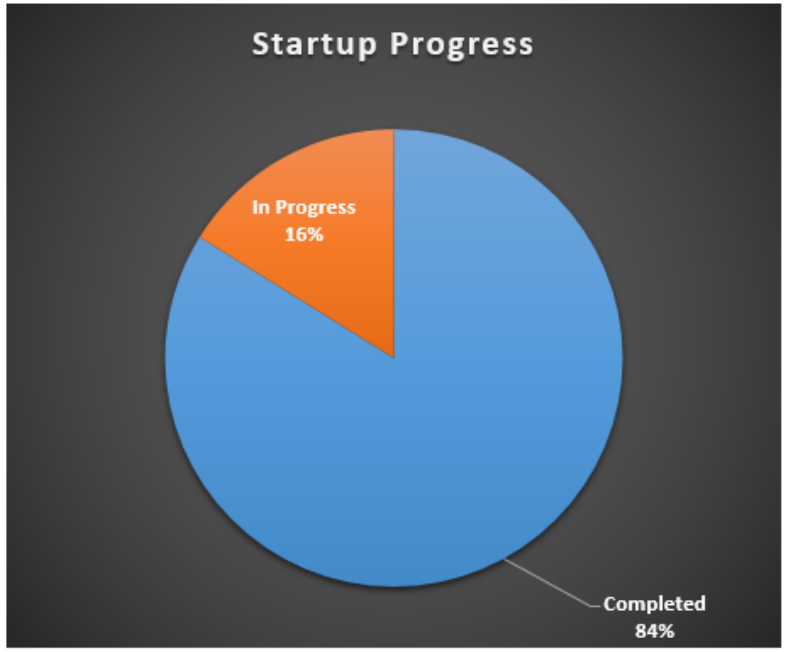
Data Entry View

High-level View

IRB: 20208	
PI: Bob Ross	
Sponsor: Happy Trees, Inc.	
IRB Submitted:	8/8/2019
IRB Approved:	9/17/2019
Contract Executed:	
Enrollment Opened:	
Primary CRC: Steve Ross	
Variances:	



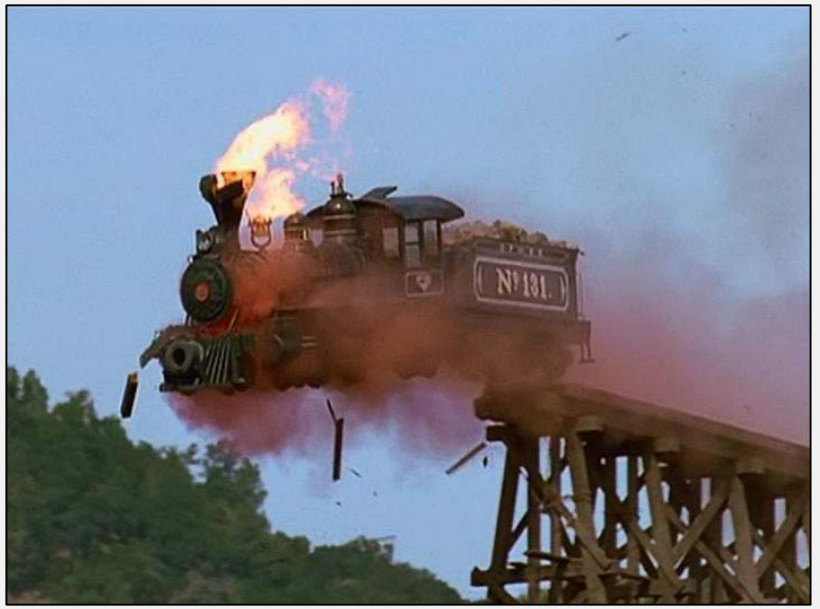
End Project View



End Project Evaluation	
Pre-Submission Days:	73
Submission to IRB approval:	68
Days for CA Approval:	42
Projected Open to Enrollment Date:	10/3/2019
Actual Open to Enrollment Date:	
Variance:	-43741
Primary Variance Due to:	

Variances (Brief Summary, Top 5 will display on Summary Page)

CASE STUDY - TAKEAWAYS



Protocol feasibility may very well save one of your trials from going off the rails

- **Communication:** Get to know the people you will rely on to make your trial a success
- **Approach:** Consider a new trial from multiple perspectives in order to maintain an objective and fair selection process
- **Recruitment:** Develop a plan upfront for better accrual outcomes
- **Education:** Continually engage and educate your Investigators and study teams
- **Tracking:** Start-up metrics will lead to evidence-based, realistic study projections for future trials

DEAL BREAKERS

Sponsors/Funders say no when:

- Site has no experience
- No eligible participants
- Inadequate staff to conduct the study
- Budget
- Poor performance on previous trials
  - Compliance Problems
  - Didn't meet enrollment

Sites should say no when:

- PI isn't interested in the study
- Don't have eligible participants
- Budget doesn't cover costs
- Study design isn't compatible with standard of care/clinic procedures
- Staff don't have time to conduct the study

SAYING NO… *THANK YOU*

- **Declining studies that are not feasible is important for a site's/PI's success**
  - Conserves resources
  - Financial stability
  - Maintains reputation as a reliable site/PI with sponsors

- **Communicate the reason(s) you are declining the study**
  - Competing studies/Time– let the sponsor know you are a good fit for future study opportunities
  - Participants – let the sponsor know what inclusion/exclusion criteria would make enrollment difficult at your site
  - Budget – let the sponsor know what particular areas of the budget do not allow you to cover your costs

TRACKING SUCCESS AND FAILURES

The best prophet of the future is the past - Panda Express

- Record the information you collected during your feasibility analysis with the benefit of hindsight/experience
- Store the information centrally where others can benefit from your experience
- Record information at the time of study/account closure
  - Much harder to re-create this information at a later date
- Track all studies
- Important because PIs/Staff they take their knowledge with them when they leave

KEY POINTS TO TRACK

- **Enrollment**
  - Expected enrollment (defined by contract/endpoints)
  - Actual enrollment and why (screen failures, time, retention)
  - Expected enrollment end date
  - Actual enrollment end date and why (sponsor issues, available participants, competing studies)
  - What recruitment tools did you use? Did they work?
- **Financial**
  - Did the study cover costs or end in deficit?
  - Which costs were higher than expected? Did you miss items in the budget? Were funds managed appropriately?

KEY POINTS TO TRACK

- **Track relationships with the Sponsor/CRO/Funder**
  - Poor, fair, good and why?
- **Resources**
  - What were the challenges? What went well? Consider scheduling, equipment, staff turnover
- **Science**
  - Were the study endpoints met?
  - Publications, collaborations, new grants/funding, impact

QUESTIONS?

REFERENCES

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