HOW TO AVOID DISASTROUS CLINICAL TRIAL DESIGN DECISIONS

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OVERVIEW

• Introduction
• Importance of Proof of Concept and early-stage trials
• Some good and bad examples
• Advice for avoiding disasters
• Conclusion
Bay View Analytics offers a comprehensive suite of consulting services in survey design and statistical research. Our services build on nearly two decades of research design, sampling, survey design, and statistical analysis expertise.
Core projects cover all stages of biopharmaceutical project development, and our experience runs the gamut, from early leads generation, pre-clinical and clinical trial designs, regulatory submissions, and late-stage commercial products.

We work with all facets of the biotech and biopharmaceutical industry, such as diagnostics, devices, digital apps, and therapeutics.

Recent Biotech/Pharma Consulting Projects

• Lead generation using genomic and proteomic data for an early-stage biotech startup.
• Proof of concept prior to an FDA meeting for a device company.
• Clinical trial design, sample size, and statistical plan writing for a biotech startup.
• Clinical trial data analysis and methods write up for publication for a biotech startup.
• Meta-analysis for an FDA submission for a new indication for a large pharmaceutical company.
• Analysis of EHR data to develop prevalence models using machine learning and other data science techniques for a large pharma company.
• SBIR, NIH, and NSF grant writing assistance for a biotech startup.
• Expert witness testimony for a global diagnostic company and for a biotechnology company.
Early-Stage and Proof of Concept Trials

Foundation for the Future
Clinical development builds on itself

**Regulatory Actions:**
- Lead Discovery
- Preclinical Testing
- Phase I
- Phase II
- Phase III
- Post-Marketing Development

**IND Application:**
- Target identification
- Laboratory and animal studies

**NDA Application:**
- In-human clinical studies

The steps of the drug development pathway flow from the prior ones – each step is dependent on the ones before it and can affect the ones following.
CLINICAL DEVELOPMENT IS NOT ISOLATED FROM THE BUSINESS DEVELOPMENT

Regulatory Actions:
- Lead Discovery
- Preclinical Testing
- Phase I
- Phase II
- Phase III
- Post-Marketing Development

Research Actions:
- Target identification
- Laboratory and animal studies
- In-human clinical studies
- Funding
- Company growth
- Skills Development
- Clinical and manufacturing skills growth
- Commercial skills growth

Business Actions:
- Funding
- Company growth
- Skills Development
- Clinical and manufacturing skills growth
- Commercial skills growth
- Competitive Intelligence

The results and details of clinical development directly affect business development, which then directly affects capabilities for clinical development.
A good early-stage / PoC trial can be the strong foundation for successful development

Getting it right early can make it easier to succeed – your early-stage clinical development and proof of concept trials are very important!
Proof of Concept (PoC) is a demonstration in principle with the aim of verifying that some concept or theory has practical potential or an idea or method is feasible.

Can the product be developed? Does the product work?
Proof of Concept Objectives in Therapeutics

- Validation of the relevance of your therapeutic or diagnostic in pre-clinical & early clinical tests
- Defining your potential market
- Show early evidence of clinical efficacy
- Eliminate blind alleys/failures early
- Provide an assessment of commercial potential
Some more notes on PoC

- PoC is not just one experiment at one time; you can have multiple PoCs during development
- PoC is different for different types of products
- Think of PoC as part of the exploratory science and have a checklist of what you need to show
- Realize that therapeutic/diagnostic studies may be valuable even if they have low power
- PoC should include estimates for market size & potential growth if you are looking for $$

Don’t undertake PoC studies (or any studies) unless you understand how you might use it to change or even cancel a project
## Proof of Concept = Pull out Checkbook $$$

<table>
<thead>
<tr>
<th>Type</th>
<th>Devices &amp; Diagnostics</th>
<th>Digital Health, Health Apps, &amp; mHealth</th>
<th>Therapeutics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Angel Investors</strong></td>
<td>Prototype &amp; preliminary in-vivo or retrospective testing</td>
<td>Prototype, algorithm, ‘vaporware’, market opportunity</td>
<td>Publishable data describing efficacy &amp; small animal testing and to support a provisional patent application</td>
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<tr>
<td><strong>SBIR</strong></td>
<td>Animal testing or in-vivo testing to show comparability to existing devices</td>
<td>Demonstrate need, user interface, comparison to non-digital solution</td>
<td>Supports pre-clinical research aimed at discovering &amp; optimizing lead molecules</td>
</tr>
<tr>
<td><strong>Investors, Partnerships, and Regulatory</strong></td>
<td>Working device &amp; sensitivity, specificity, equivalence, enough in-vivo data for comparisons</td>
<td>Beta testing, effectiveness compared to non-digital solution, Engagement, Retention</td>
<td>Establish the safety of drug/biologic candidates in the target population and explore the relationship between the dose and the desired outcome.</td>
</tr>
</tbody>
</table>
What can a PoC influence?

- Regulatory Approval
- Company Financing

Required
What can a PoC influence?

- Regulatory Approval
- Company Financing
- Marketing Claims
- Insurance Reimbursement
- Guideline Inclusions

Required

Directly Derived from Development Results
What can a PoC influence?

Required
- Regulatory Approval
- Company Financing

Directly Derived from Development Results
- Competitive Advantage
- Marketing Claims
- Insurance Reimbursement

Internal Strategy
- Product Lifecycle
- Company Growth Plans

Bay View Analytics
YOU NEED A DEVELOPMENT PLAN FOR PoCs

- Work backwards
- Develop your plan from molecule/NCE through approval
- Identify costs, timelines, clinical trial designs
- Incorporate clinical trial designs into pre-clinical model (i.e.; prophylaxis vs. treatment models)
- Use the plan daily to ensure consistency and compliance

Remember: Approval is the bare minimum! You still need a competitive product to continue to succeed.

Think forward – plan for what will be required, not what is currently.

Plus, it is impressive to potential investors ($) to have this plan.
SOME REAL LIFE EXAMPLES
Some Major League PoC Failures

• Gilead Remdesivir – repositioning of a failed compound initially showed shortening of recovery time but ...

• Biogen Aduhelm – approved by FDA in 6/2021 but …

• HeartMan mobile CHF app – could not recruit required sample size & both control & intervention showed significant improvements but …

• One way to improve your chances of FDA approval even with PoC failure is an EUA or orphan drug designation
Development Timeline: Jan 2015 – Sep 2021

1. Develop and design StoneClear & BreakWave with UWash
2. Small single arm clinical trial to show efficacy in man
3. Applies/Receives first SBIR ($1.75M) for design of all parts of BreakWave
4. Identify specific application and possible growth opportunities: Partnership with NASA to accelerate development ($350K)
5. SBIR FastTrack NIH grant ($1.75M)
6. First funding round Series A led by MedVentures ($4.6M)
7. SBIR Commercial Readiness program grant NIH for StoneClear ($1.0)
8. GE/SonoMotion strategic partnership
9. FDA/ITA approval for First-In-Human clinical trials
10. Approval of StoneClear in June 2019 with single-arm clinical trial of StoneClear compared to historic data
11. BreakWave PoC non-inferiority trial is too small – revise & resubmitted to FDA in Oct 2021

PoC CASE STUDY - DEVICES: SONOMOTION
PoC Case Study - Devices: CareTaker MedicalTM Continuous BP & HR Monitor

- Bluetooth, wireless, encrypted, HIPAA compliant
- Continuous Beat-by-Beat BP
- Mobile, integrates with hospital network
- Designed for use in OR, Hospital, at home

PoC for mezzanine round:
- Small clinical trial
- Compare device to arterial line (SoC)
- Examine correlations

PoC for success: Measures BP & HR changes under anesthesia

PoC Variables Considered:
- Patient population – Multiple types of surgery monitoring, including pregnant women
- SoC – Direct synchronous comparison with invasive SoC
- Stats – Analysis planned based on historical precedent
- Publication Plan – Trials designed and timed for journal submissions
- Marketing – Usability attributes surveyed and compared to SoC
No easy way to transfer the data for analyses, no easy way to match CareTaker data to the arterial line data
PoC Case Study – Digital & mHealth:

How to measure ROI

- Minutes of engagement
- Minutes saved using App
- Times used per day/week/etc
- Continued engagement/adoption

For digital health the outcome must also include information on the ease of use & objective outcomes
Founded in 2011 by Tobias Ritter, PhD, MBA

The Proof of Concept (for the next round of funding & for Big Pharma partners) was to show the improved profile of 20 marketed pharmaceutical compounds chosen from a database that shows compounds:

- We can fluorinate with high probability;
- We can own (i.e. the fluorinated version is a NCE we can patent); and
- Once fluorinated, have the potential to improve drug properties
  - increased half-life / reduced dosing frequency
  - blood-brain-barrier / cell membrane penetration
  - increased bioavailability

• Raised $250,000 from VC Angels

Did they succeed?
SF0166 is a small molecule integrin antagonist designed to treat retinal disease, including Age-related Macular Degeneration (AMD) and Diabetic Macular Edema (DME), via topical administration to the eye.

SF0034 is a potent and selective KCNQ2/3 activator designed for suppressing neuronal hyperexcitability that may be a superior anti-epileptic drug (AED) for treating patients with partial-onset epilepsy.

PoC proved the technology worked, but they still needed a way to explain their concept and sell the idea.
POC CASE STUDY – THERAPEUTIC: SCI FLUOR (NOW OCUTERRA)

Patents/ Patients/ & $$$

- December 19, 2017 – SciFluor Sciences Announces Positive Results of Phase 1/2 Study in Wet Age-Related Macular Degeneration
- September 28, 2017 – SciFluor Life Sciences Announces Positive Results of Phase 1/2 Study in Retinal Diseases
- Oct. 17, 2016 - SciFluor Life Sciences Announces First Patients Dosed in Retinal Program with Investigational New Drug Application for SF0166 Topical Ophthalmic Solution
- August 1, 2016 - SciFluor Life Sciences Enters Clinical Trial Stage for Novel Treatment for Retinal Diseases
- March 9, 2016 - SciFluor Life Sciences Awarded Second U.S. Patent for Integrin αvβ3 (SF0166) Inhibitors Designed for the Topical Treatment of Retinal Disease … 6 additional patents in 2017
- June 17, 2015 - SciFluor Life Sciences Patented Compound SF0034 Highlighted in Research Published in The Journal of Neuroscience
- April 22, 2015 - SciFluor Life Sciences Raises $30 Million and Names William Koster, PhD, Former CEO of Neurogen Corp., as Chairman

SciFluor rebranded as OcuTerra based on success of first asset in retinal disease. The asset, OTT166, is currently in Phase II while the company just closed a $35M Series B funding round.
SMALL INTERLUDE: DATA

IT’S USUALLY ALL ABOUT THE SAMPLE SIZE AND POWER BUT FINDING SIGNIFICANCE IN SUBGROUPS WILL NOT HELP
Where will you need data?

- Proof of concept
- Understanding competitors – what is the state of the art right now?
- Assay Validation – what is your CV?
- Due diligence
- Engineering specifications - what goes into your device?
- Ease of use – training time?
- In vitro models
- Pre-clinical/Animal models/drug delivery
- Diagnostic accuracy / sensitivity / specificity
- Clinical trials (that FDA end of Phase II meeting)
- Beta testing your app
- Manufacturing specifications
- Digital users – the GUI
- Compliance – are you using rfd tagging?
- Quality Control – shipping/shelf life/heat/cold…
- Quality Assurance

...EVERYWHERE
Your research = Your data

- Data are and will be the basis for funding, development, approval, uptake, etc. of your product
- Think carefully about what you collect and how you collect it
  - Consider what variables you measure and what ones you don’t
- Value good data storage, curation, and analysis

It is easier to develop a bad product with good data than a good product with bad data.
What kind of data should you collect?

- Data come in many levels: nominal, ordinal, interval, ratio
- Metrics are important but consistency and spread are more important. Investors will care more about your variability than your average performance* - consistency, reliability, reproducibility*
- Charts always win over tables – but don’t get creative with your axes
- And don’t get creative with your statistics (change, percent change, relative change, relative percent change, fold change, …)**

**2015, StatTools in Quality Progress
What should you do with this data?

• Protect it
• Don’t talk about it
• Don’t publish it
• Don’t share it
• Always get an NDA
• Patent Attorney
• Continue to Innovate
SOME TAKEAWAYS FOR DESIGNING GOOD EARLY TRIALS

OR HOW TO AVOID POOR ONES
ADVICE FOR YOUR EARLY-STAGE RESEARCH

Plan
Consider the when, how, and why to perform a PoC

Consider Outcomes
How can a positive or negative (or inconclusive) result impact development and investment pitch story

Think Ahead
Understand the outcomes (data) can impact long-term strategy
THANK YOU!
ANY QUESTIONS?

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