How to avoid disastrous clinical trial design decisions

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Julia Seaman & I. Elaine Allen

Overview

- Introduction
- Importance of Proof of Concept and early-stage trials
- Some good and bad examples
- Advice for avoiding disasters
- Conclusion

Introduction to Bay View Analytics

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.

Julia Seaman, Ph.D.
Director of Research

I. Elaine Allen, Ph.D.
Senior Advisor &
Professor of Epidemiology
& Biostatistics, UCSF

Statistical and Scientific 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:

IND Application

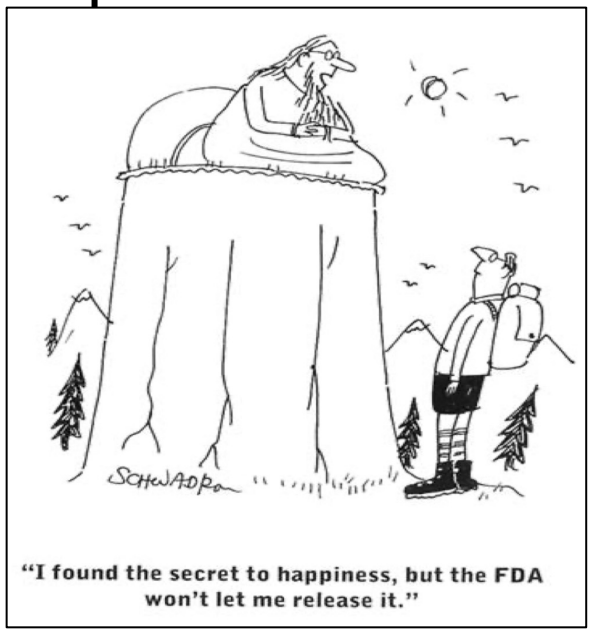
NDA Application

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



"I found the secret to happiness, but the FDA won't let me release it."

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:

IND Application

NDA Application

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

Business Actions:

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

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

Asset testing

Cell and animal model

Early-stage and Proof of Concept (PoC) trials

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 IS A KEY TEST FOR ANY PRODUCT

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

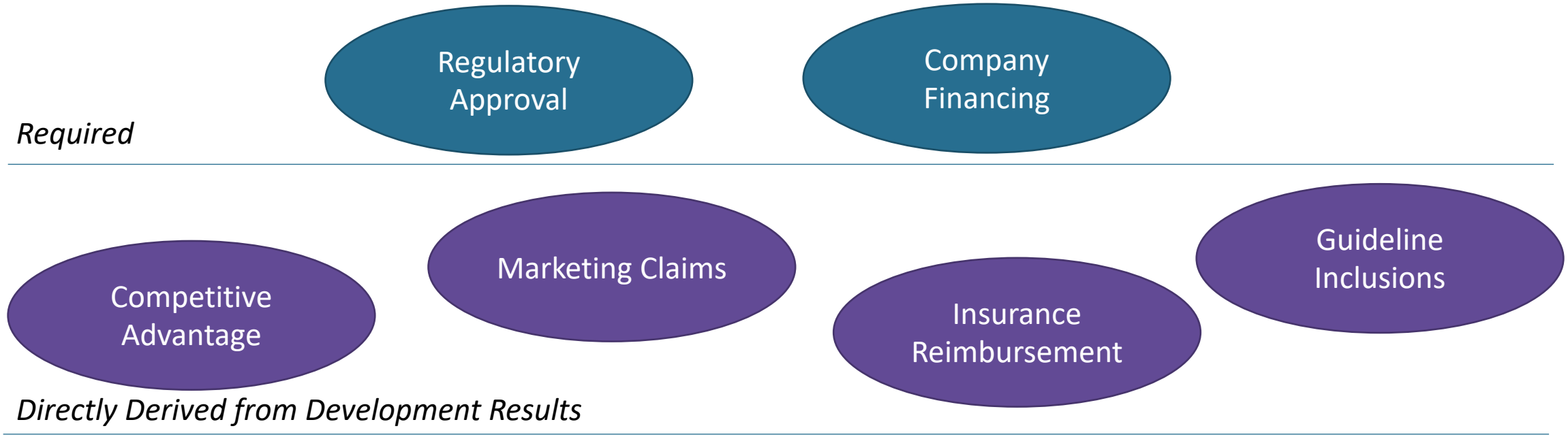
Proof of Concept = Pull out Checkbook $$$

Everyone looks for something different from a PoC

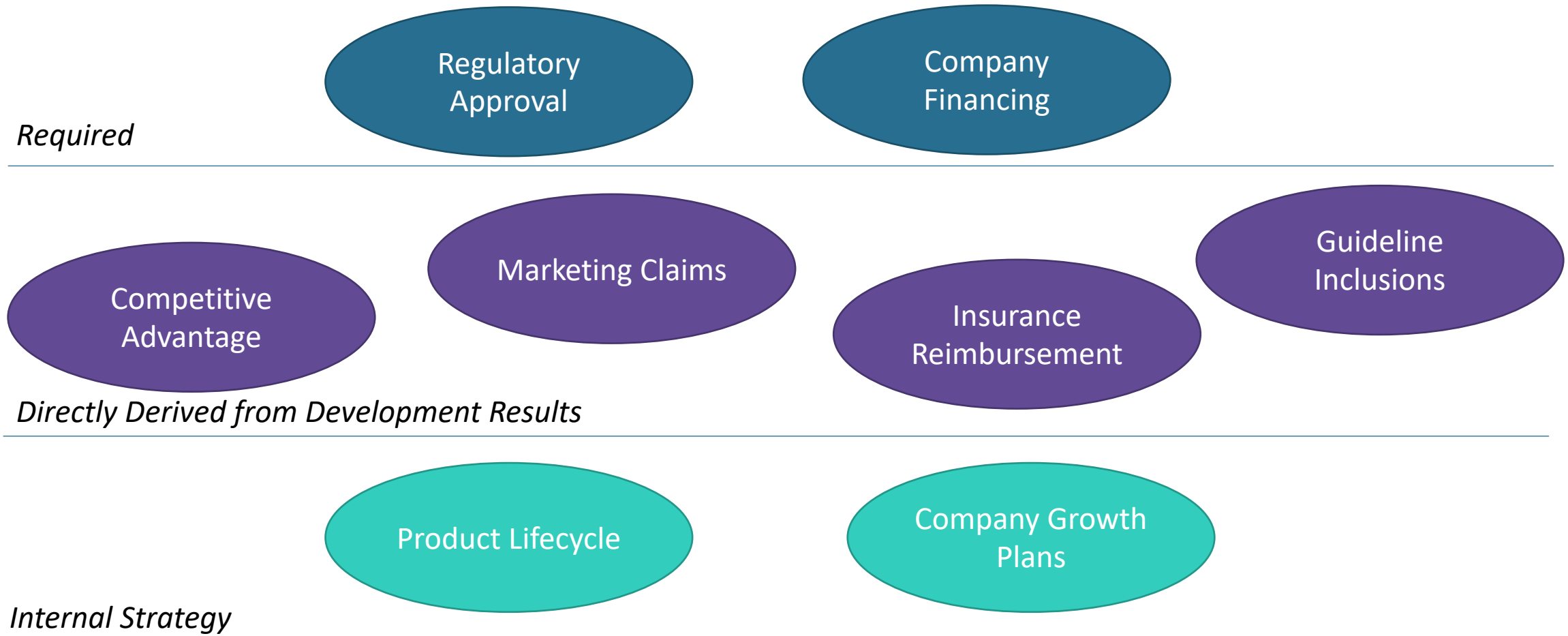
Type	Devices & Diagnostics	Digital Health, Health Apps, & mHealth	Therapeutics
Angel Investors	Prototype & preliminary in-vivo or retrospective testing	Prototype, algorithm, 'vaporware', market opportunity	Publishable data describing efficacy & small animal testing and to support a provisional patent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

What can a PoC influence?

What can a PoC influence?



What can a PoC influence?



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*

PoC Case Study - Devices: SonoMotion

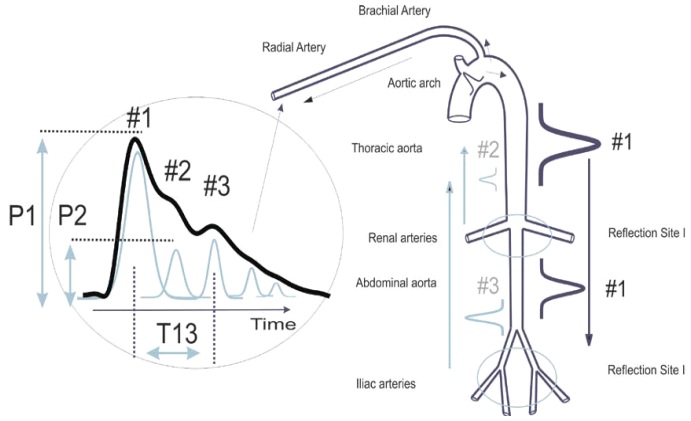
SonoMotion

Innovations in Non-Invasive Stone Treatment

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 **PoC**
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:
CareTaker MedicalTM Continuous BP & HR Monitor



PoC for mezzanine round:

- Small clinical trial
- Compare device to arterial line (SoC)
- Examine correlations

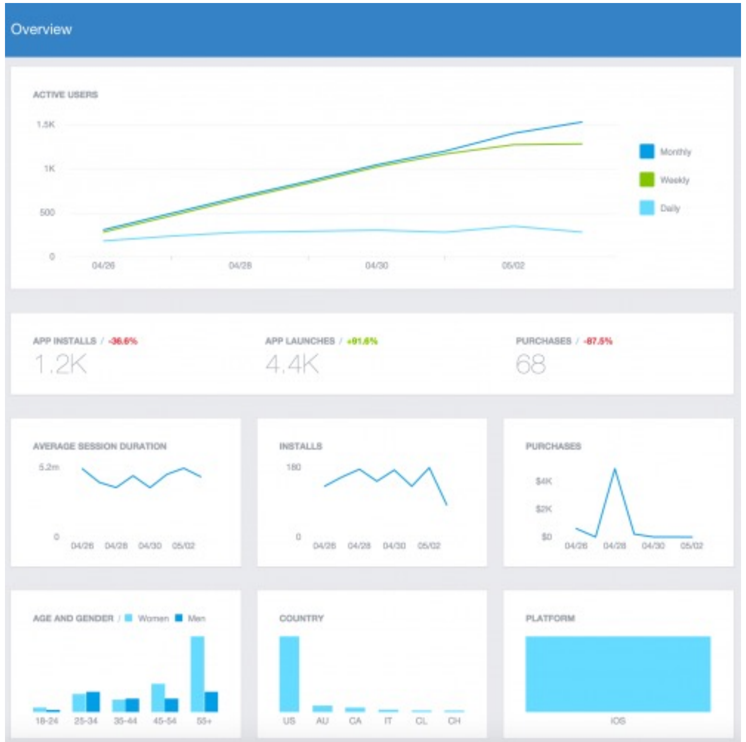
PoC for success: Measures BP & HR changes under anesthesia

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

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

PoC Case Study – Digital & mHealth: Spire^{TM}/HEART beta test



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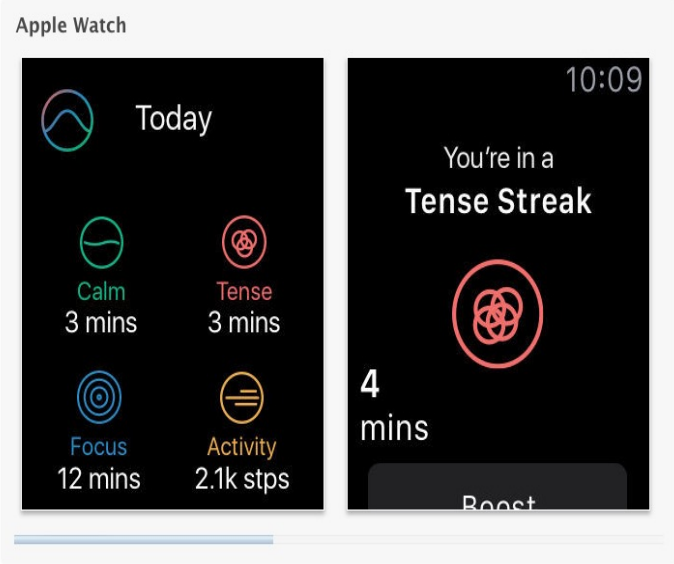
No easy way to transfer the data for analyses, no easy way to match CareTaker data to the arterial line data

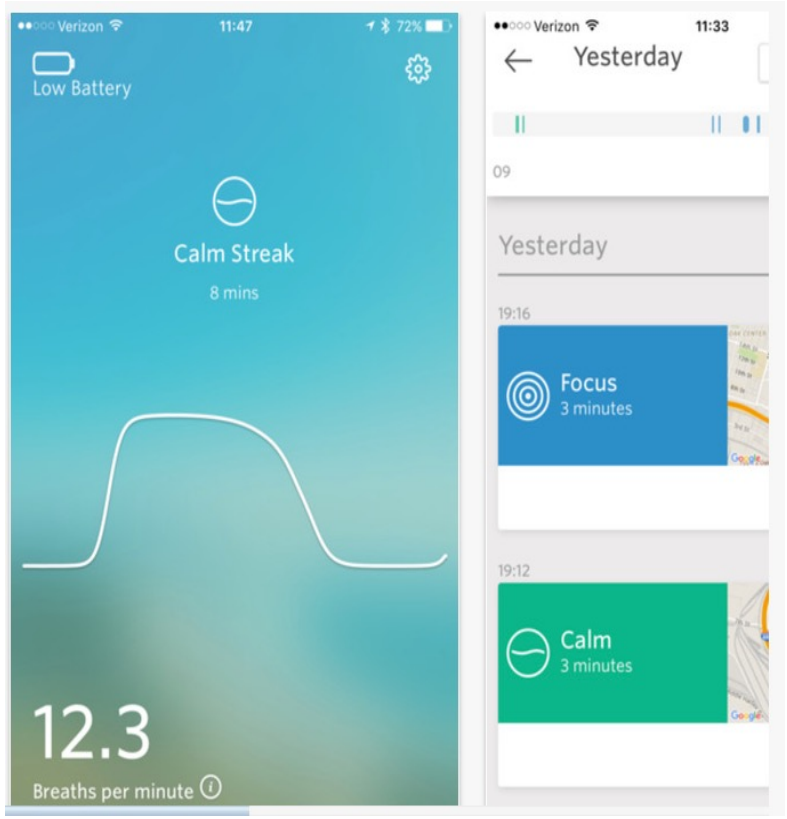
https://www.mhealthevidence.org/
https://mhealth.jmir.org/

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

https://www.mhealthevidence.org/
https://mhealth.jmir.org/

PoC Case Study – Therapeutic: SciFluor (now OcuTerra)

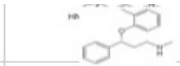
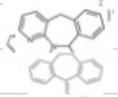
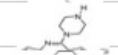
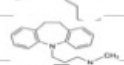
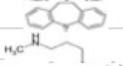
Founded in 2011 by Tobias Ritter, PhD, MBA

Prof @ Harvard in Chemistry

Takeru Furuya, PhD

- 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?

4. A fluorinated atomoxetine.		63-94%	40%	5 h	Hepatic, via CYP2D6	SNRI	under patent until 2017 but maybe an earlier entry of a generic into the US market	
5. A fluorinated sertraline.		44%	96%	26 h	Hepatic (N-demethylation mainly by CYP2B6)	SSRI	generic since 2006	
6. A fluorinated trazodone.		high	90-95%	3-6 h	Hepatic	SARI	approved in 1981	
7. A fluorinated mirtazapine.		50%	85%	25-40 h	Liver (enzymes CYP2D6 and CYP3A4)	noradrenergic and specific serotonergic antidepressants		
8. A fluorinated amitriptyline.		30-60%	>90%	10-50 h (avg. 15 h)	Hepatic CYP2C19, CYP1A2, CYP2D6	tricyclic antidepressant (TCA)	approved in 1961	
9. A fluorinated amoxapine.				8-10 h (30 h for major metabolites)	Hepatic (cytochrome P450 system)	tricyclic antidepressant (TCA)		One of its major metabolites, 7-hydroxyamoxapine, has a dopamine receptor blocking effect, making this drug a common cause of neuroleptic malignant syndrome. Amoxapine is also associated with acute extrapyramidal symptoms and tardive dyskinesia.
10. A fluorinated clomipramine.		Oral ~50%	98%	Clomipramine ~35 h Desmethylclomipramine (main active metabolite) ~50 h	Hepatic	tricyclic antidepressant (TCA)	developed in the 1960s and has been in clinical use worldwide ever since.	
11. A fluorinated imipramine.		30-75%; doubled by cimetidine	95%	11-25 h	Hepatic Main active metabolite desipramine	tricyclic antidepressant (TCA)	developed in the 1950s	
12. A fluorinated nortriptyline.		50-80%	95%	parent drug: 20-30 E-10 metabolite: 8	Hepatic	tricyclic antidepressant (TCA)		
13. A fluorinated trimipramine .		40%	95%	11-23 h	Hepatic	tricyclic antidepressant (TCA)		demethylation and 2-hydroxylation of the arene are the major metabolism
14. A fluorinated maprotiline.		66-70%	88%	27-58 h	Hepatic	tetracyclic antidepressant (TeCA).	developed in the 1980s	
15. A fluorinated nefazodone .		high	99%	3-6 h	Hepatic	SARI		
16. A fluorinated sibutramine.		Absorption 77%, considerable first-pass metabolism		sibutramine approx. 1 h Metabolite 1: 14 h Metabolite 2: 16 h	Hepatic (CYP3A4-mediated)	oral anorexiant	It has been associated with increased cardiovascular events and strokes and has been withdrawn from the market.	Mono-demethylated and di-demethylated compounds are active metabolites

2013-2014 Identify the most promising

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: SciFluor (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
- Jan. 8, 2015 - SciFluor Life Sciences Awarded U.S. Patent for KCNQ2/3 Activator Designed for Treatment of Epilepsy and Related Neurological Disorders

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, …)**

*2004, 2009, 2012 StatTools in Quality Progress
**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?

Julia@bayviewanalytics.com