The process of investigator sponsored research to move advances in cardiology

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Disclosures

- Dr. Cavalcante is a full-time employee of Boston Scientific
  - Before joining BSC…
    - Alumnus of the William J. Harrington Program for LATAM students & Physicians – Univ. of Miami School of Medicine
    - Interventional Cardiologist at the University of Sao Paulo
    - PhD in coronary imaging
    - Post-doctoral research fellowship at Cardialysis / Erasmus MC, Rotterdam
  - Now…
    - Chairman of BSC Global Investigator Sponsored Research Committee
    - Member of BSC Clinical Evidence Strategy Committee

Product Lifecycle

Multiple research components

Research pathways in partnership with Industry

- Bench / pre-clinical research
- Company sponsored trials
  - FIH, EFS, Pivotal IDE trials, PMCF, Phase IV trials
- Investigator Sponsored Trials (Company act as grant giver)
  - Post-market, indication expansion, market expansion, evidence building, cost-effectiveness studies
- Collaborative research agreements
  - Investigator sponsored
  - Certain activities performed by the company (grant giver)

Company sponsored clinical trials

- Principal investigator roles
  - Extensive research knowledge / experience
  - Track record in the specific field
  - Leadership
  - Experience with regulators
  - Podium influence
- Steering committee
- **Site investigator roles**
  - **Frequently, the first experience with Industry trials**
  - **Track record of clinical results**
  - **Volume of cases eligible for enrollment**
  - **Site research infra-structure (contracting team, research coordinators, fellows)**
  - **Drive / commitment of site PI / team**

Site selection

Critical for trial execution

The average **cost to open an investigation site is $50,000**[1]

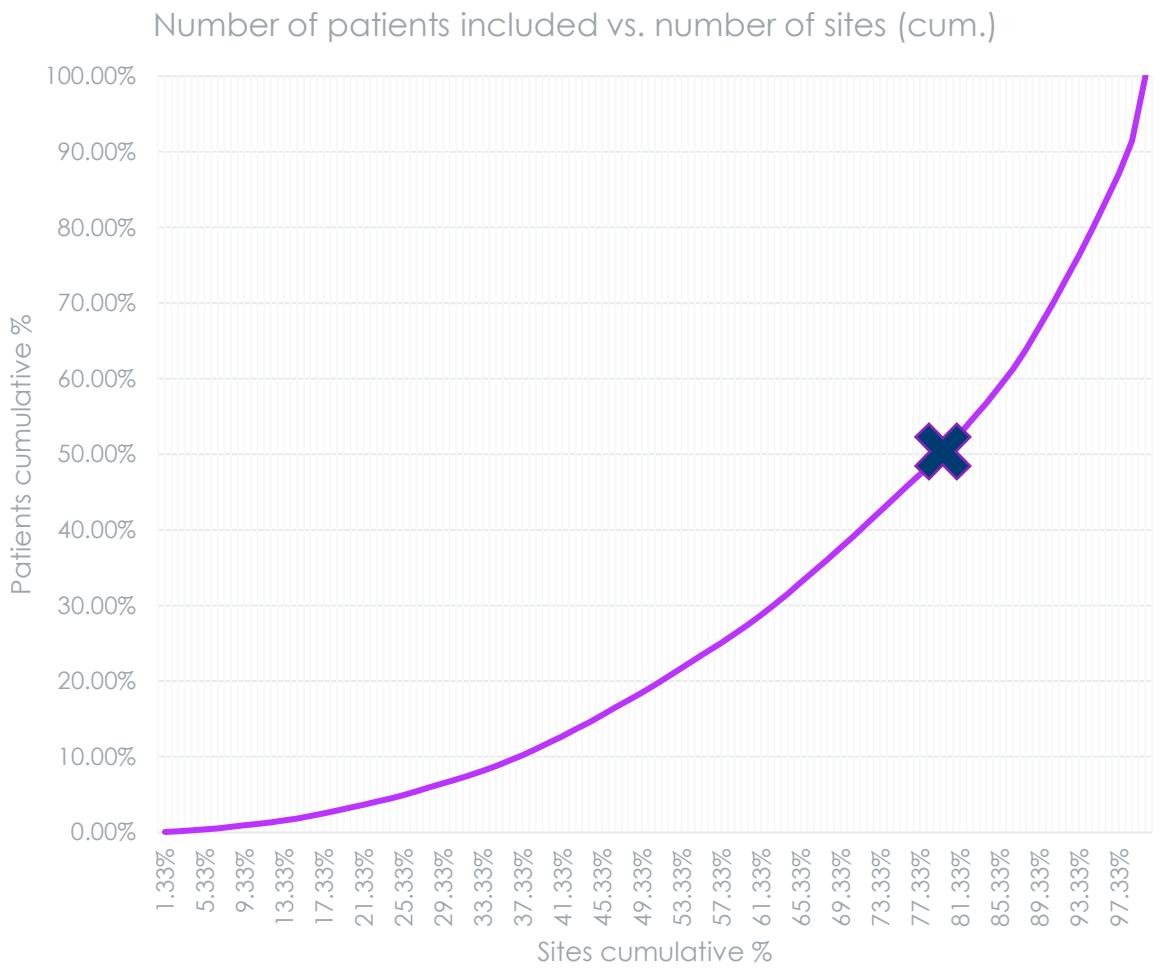
11% of sites enrolled **ZERO** participants[1]

Poor selection of trial sites, **increase the cost by > 20%**[2]

[1] https://www.advarra.com/blog/strategies-for-successful-site-selection-in-clinical-trials/
[2] https://www.pharmavoice.com/news/2182/614012/

Site selection

Share of Patient Enrolment is Uneven

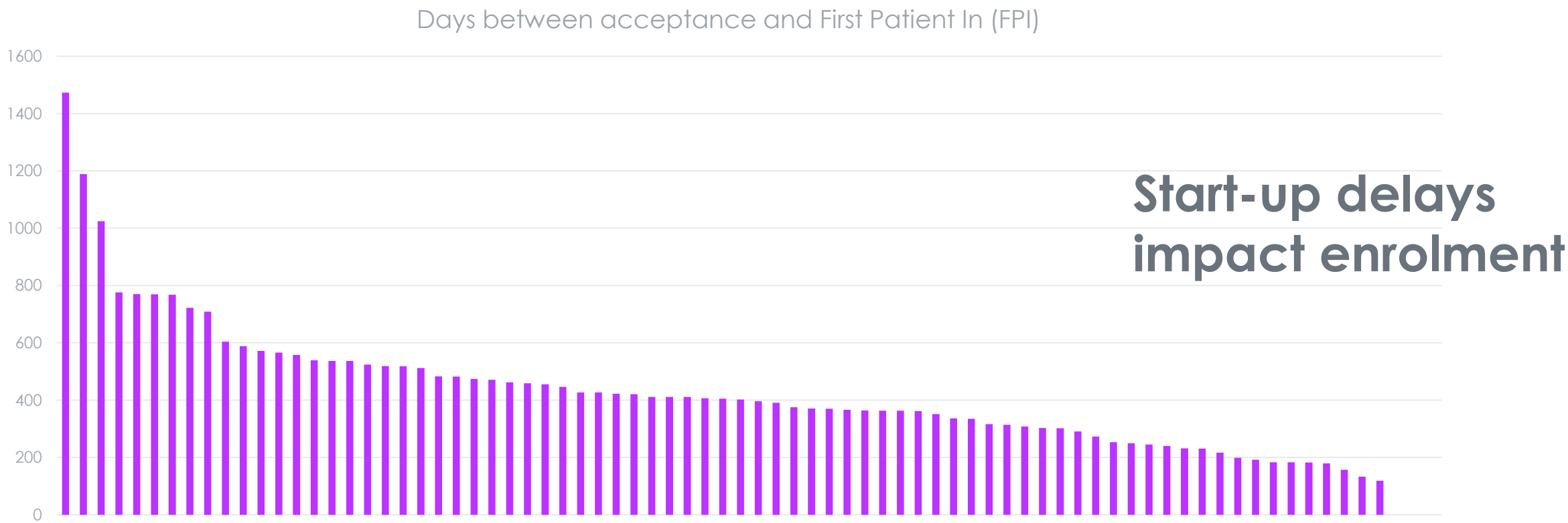


- 75 enrolling sites
- 1528 out of 1670 patients included

50% of patients enrolled by 20% of sites (15 out of 75)

Site selection

Start-Up Time Influences Time-to-Market

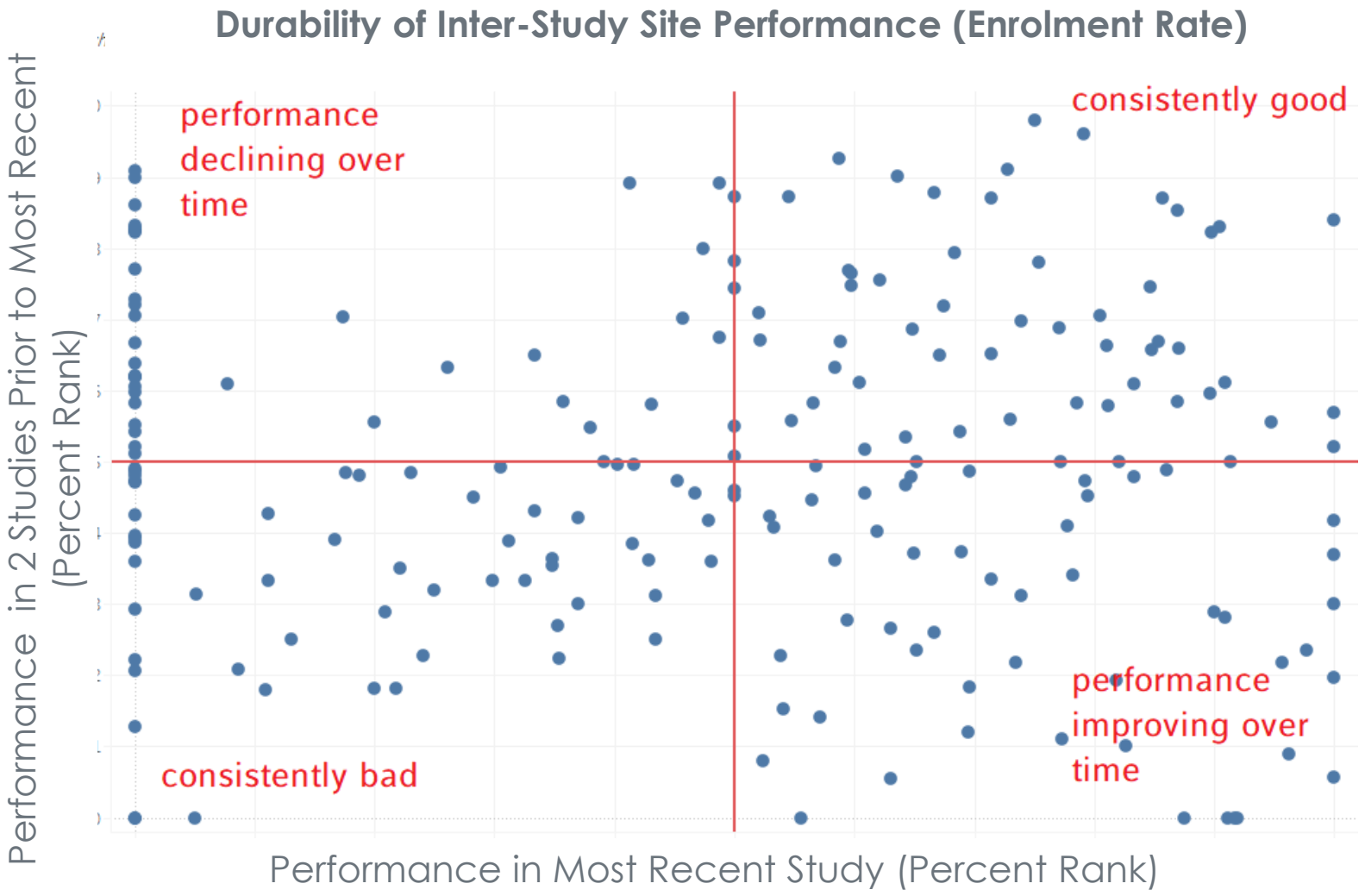


Start-up delays impact enrolment

Average start-up time (from acceptance to FPI) is 405 days, however big outliners

Site selection

Past Performance Alone is not Predictive



Historical Single-variate Data Analysis is not Predictive of Future Site Performance

Site selection

Data quality issues

- Data quality issues = more monitoring required = ↑ costs
- Case selection introducing bias
- Completeness of patient follow-up

A good research site

It's about structure and commitment

- Good case volume / Strong referral base
- Committed, driven, accessible, responsive PI and research team
- Fast, agile contracting team
- Fast IRB review and approval
- Dedicated research coordinators
- Timely and accurate data entry
- Complete clinical follow-up

Investigator Sponsored Research

What is it?

Sponsor responsibilities

- Study design
- Protocol development
- Appropriate regulatory / ethics approval
- Study registration
- Study conduct (all aspects)
- Select/Coordinate/contract Sub-Investigators
- Analysis and interpretation of study data
- Communication of the study results
- Generation of abstract and/or publication
- Presentation at scientific forums
- Safety and Complaint reporting

Grant giver responsibilities

- Review, suggest edits and approve protocol internally
- Contract with sponsor
- Develop payment milestones in agreement with sponsor
- Provide timely payments according to contracted milestones
- Request regular updates on trial progression

Investigator Sponsored Research

Why to do it?

- Lack of bandwidth to sponsor/conduct all trials internally
- Invest in original ideas not generated internally
- Reduce research costs / increase efficiency of evidence generation
- Expand body of evidence for therapies/devices
- Better understand real-world use of technologies/devices
- Expand research infra-structure worldwide and disseminate good clinical research practices

A robust ISR proposal…

It's about planning and organization

- Demonstrates deep trial design understanding
  - Relevant research question – aligned with company's strategy
    - Avoiding duplication of efforts (published and ongoing trials)
  - Appropriate endpoint selection
  - Assumptions for sample size calculations (major cost impact)
    - Based on literature and/or site own retrospective data
    - Over-optimistic assumptions = ↑ risk of underpowered trial (unanswered question)
- Avoids over-restrictive inclusion/exclusion criteria
  - Impacts on enrollment and external validity
- Projects realistic (and reasonable) enrollment timeline
  - Based on volume of eligible cases at (each) institution
  - Account for attrition
  - Incorporating site start-up time (if multicenter)
- Details individual trial activities and respective parties responsible
  - Inform on internal or external (CRO) capabilities
- Provides reasonable and realistic budget estimations
  - Based on each individual trial activity (line-item budget)

"*Extraordinary* ***claims*** ***require*** *EXTRAORDINARY* ***evidence***"

Carl Sagan