CASE STUDY

Biotech Interim Clinical Leadership

FEBRUARY 12, 2026

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The Phoenix Protocol: Operational Turnaround of a Stalled Clinical Asset

Case Study Disclaimer:

This case study is a composite illustration based on HYGEIA Group's interim clinical leadership and fractional CXO framework. While names and figures are anonymized/fictionalized for confidentiality, the operational risks and remediation strategies reflect real-world execution challenges in today's biotech landscape. Any resemblance to actual companies, individuals, or specific investment events is purely coincidental.

This case study is not investment advice, nor does it endorse or critique any real entity. It is intended to demonstrate frameworks and principles of interim clinical leadership and intervention for biotech venture capital portfolio companies.

Executive Summary

In early 2022, **Aurora Biopharma**, a promising clinical-stage oncology company, faced an existential crisis. Its lead asset, *Aurafenib* (a novel Type II RAF kinase inhibitor for pediatric brain tumors), was showing scientific promise, but the operational machinery was failing. The company had gone public the year prior, trading under the ticker symbol ABRO on the NASDAQ. In January 2022, the stock traded around $15/share below its IPO price of $23/share the year prior. The incumbent CRO that was awarded the contract for the pivotal Phase 2 *LUMINA Trial* was plagued by high turnover in project managers resulting in a lack of leadership on the Trial. The CEO of Auroa Biopharma, **Mark Blinders** was a middle-aged, seasoned industry veteran of the biotech industry with two prior successful exits under his belt. Blinders was brought onboard by the lead investor for the crossover funding round to oversee the IPO of Aurora Biopharma. It was January 2022, and Blinders had just stepped off the podium at the 40th Annual JP Morgan Conference in San Francisco when he was approached by **Kaushal Trivedi**, Partner at HYGEIA Group. Trivedi was interested to learn more about the timelines for the final analysis of the LUMINA Trial and the status of the sister study, RADIANCE Trial. Blinders knew of Trivedi from a biotech colleague who had engaged the services of HYGIEA Group to conduct operational due diligence for an Immuno Oncology asset. Blinders explained to Trivedi that the LUMINA trial was experiencing data backlog issues, site fatigue, and the looming deadline to present interim analysis topline data for the first 25 patients at a major medical conference in June 2022 and he was worried about missing this milestone.

Back in his office the following week, Blinders discussed with his executive leadership team at Aurora Biopharma the potential stock collapse and loss of investor confidence, that could result if the Company was not able to bring in a strong leader to rescue the Phase 2 LUMINA Study. Before long, the Board engaged the services of **HYGEIA Group** to deploy an **Interim Fractional Clinical Leadership Team** to oversee the incumbent CRO and salvage the Study.

This case study details how HYGEIA assigned, **Erfan Mansouri,** a strong industry veteran with experience in precision oncology and cancer genomics to immediately step in as Interim Project Director for Aurora Biopharma, to stabilize the study, accelerate the data cleaning of the first 25 critical patients, and ensure timely release of pivotal topline interim analysis data. The intervention not only salvaged the trial timelines but underpinned a successful capital raise, extending the company's runway into 2026.

1. The Crisis: Great Science, Stalled Engine

The Patient Need:

Erfan Mansouri set up a series of meetings within the first week with key executives within Aurora Biopharma and the CRO Account Director to conduct a "Deep Dive" on Aurora Biopharma's Phase 2 Program.

Pediatric Low-Grade Glioma (pLGG) is the most common brain tumor in children. For decades, there was no approved systemic therapy. Children endured years of chemotherapy with severe toxicities. Many cases were driven by specific genetic mutations, primarily alterations in the *BRAF* gene (specifically V600E mutations).

Aurora Biopharma's *Aurafenib* offered a new hope. It was an oral, targeted therapy designed as a Type II RAF kinase inhibitor to shut down the MAPK pathway, which is activated by BRAF alterations that result in downstream activation and proliferation of these tumors. Aurafenib represented a paradigm shift towards precision medicine for pediatric brain tumors.

Aurora Biopharma had met with the FDA for the Pre-IND meeting to discuss an innovative trial design; the choice of a single-arm study with the primary endpoint of Objective Response Rate (ORR). Gaining this early alignment was critical to prevent late-stage surprises. Formal NDA application to the FDA occurred in 2021 to begin the clinical trial, containing all preclinical (Insilco, invitro and in vivo/ animal) data, manufacturing CMC information, and detailed clinical protocol.

Breakthrough Therapy Designation status was granted by the FDA to expedite the development of Aurafenib as preliminary evidence indicated substantial improvement over

available therapy for this serious condition. In addition, FDA granted Aurora Biopharma with Rare **Pediatric Disease Designation** since Aurafenib was focused on pediatric low-grade gliomas. In consultation with the FDA and the incumbent CRO, Aurora Biopharma had settled on Adaptive Clinical Trial Design for the LUMINA Study.

A Seamless Phase II/III, Single-Arm, Open-Label Study.

- **Seamless Design:** The study structure allowed the trial to seamlessly transition from an exploratory phase (dose-finding, initial efficacy) which was focused on establishing the maximum tolerated dose (MTD) and the Required Phase 2 Dose (RP2D) to a confirmatory phase 2b/3a (registrational trial) without stopping. The design included provisions for Simon's Two-Stage Optimal design with pre-defined futility boundary criteria.
- **Single-Arm, Open-Label:** Due to the lack of an established effective therapy for this specific patient population, a randomized, placebo control arm was deemed unethical. Efficacy was measured against predefined response rate thresholds. Both investigators and patients knew the treatment that was being administered.
- **Patient Population:** Children aged 6 months to 25 years with recurrent or progressive pLGG harboring a known activating *BRAF* alteration.
- **Ethical Framework:** Rigorous consent/assent process, oversight by an Independent Data Monitoring Committee (IDMC) to ensure patient safety.
- **Primary Objective:** To evaluate the efficacy of Aurafenib, measured by Overall Response Rate **(ORR)** where ORR was defined as the percentage of patients whose tumors shrunk (partial response, PR) or disappeared (complete response, CR). A key endpoint for single-arm oncology trials seeking accelerated approval.
- **Key Secondary Objectives:**
  - Duration of Response (DoR)
  - Progression-Free Survival (PFS)
  - Safety and Tolerability

The Operational Reality:

By Q1 2022, the scientific thesis was strong, but Mansouri observed that the operational execution was buckling under the complexity of the adaptive clinical trial design.

- **The Bottleneck:** An **adaptive clinical trial design** while scientifically elegant, created a massive burden on clinical sites. Protocol amendments were frequent; data entry was lagging by at least two months at key sites. Data entry backlog stood at >14 weeks against a KPI of 2 weeks. Query resolution rate was <40%, meaning the database was

effectively 'frozen'. Data Cleanliness required for a regulatory-grade snapshot was at less than 60% because the incumbent CRO had cycled through three Project Managers within a span of 6 months. The Data Management Lead was not being held accountable to adhere to the Data Cleaning Plan.

- **The Stakes:** The company had promised Wall Street an early look at the data (the "First 25 Patients") by June 2022. Missing this milestone would likely trigger a sell-off and jeopardize the company's ability to raise the next tranche of capital. In the words of Mansouri,

> **"The Science was ready to fly, but the runway was covered in debris."**
>
> *— Erfan Mansouri, Interim Project Director (HYGEIA Fractional CXO).*

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2. The Intervention: HYGEIA's "Flash-to-Bang" Protocol

HYGEIA Group's Erfan Mansour was parachuted in with a mandate to act as the **Interim Project Leadership** for a period of 6 months with the optionality to renew for an additional 6 months. The engagement was structured not as "advisory," but as "command and control" meaning HYGEIA was granted delegated decision-making authority by Aurora Biopharma's Board, moving beyond an advisory role/ Consultant role to active operational command

Phase 1: Stabilization (Weeks 1-2)

- **Diagnosis:** The team identified that the bottleneck wasn't patient recruitment. It was data velocity. Sites were treating patients but failing to enter in a timely manner into the electronic data capture system (EDC) the complex radiographic response data needed to confirm efficacy.
- **Action:** In consultation with Aurora Biopharma, Mansouri instructed the CRO Project Manager to immediately deploy a "SWAT Team" of Clinical Research Associates (CRAs) to the top 10 enrolling sites (primarily large academic medical centers). Their sole job was to sit with study coordinators and clear the data entry backlog and make sure the sites were ready at a moment's notice to withstand audit scrutiny.

Phase 2: The "First 25" Sprint (Weeks 3-6)

- **Target:** To present valid efficacy data, Aurora Biopharma needed a "Clean Cut" of the first 25 evaluable patients.
- **The Challenge:** Assessing tumor shrinkage in gliomas requires specialized RANO (Response Assessment in Neuro-Oncology) criteria. Discrepancies between local site reads and Central Independent Review were high.
- **The Fix:** Mansouri worked with the CRO Project Manager to establish a **Daily Adjudication Huddle**. Every morning, the Interim Project Director (HYGEIA), the Medical

Monitor, and the Data Management Lead reviewed every single data point for the initial cohort. Discrepancies were resolved in real-time, not via weeks of email ping-pong.

Phase 3: Adaptive Management (Ongoing)

- Simultaneously, Mansouri took over oversight of **PROJECT RADIANCE**, a sub-protocol for solid tumors.
- The Team implemented a **"Traffic Light" Dashboard** for Aurora Biopharma's Board. Instead of 30-page reports, the Board received a one-page weekly view: Green (On Track), Yellow (Risk), Red (Blocker). This transparency restored Board confidence and allowed for rapid decision-making. Detailed reports were available upon request to corroborate the Traffic Light Dashboard data.

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3. The Outcome: Delivering the Data

In June 2022, Aurora Biopharma released the interim data for the first 25 randomized patients. The results were not just scientifically positive; they were operationally bulletproof.

- **The Data:** An Overall Response Rate (ORR) of **67%** and a Clinical Benefit Rate (CBR) of **93%**.
- **The Market Reaction:** By the time of the press-release in May 2022, the stock price of Aurora Biopharma had dropped to $6.60/ share. When the topline readout was made publicly available in June, ABRO stock price jumped 3x to $27.50/ share. The data was presented at ASCO (American Society of Clinical Oncology) to a standing-room-only crowd. The "cleanliness" and robustness of the data set; verified by the rigorous HYGEIA process; stood up to scrutiny from top Key Opinion Leaders (KOLs).
- **The Financial Impact:** In July 2022, following the data release, Aurora Biopharma commenced an underwritten public offering of shares of its common stock. The integrity of the dataset allowed the company to price the offering at a minimal discount to market, preserving founder and early-investor equity. The company successfully executed a **$172.5 Million public offering,** and this capital injection extended the cash runway into 2026, saving the company from a distressed "down round."

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4. Lessons for Investors: The "Fractional CXO" Advantage

When a portfolio company enters a crisis, the traditional instinct is to fire the CEO or hire a massive consulting firm to fix the problem. This case study demonstrates a third, more agile option: **The Interim Fractional CXO**.

Why it Works:

1. **Speed:** A Fractional Project Director can be deployed within 48 hours of a signed

contract. Hiring a full-time executive can take up to 6 months and permanently increase the payroll of the portfolio company in the absence of any recurring revenue streams.
2. **Objectivity:** Because HYGEIA is independent, it was able to report the "ugly truth" about data backlogs or vendor failures without fear of internal portfolio company politics.
3. **Cost-Efficiency:** You pay for the "Turnaround," not a permanent salary. Once the crisis is resolved (as it was with LUMINA Study), the Fractional Leader handed the keys back to the permanent team.

The "Phoenix" Effect:

Just as Aurora Biopharma rose from operational uncertainty to a market-leading position, a stalled asset can be revived, but only if you have the courage to intervene operationally, not just financially.

This case study details how HYGEIA's Partner stepped in as Interim Project Director with delegated decision-making authority to stabilize an oncology study, accelerate the data cleaning of the first 25 critical patients, and flawlessly execute the release of pivotal topline data. The intervention not only salvaged the trial timelines but underpinned a successful capital raise, extending the company's runway into 2026.

Appendix: Study Design Reference

- **Target Indication:** Pediatric Low-Grade Glioma (pLGG) with BRAF alterations.
- **Drug Class:** Type II RAF Kinase Inhibitor.
- **Trial Design:** Open-label, single-arm, Adaptive Phase II/III Clinical Trial design (Pivotal).
- **Regulatory Status:** Breakthrough Therapy Designation (BTD); Rare Pediatric Disease Designation.

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