HYGEIA

CASE STUDY

The "Great Reset" in Biotech Investing: Operational De-Risking of a Portfolio Biotech

Case Study Disclaimer:

This case study is a composite illustration based on HYGEIA Group's operational due diligence frameworks. 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 operational due diligence in biotech venture capital.

Executive Summary

In November 2024, 313 Ventures, a Silicon Valley biotech venture capital firm, faced a critical investment decision. They were considering leading a $125 million Series D financing for Himalaya Biotech to fund a Phase 2b trial for HMLY-110, a novel immuno-oncology asset for Lynch Syndrome. While the scientific data was promising, the post-COVID market correction, often termed "The Great Biotech Reset", demanded a higher standard of diligence. 313 Ventures engaged HYGEIA Group for a ***4-Week Operational Due Diligence Sprint*** to validate the execution plan.

This case study details how operational stress-testing revealed significant hidden risks in enrollment projections, vendor selection, and budget forecasting, ultimately reshaping the valuation and deal structure.

1. The Investment Context: Investing in a Bifurcated Recovery

By the second half of 2025, the biotechnology sector begun to stabilize following the severe correction of 2022–2024. However, the recovery was highly bifurcated. As noted in industry reports, capital was flowing decisively only to companies with robust data and de-risked clinical pathways, while others struggled to survive.

Sarah Chen, a Senior Partner at 313 Ventures, sat in her Palo Alto office reviewing the term sheet for Himalaya Biotech. "In the exuberance of 2021, we were eager to fund great science," Chen noted. "However, we are now focussing on funding execution. Scientific

feasibility is table stakes; operational feasibility is where the alpha is generated."

Himalaya Biotech, based in Shanghai with US operations in Boston, had approached 313 Ventures with positive Phase 1b data for HMLY-110 for Lynch Syndrome (LS). Lynch Syndrome is a common hereditary condition that significantly increases a person's lifetime risk of developing multiple cancers. HMLY-110 was an off-the-shelf immunotherapy biologic designed to induce T-Cells against neoantigens present in tumors and precancerous lesions in LS-Carriers with microsatellite instability (MSI).

313 Ventures was a Silicon Valley venture capital firm that had led Himalaya's Series C round and was now considering participating in the Series D round that would fund Himalaya through the data readout for the Phase 2a/b trial, End-of-Phase-2 meeting (EP2) with the FDA and prepare for Phase 3 if Himalaya saw a strong efficacy signal for HMLY-110.

The asset had demonstrated robust immunogenicity and potential cancer interception signals in Lynch Syndrome (LS) carriers in Phase 1 trials. **Sandra Yu** was the Founder and CEO of Himalaya Biotech and was on the phone with Sarah Chen at 313 Ventures, "I have emailed you the documents. We are seeking $100M–$150M to fund the company through three critical value inflection points:

1. Phase 2b Proof-of-Concept (POC) data readout.
2. End-of-Phase 2 (EOP2) meeting with the FDA.
3. Preparations for a global Phase 3 trial.

We have a great relationship with 313 Ventures and appreciate all your support to help us get to this point in developing HMLY110. Let's set up a follow-up call once you've had a chance to review the documents I just sent."

Despite the strong scientific thesis and the positive Phase 1b data, Chen was wary. The "Great Biotech Reset" had left many investors with portfolios full of scientifically sound companies that had failed operationally, either running out of cash due to enrollment delays or poor vendor management. She was also jaded by a recent experience at 313 Ventures with one of their infectious disease portfolio companies that had undergone a **"phoenix event."** Chen had spent countless hours trying to salvage the remaining assets in the product pipeline and averted an existential crisis by working with other investors to structure a non-dilutive debt facility and a modest equity round tied to milestones, just narrowly avoiding a down round that would have wiped out prior equity.

Chen needed to know if Himalaya's roadmap was realistic. 313 Ventures required a rigorous validation of the operational assumptions underpinning this next capital deployment. Chen reached out to **Kaushal Trivedi**, a Senior Partner at HYGIEA Group who she met at the JPMorgan Conference the year prior. HYGEIA Group was a Canadian Investment & Capital Advisory firm focussed on providing biotech investors with the specialized, on-the-ground

operational intelligence needed to identify and mitigate risks associated with venture capital operational blind spots before they destroy capital. 313 Ventures enlisted the services of HYGEIA Group.

2. The Challenge: Operational Opacity

Trivedi sent Chen a detailed email requesting the following:

From 313 Ventures:

- Introduction email to Himalaya management positioning HYGEIA as their operational diligence partner.
- Access to their most updated Virtual Data Room (VDR).

From Himalaya (Founder & CEO – Sandra Yu):

- **Clinical Budget (Excel source):** Detailed line-by-line breakdown of the $125 Million funds being requested for the Series D round.
- **Clinical Summary Report:** HYGEIA requested access to the CSR for the Phase1b trial. Himalaya informed Trivedi that the CSR for the phase 1b trial was still under development and sent a slide deck with the Phase 1b topline data and associated Tables, Listings and Figures (TLF).
- **Draft Protocol/ Synopsis:** HYGEIA requested access to the draft Phase 2 protocol and the most recent Investigator's Brochure for HMLY-110.
- **Enrollment Logs:** HYGEIA asked for all anonymized site-level data from the Phase 1 a/b trials (SAD/ MADD studies) including but not limited to (Screened patients, Screen-Fails, Randomized, Dropouts, LTFU).
- **Gantt Charts:** Himalaya's Project Manager furnished HYGEIA with their proposed operational timeline for the Phase 2b study.
- **Vendor Contracts:** Himalaya's CEO provided HYGEIA access to all current MSAs, and Work Orders for the incumbent CRO, and other clinical trial service providers (e.g. eCOA vendor, Central Labs, EDC, TMF vendors and Recruitment Vendor).
- **Availability:** 2 x 60-minute interview slots with the Himalaya's CMO and Vice President of Clinical Ops in Week 2.

Upon initial review, Himalaya's Virtual Data Room (VDR) presented a "clean" picture: a 24-month runway, a lean budget, and aggressive enrollment targets (18-month subject recruitment period). Sarah Chen informed Trivedi that 313 Ventures had already conducted a robust scientific diligence in the prior funding rounds to validate the molecule (HMLY-110). However, Trivedi knew from experience that HYGEIA had validated the execution plans for other clients and was able to identify the "VC Operational Blind Spots" such as unrealistic budgets, flawed vendor protocols, and recruitment optimism that typically cause 80% of

clinical trial failures.

Applying the **HYGEIA 10-Point Operational Due Diligence Checklist**, Trivedi and his team conducted an initial sweep of the data and noted several potential "Red Flags" that 313 Venture's standard scientific, legal and financial diligence had missed:

- **Red Flag #1 (The "Hockey Stick" Model):** The enrollment timeline assumed an immediate uptake in recruitment with no "ramp-up" period, a common error in rare or niche indications like Lynch Syndrome.
- **Red Flag #6 (Vendor/CRO Misalignment):** Himalaya was planning to use the incumbent Contract Research Organization (CRO) based on their satisfactory performance on phase 1 trials. This mid-sized CRO had been selected after a brief tendering process and the final decision was based solely on cost, without assessing their global footprint for multi-regional phase II/III trials. This CRO had provided boiler-plate site lists for the phase 2 study without reaching out in advance to any Key Opinion Leaders (KOLs) with feasibility questionnaires to verify access to target patient populations. The CRO's bid-defense pitch deck included unrealistic enrollment projections with disclaimers indicating plans to use sub-contracted vendors in certain key geographies where the CRO did not have "boots on the ground."
- **Red Flag #7 (Budget Optimism):** The budget for clinical supply chain and site activation appeared 20–30% lower than industry benchmarks. In HGYEIA's experience this CRO was known to use a **"bait-&-switch"** approach during the bidding process to win awards from sponsors and then later executing change orders mid-stream.

Trivedi scheduled a follow-up Zoom Call with Sarah Chen at 313 Ventures and alerted her to these Red Flags as part of HYGEIA's initial sweep. Recognizing these gaps, 313 Ventures formally engaged HYGEIA Group for a specialized 4-Week Due Diligence Sprint to ensure no delay to the term sheet. This 4-Week sprint was to be executed in parallel with 313 Venture's ongoing scientific and legal diligence for the Series D round.

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3. The Intervention: The 4-Week Operational Sprint

HYGEIA deployed a rapid-response operational team to stress-test Himalaya's assumptions. The sprint was structured to move beyond the initial ***"checking of the boxes"*** in the 10-Point Due Diligence Checklist to performing a forensic analysis of the Clinical Development Plan (CDP) for HMLY-110.

Week 1: Protocol & Site Strategy Stress-Test

- **Focus:** Ingesting the "As-Sold" plan and identifying immediate gaps.
- **Activities:**
    - Review of Virtual Data Room (VDR): Protocols, Investigator Brochures (IB), Clinical Development Plan (CDP). HYGEIA reviewed the Phase 1 protocols and the draft Phase 2b protocol against the proposed CRO site list.
    - Detailed analysis of previous Phase 1b enrollment rates and site performance metrics.
    - Review of current CRO Master Services Agreements (MSA) and Change Orders including review of all vendor contracts to verify in-scope and out-of-scop activities.
- **Finding:**
    - HYGEIA noted that Himalaya planned to activate 40 sites globally for the Phase 2b trial but had only actively engaged 15 in the United States so far.
    - The protocol required a specific genetic screening assay that 50% of the proposed sites in Eastern Europe did not have the infrastructure to support.
    - Finally, the CRO did not have "boots on the ground" in key geographies in Europe and Asia and was planning to subcontract with other local CROs thereby exposing Himalaya's data to additional project oversight risks.
- **Week 1 Deliverable:** *Initial Gap Analysis Memo & Information Request List*.

Week 2: Vendor & Budget Forensic Audit

- **Focus:** Validating assumptions directly with portfolio company's management (Himalaya's Board and Clinical Project Manager) and the market.
- **Activities:**
    - **Management Interviews:** HYGEIA conducted 1:1 deep-dive sessions with CEO, CMO, and VP of Clinical Operations to assess the "Founder-Operator Gap" and team's capability to execute on the Phase 2 Proof-of-Concept Study design.
    - **Site Feasibility Check:** HYGEIA independently contacted 3-5 potential vanguard high-value KOL sites in key geographies (in addition to its proprietary feasibility data) to validate Himalaya's enrollment projections.
    - **Vendor Audit:** HYGEIA audited all CRO bids and internal operational budget. HYGEIA assessed the incumbent CRO's performance on the Phase 1 trials and their proposed Phase 2b strategy by conducting a 1:1 meeting with CRO Account Director.
- **Finding:**
    - Himalaya's VP had built in a recruitment projection of 1-2 patients/site/month whereas HYGEIA's due diligence resulted in a more realistic estimate of 0.5

patients/site/month for LS interception.

- HYGIEA Group suggested 313 Ventures underwrite series D funding subject to issuing another Request for Proposals (RFP) and inviting new bids to critically appraise the incumbent CRO's Phase 2 trial protocol and cost assumptions.
- The CRO contract had significant "out-of-scope" exclusions. Critical line items like patient travel reimbursement (crucial for LS carriers who are asymptomatic and less motivated to travel) were under-budgeted by $1.2M. The CRO had detailed a list of vendors for the Phase 2 trials (such as ePRO, Patient Recruitment, and medical writing) without including estimates of the associated Pass-Thru costs for these vendors within the Pass-thru budget. Finally, the investigator grant budget had detailed per-patient-per site costs that were below "Fair Market Value" thereby exposing Himalaya to lower quality sites and future change orders to align investigator grants to "fair-market value."

- **Deliverable:** *Operational Risk Matrix (High/Medium/Low).*

Week 3: Enrollment Modeling & Timeline Validation

- **Focus:** Money and Market Access.
- **Activities:**
  - **Shadow Budgeting:** HYGEIA built a bottom-up clinical budget to compare against Himalaya's ask. This cross comparison revealed a 20-30% under-budgeting by Himalaya.
  - **Enrollment:** HYGEIA rebuilt the enrollment model using Monte Carlo simulations to account for site activation delays and competitive trials.
  - **Regulatory & Reimbursement Scan:** HYGEIA conducted a quick check on the "Interception" regulatory pathway risks and payer hurdles (e.g., surveillance vs. therapy pricing).
- **Finding:**
  - Himalaya's "Base Case" was statistically unlikely (Probability < 10%). HYGEIA Group's realistic "Risk-Adjusted" timeline showed a 9-month delay to Phase 2b Proof-of-Concept (POC) data readout thereby pushing out all downstream dates relative to the targeted End-of Phase 2 (EOP2) meeting date that Himalaya had referenced in their Series D pitch deck.
- **Deliverable:** *Budget Variance Report & Timeline Forecast.*

Week 4: Valuation Impact Analysis

- **Focus:** Finalizing the Investment Thesis.
- **Activities:**
  - Analysis of all operational, financial, and team assessments. HYGEIA

Synthesized operational delays into the financial model to determine the impact on cash runway and valuation.
    - Drafting the final investment memo inputs.
    - **Final Presentation:** Walkthrough with Sarah Chen (Sr. Partner), a General Partner, and the 313 Ventures Investment Committee.
- **Deliverable:** *Final Due Diligence Report with GO/NO-GO Decision.*

4. Key Findings: The Operational Reality Check

The Due Diligence Sprint uncovered a critical misalignment between the capital request and the operational reality.

Table 1: Himalaya Biotech – Founder Assumptions vs. Diligence Findings

Operational Metric	Himalaya "Pitch Deck" Assumption	HYGEIA Diligence Finding	Impact
Enrollment Timeline	18 Months (Linear Ramp)	27 Months (Staggered Ramp)	**9-Month Delay** to Data POC Readout
Site Feasibility	40 Sites (US/EU/China)	only 15 Sites realistically viable immediately	**Slower Start**; urgent need for new regions
Cost Per Patient	$85,000	$112,000 (inc. genetic screening and adjusting to fair-market-value)	**32% Cost Increase**
Cash Runway Need	$125M to reach Phase 3 prep	$125M runs out *before* Phase 2b data	**Bridge Round Risk**

The "Bridge to Nowhere" Risk:
The most critical finding from the **4-Week Due Diligence Sprint** was the timeline extension. Had 313 Ventures invested $125M in Series D funding based on the original plan, Himalaya would have run out of cash just three months shy of the Phase 2b topline data readout and

press-release date. This would have forced the company to raise a "distressed bridge" round in a down market, a scenario known to dilute early investors significantly.

5. Valuation Analysis: Adjusting for Risk

To quantify the impact of these operational risks, HYGEIA utilized a valuation framework aligned with modern VC methodologies.

The Formula:

$$Pre\text{-}Money\ Valuation = (rNPV) - (Capital\ Required + Operational\ Buffer)$$

Where $rNPV$ (Risk-Adjusted Net Present Value) is derived from:

$$rNPV = (Peak\ Sales \times Multiple \times PoS \times PSP) \times Discount\ Factor$$

Step 1: Establishing the Inputs (The "Tech Tree" Logic)

- **Theoretical Peak Sales:** $1.1 Billion (US Market)
- **Valuation Multiple:** 3.0x (Standard for high-growth IO assets)
- **Theoretical Exit Value:** $3.3 Billion

Step 2: Applying Risk Metrics (The "Haircut")

- **PoS (Probability of Success):** 25% (Phase 2 to Approval for novel interception).
- **PSP (Peak Sales Potential - Commercial Risk):** 50% (0.5). *Note: This was adjusted down from 0.7 by HYGEIA due to identified payer friction for "preventative" therapies.*

$$Risk\ Adjusted\ Value = \$3.3B \times 0.25(PoS) \times 0.5(PSP) = \$412.5\ Million$$

Step 3: The Operational Adjustment (Pre-Money Calculation) The capital requirement had to be adjusted.

- *Original Ask:* $125M.
- *Revised Need (per Diligence):* $148M (to cover the 9-month delay and higher site costs).

$$Pre\text{-}Money\ Valuation = \$412.5M\ (rNPV) - \$148M\ (Required\ Capital)$$

$$Pre\text{-}Money\ Valuation = \$264.5\ Million$$

Comparison: Himalaya's asking Pre-Money valuation was **$350 Million**. The diligence revealed an **$85.5 Million valuation gap** driven purely by operational and commercial execution risks.

6. Conclusion: The "Go" Decision with Guardrails

Armed with this data, Sarah Chen and 313 Ventures did not walk away from the deal. Instead, they restructured the deal. The science was still sound, but the execution plan was flawed.

The Restructured Deal:

1. **Tranche Financing:** The $125M investment was split. Tranche 1 ($60M) was guaranteed; Tranche 2 ($65M) was contingent on hitting specific *operational* milestones (e.g., "50% enrollment by Month 12") rather than just scientific ones.
2. **Operational Governance:** 313 Ventures mandated the appointment of a specialized Clinical Operations Advisor (Interim fractional CXO role provided by HYGEIA) to oversee vendor selection and site activation for the first 6 months.
3. **Valuation Adjustment:** The Pre-Money valuation was renegotiated to **$275M** (closer to the HYGEIA calculated $264.5M), giving 313 Ventures' investors better ownership stakes to compensate for the extended timeline risk.

Outcome:
Himalaya Biotech accepted the terms. The Phase 2b trial launched in March 2025 with a realistic budget and timeline.

7. Summary for Investors

In the "Great Biotech Reset," operational diligence is not an administrative task. It is a tool for valuation and risk control. As demonstrated in the Himalaya case, a 4-Week Diligence Sprint can:

1. **Prevent Capital Loss:** By identifying the "Bridge to Nowhere" cash trap.
2. **Optimize Ownership:** By grounding valuation in operational reality ($350M vs $275M).
3. **Secure the Exit:** By ensuring the funded runway actually reaches the value inflection point.

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