Why is ACLF Drug Development Unique ? Industry Perspective

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1- Why ACLF is a Unique Development Challenge?

- *ACLF is a distinct syndrome with acute deterioration, systemic inflammation, multiorgan dysfunction, high short-term mortality, and a narrow therapeutic window for disease reversibility*

- *Definitions have historically varied across regions, and this has complicated standardization of diagnosis, prognosis, treatment strategy, and investment in new therapies*

- *The recent Barcelona harmonization work is valuable as a* **foundation**

- *Early-phase endpoints remain a major unresolved gap.*

2- Why ACLF is a Unique Development Challenge?

- *Industry needs a development model that accepts:*
  - **acuity,**
  - **heterogeneity,**
  - **time pressure,**
  - **endpoint complexity** *as design inputs, not annoyances.*

- *Oncology has already built methods for developing drugs in life-threatening, heterogeneous settings under uncertainty:*
  - *early development directly in patients when benefit-risk differs from healthy populations,*
  - *seamless early Phase I/II designs and Master protocols/platform trials for difficult, heterogeneous diseases*
  - *modern dose optimization to identify safe and active doses faster*
  - *biomarker-guided patient selection to reduce heterogeneity*

Industry Conclusion

- *"First,* **go directly to the intended population***. In oncology, early studies are commonly done in patients rather than healthy volunteers because the relevant benefit-risk calculus lives in the target population. Internally, we have already framed this as one of the most transferable principles for ACLF."*

- *"Second,* **treat heterogeneity as a design variable***. In oncology, biomarker-driven selection is not an optional refinement; it is often the only way to reduce noise and see signal. ACLF will need its own version of that logic, whether through inflammatory phenotype, precipitant biology, organ failure pattern, or trajectory-based enrichment."*

- *"Third,* **learn dose and activity together, not sequentially when possible***. Modern oncology has moved beyond purely toxicity-driven escalation toward approaches that integrate activity, PK/PD, and optimal biological dose thinking. That is particularly relevant in ACLF, where disease manifestations can mimic toxicity and where waiting too long to refine dose may cost time the field does not have."*