Accelsiors

Issue #3

Special Edition: Metabolic Trials Under Pressure

Protecting Integrity in Obesity, MetALD, and MASH

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EDITOR'S NOTE

Why Metabolic Trials Need a New Operational Playbook

Metabolic drug development has entered a more operationally demanding era

In obesity, studies are no longer running against a neutral background. GLP-1 therapy is reshaping patient expectations, treatment history, and standard-of-care realities across regions. In MetALD, sponsors are entering a biologically important but operationally fragile overlap phenotype where alcohol exposure must be governed actively if the dataset is to remain interpretable. In MASH, scientific and commercial momentum continues, but long-standing execution challenges around screening, burden, and endpoint protection remain highly relevant.

Taken together, these shifts point to the same conclusion: the next generation of metabolic trials will not be differentiated by scientific promise alone. They will be differentiated by whether the operating model is strong enough to protect that promise under real-world conditions.
That is why this issue focuses on trial integrity under pressure.

Many of the most serious risks in modern metabolic studies do not emerge late. They begin before first patient in: unstable baseline conditions, under-specified co-interventions, inconsistent counselling delivery, phenotype drift, endpoint source-of-truth gaps, burdensome participation models, weak vendor governance, and reactive oversight that identifies risk only after it has already entered the data.

ICH E6(R3) now frames GCP more explicitly around quality by design, prospective identification of Critical-to-Quality factors, and proportionate risk-based controls. For sponsors, that means shifting attention away from low-value administrative overcontrol and toward the factors that truly matter for participant safety and reliable results.

At Accelsiors, we see this not just as a compliance shift, but as a strategic opportunity. Sponsors who pressure-test earlier, define CtQs more explicitly, align protocol and SAP logic more tightly, and govern their studies through clear Trigger → Action → Evidence frameworks will be better positioned to recruit efficiently, retain patients, defend endpoints, and withstand regulatory scrutiny.

In the pages that follow, we focus on where obesity and MetALD programs are becoming most vulnerable, what MASH still teaches us about metabolic execution discipline, and how quality by design can convert operational fragility into a governed system. Because in metabolic development today, execution is no longer downstream of strategy.

It is part of the strategy.

THE CLINICAL PULSE

The New Metabolic Trial Landscape: Why Obesity and MetALD Are Becoming Operationally Decisive

Metabolic research is advancing quickly, but trial operations are becoming more exposed at the same time.

Sponsors are now working in a landscape where baseline conditions are less stable, patient expectations are changing, hybrid and decentralized models are more common, and treatment environments evolve during the life of a study. These pressures are visible across metabolic indications, but they are especially pronounced in obesity and MetALD.

In obesity, the trial environment has changed fundamentally. Patients may enter studies with prior GLP-1 exposure, ongoing behavioural support, unequal access to obesity services, or expectations shaped by marketed therapies. Obesity is no longer being studied as an isolated weight-loss event. It is increasingly managed as a long-term care condition, which means protocols that assume a clean, static baseline are becoming less realistic.

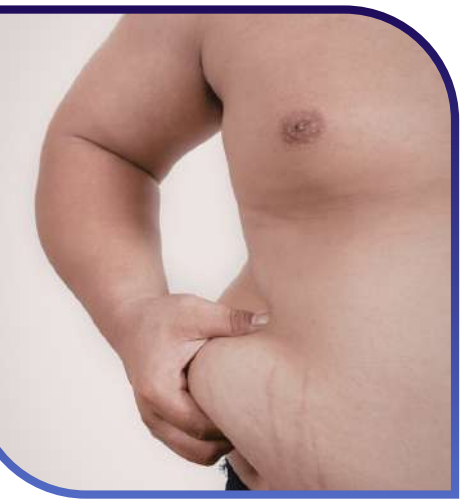
MetALD presents a different kind of fragility. Here, the core challenge is phenotype integrity. The enrolled population exists in a narrow overlap zone between metabolic dysfunction and moderate alcohol use. That phenotype can be diluted at screening, drift during treatment, and become difficult to interpret if alcohol exposure is not governed with both behavioural and biomarker-based controls.

MASH remains highly relevant in this picture, not because it should dominate every metabolic conversation, but because it has already exposed many of the operational failure modes the field must now handle more deliberately: high-burden screening pathways, endpoint protection challenges, participant attrition, and the need to balance scientific rigor with feasibility.
What links these three areas is a broader lesson: trial operations can no longer be treated as downstream execution. They now shape scientific credibility directly.

That is why quality by design, CtQ designation, and risk-based oversight are becoming central rather than optional. Sponsors need to decide earlier which variables truly threaten participant safety or reliable results, and then build proportionate controls around them.

FEATURE INSIGHT

Obesity Trials in the GLP-1 Era: Why Baseline Stability Is Now a CtQ Factor



Obesity trials are no longer being conducted against a stable background.

Today's participants may arrive with prior or ongoing exposure to GLP-1 therapy, differing access to obesity care, variable counselling histories, and very different expectations of what trial participation should deliver. Across countries and even within regions, standards of care are diverging based on reimbursement, infrastructure, public health adoption, and commercial availability. In that environment, baseline conditions are not simply descriptive. They are operationally decisive.

Obesity Is No Longer a Clean-Baseline Indication

If background weight-active therapies, digital weight-management tools, devices, and behavioural support are not governed prospectively, the study inherits preventable noise from the outset. Weight trajectories become harder to interpret. Randomization becomes less protective. Rescue or discontinuation events become more difficult to classify. And regional differences in access can quietly undermine both feasibility and comparability. This is why baseline stability should increasingly be treated as a Critical-to-Quality factor in obesity studies.

A modern protocol should define, before screening begins, how background GLP-1 therapy and other weight-active interventions are handled: excluded, stabilized, allowed with controls, or stratified. It should also define how region and access variability will be monitored so that unequal treatment exposure does not become a hidden confounder

Counselling Is Part of the Intervention Environment

WHO's 2025 GLP-1 guidance positions obesity pharmacotherapy within comprehensive, long-term obesity care. It also describes context-appropriate counselling on behavioural and lifestyle change as a foundational element, with intensive behavioural therapy potentially used as a co-intervention within a broader multimodal model.

Operationally, that means counselling should not be treated as an informal site courtesy. If it is part of the care model, it should be operationalized, documented, and governed consistently. When counselling is under-delivered, variably documented, or allowed to differ materially across sites and regions, the study begins to lose control of the behavioural stream that sits alongside the pharmacologic one.

Hybrid Execution Requires a Source-of-Truth Decision

Hybrid and decentralized models can improve retention and reduce burden, but they also create source-of-truth risk if the protocol does not clearly define what counts as primary, what counts as supportive, and how discordance is handled.

Many sponsors still designate clinic weight as the primary endpoint source and use home weight as supportive data, but the source-of-truth hierarchy should be prospectively defined and justified. If home-based measures are included, the reconciliation workflow, device provenance requirements, and handling of missing or discordant data should be explicit in the protocol and associated data plans.

For example, if a participant's home weight suggests a rapid decline but the clinic assessment does not confirm it, the issue should trigger a predefined reconciliation pathway rather than an ad hoc discussion weeks later.

From Monitoring More to Designing Better

ICH E6(R3) now frames GCP more explicitly around quality by design, prospective CtQ identification, and proportionate risk-based controls. In obesity studies, that means defining **Trigger → Action → Evidence** loops around:

- baseline instability,
- counselling under-delivery,
- weight discordance,
- rescue or switch events,
- temporary hybrid data gaps,
- and safety escalations.

Obesity trials can no longer be run like short-term efficacy experiments in a static patient population. They need to be run as long-term care studies with structured monitoring, realistic retention logic, clearer behavioural governance, and auditable oversight across multiple data sources and delivery modes.

What This Means for Sponsors

- Treat baseline stability as a CtQ factor, not a screening detail
- Define how background GLP-1 therapy and other weight-active interventions are governed before FPI
- Operationalize counselling as a minimum standard of care
- Prospectively define and justify the endpoint source-of-truth hierarchy
- Align protocol, SAP, DMP/CMP, vendor oversight, and trigger logic before launch

FEATURE INSIGHT

MetALD Is Not "MASH + Alcohol": How to Protect Phenotype Integrity from Screening to Readout

MetALD is one of the most promising emerging areas in hepatology - and one of the easiest to destabilize operationally.

A Narrow Overlap Phenotype Requires More Precise Governance

MetALD sits in a narrow overlap zone where metabolic dysfunction and moderate alcohol exposure interact over time. That makes the enrolled phenotype inherently fragile and the study highly vulnerable to three predictable risks:

- misclassification at screening
- phenotype drift during treatment
- alcohol-related confounding that can mimic or mask drug effect

A modern MetALD protocol should therefore define the target phenotype precisely and consistently. In practical terms, many sponsors are working with an operational target phenotype window aligned with current nomenclature and reviews - roughly 20-50 g ethanol/day for females and 30-60 g/day for males, consistent with MASLD criteria plus moderate alcohol exposure in the MetALD range.

Our approach

At Accelsiors, we sometimes refer to this as an operational “golden zone” for enrollment integrity - not as formal consensus terminology, but as a practical shorthand for the range in which phenotype dilution is less likely.

The Active Consumption Problem

One of the most common MetALD screening mistakes is relying on a single current-use question. That approach misses the central issue: whether alcohol is actively contributing to the phenotype now. A stronger enrollment model requires:

- a structured active history window, typically TLFB over 90-180 days
- alcohol captured as grams/day
- and objective support for recent exposure where appropriate

PEth Is Useful - but Protocol Interpretation Should Be Predefined

PEth can strengthen enrollment and on-study alcohol governance when paired with structured self-report. It offers an objective adjunct to self-report and can help identify discordance or drift that may otherwise remain hidden.

That said, protocol teams should predefine how PEth will be interpreted, recognizing that intermediate thresholds are still evolving and should be justified in context. Recent literature commonly supports <20 ng/mL as compatible with abstinence or very low intake, and ≥200 ng/mL as more concerning for heavy or excessive drinking, but intermediate bands are not yet cleanly standardized as universal trial norms.

For external communication, it is therefore more accurate to describe these as illustrative operational examples, not default standards.

Governance Should Be Prospective, Not Reactive

Even a well-screened MetALD cohort can drift. Participants may move toward abstinence, making them more MASLD-like, or escalate toward harmful use, creating both safety concerns and major confounding. This is why many teams are now using a dual-stream governance approach:

- subjective alcohol data through eDiary or TLFB
- objective verification through biomarkers such as PEth

These streams should be linked through a predefined reconciliation workflow.
A simple example might be:

- self-report suggests no recent alcohol intake
- biomarker data suggests ongoing exposure
- the protocol routes the case to a supportive reassessment and documented reconciliation step

This kind of discordance workflow is not a punitive compliance mechanism. It is a data-integrity and participant-safety process.

Endpoint Strategy Must Work in a Guidance Gap

Because MetALD does not yet have a clearly established standalone regulatory pathway, sponsors often need to justify endpoint strategy proactively. One practical approach is to build on the overlap in downstream injury pathways with MASH, while explicitly governing alcohol exposure as a covariate of interpretability rather than ignoring it as background context.

That argument becomes more credible when sponsors can show that:

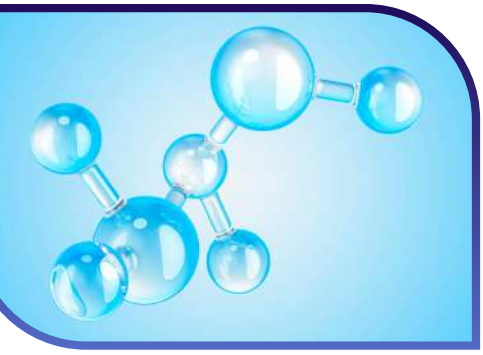
- phenotype stability is being monitored,
- discordance is being managed prospectively,
- and endpoint interpretation is linked to a defined alcohol-governance framework.

What This Means for Sponsors

- Define the target phenotype precisely and consistently across protocol and systems
- Use active consumption history, not just a current-use question
- Consider PEth as an objective adjunct, with protocol-specific interpretation rules
- Use a predefined discordance workflow rather than retrospective data cleaning
- Align endpoint strategy with explicit alcohol-governance logic in the SAP

SUPPORTING INSIGHT

MASH Trials Beyond the Molecule: What MASH Still Teaches Us About Screening and Endpoint Protection



MASH continues to teach the field hard lessons about screening, burden, and endpoint protection - even as the treatment and regulatory landscape moves forward.

The field has already shown sponsors what happens when screening is broad but poorly sequenced, when endpoint protection is underbuilt, and when participant burden is treated as a secondary issue rather than a core design variable.

Lesson 1: Screening Strategy Matters as Much as Recruitment Reach

In MASH, recruitment volume alone rarely solves efficiency problems. Without a disciplined funnel, sponsors can generate high interest while still accumulating costly screen failures, unnecessary biopsies, and avoidable dropout. This has practical consequences not only for timelines, but also for site morale when large numbers of referred patients cannot progress.

Lesson 2: Endpoint Integrity Must Be Designed, Not Assumed

Histology remains important, but endpoint protection depends on more than biopsy alone. Sponsors still need standardized collection pathways, clear review models, and operational discipline around timing, burden, and retention.

Lesson 3: Patient Burden Affects Data Quality

When visit schedules, biopsy pathways, and support models are unrealistic, retention weakens and endpoint quality suffers.

These lessons now apply beyond MASH itself. Obesity and MetALD programs are increasingly facing parallel challenges in different forms.

What This Means for Sponsors

- Build a screening funnel, not just a recruitment plan
- Reduce unnecessary burden before it becomes attrition
- Protect endpoints through central discipline, not post hoc explanation
- Use MASH's operational lessons to strengthen adjacent metabolic programs

THE PATIENT VOICE

Designing Metabolic Trials Patients Can Actually Complete

Metabolic protocols are often designed as if participants experience them the way sponsors do - as schedules, assessments, and data streams. They do not. Participants experience them as disruption.

In Obesity, Convenience Is Now Competitive

Participants may have prior treatment experience, active commercial options, or expectations shaped by real-world obesity care. If the study is harder to complete than the alternatives they know, retention will suffer.

In MetALD, Trust Is a Data Quality Variable

Participants may have heightened sensitivity around alcohol reporting. If the study atmosphere feels judgmental or punitive, underreporting and disengagement become more likely.

In MASH, Burden Shapes Completion

Screening pathways that are too invasive and follow-up schedules that are too demanding can weaken retention even in scientifically sound studies.

True patient-centricity means:

- realistic visit frequency,
- low-friction logistics,
- transparent communication,
- indication-specific support,
- selective use of decentralized elements reduce burden without weakening interpretability.

What This Means for Sponsors

- Treat burden as an operational risk to retention and data quality
- Build indication-specific support: convenience in obesity, trust in MetALD, burden reduction in MASH
- Use decentralized elements selectively, not ideologically
- Design for completion, not just recruitment

PROTOCOL PRESSURE TEST

Five Questions Every Sponsor Should Ask Before Launching an Obesity or Metabolic Liver Study

1. **Is the baseline population stable enough to support the endpoint?**
In obesity, this means governing background GLP-1 use and other weight-active interventions. In MetALD, it means ensuring alcohol exposure is active, in-range, and defensible.

2. **Are co-interventions being governed explicitly?**
Counselling, IBT, digital tools, concomitant therapies, and evolving standards of care can all become hidden confounders if they are not prospectively defined.

3. **Which variables are truly Critical-to-Quality?**
Not everything deserves maximum oversight. The key is to identify which variables most directly threaten participant safety or reliable results.

4. **Can participants realistically complete the study as designed?**
Long-term retention, demanding visits, invasive procedures, remote-device friction, and social burden all shape whether data remain complete enough to be meaningful.

5. **Are protocol, SAP, DMP/CMP, monitoring, and vendor oversight genuinely aligned?**
If source-of-truth rules, escalation paths, intercurrent event handling, and evidence requirements are not aligned, drift becomes likely.

INTERACTIVE CASE STUDY

Recruitment Is Lagging in an Obesity Trial: What Would You Change?

Scenario

A Phase II obesity trial is 20 weeks into enrollment and trending behind target. Screen failures are increasing, especially among participants with prior GLP-1 exposure or unstable baseline conditions. Sites also report that the visit schedule feels heavy for a long-duration study, and dropout risk is rising.

Possible responses

A. Add more sites and increase recruitment advertising
B. Maintain the protocol and intensify site training only
C. Reassess baseline stability rules, visit burden, hybrid execution, and retention strategy
D. Narrow eligibility further to create a cleaner dataset

Accelsiors view

The strongest response is usually C.

Recruitment in obesity is often not just a volume problem. It is a realism problem. If eligibility assumptions do not reflect the current treatment landscape, if GLP-1 exposure is poorly governed, or if the burden profile is out of step with what participants can sustain, expanding site count may raise cost without fixing the funnel. Narrowing eligibility further often worsens the same problem.

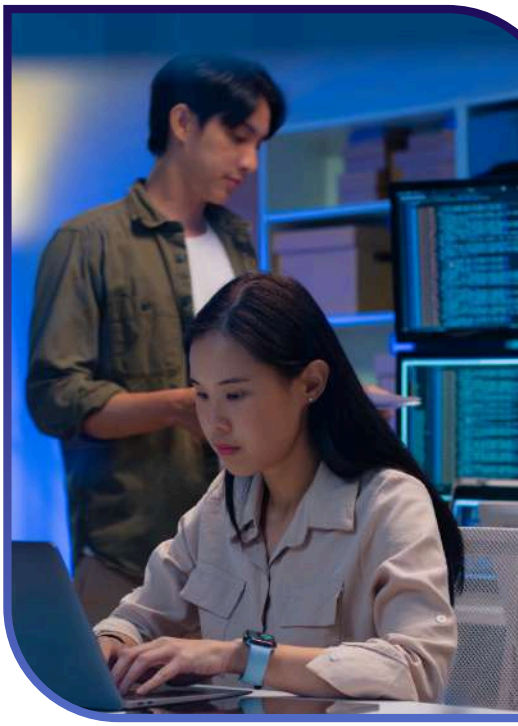
A more effective response is to stress-test the operating model:

- Are baseline rules feasible and explicit?
- Are counselling and support standardized?
- Can portions of follow-up be hybridized without weakening endpoint integrity?
- Are retention risks being detected prospectively?
- Are access and standard-of-care differences distorting feasibility?

In today's obesity environment, speed is rarely restored by effort alone. It is more often restored by removing avoidable friction from the design.

INTERACTIVE CASE STUDY

A MetALD Trial Is Drifting Off-Phenotype: What Is the Right Operational Response?



Scenario
Several months into a MetALD study, biomarker results are increasingly diverging from participant-reported alcohol intake. Some participants appear to be drifting outside the intended phenotype.

Possible responses
A. Continue as planned and clean the data retrospectively
B. Treat self-report as primary and biomarkers as context only
C. Activate a predefined discordance workflow, reassess phenotype stability, and escalate safety cases per protocol
D. Reduce biomarker monitoring to simplify execution

Accelsiors view

The strongest response is usually C.

In MetALD, discordance is not a minor data-cleaning issue. It is an integrity signal. If self-report and biomarker data diverge, the protocol should already define:

A more effective response is to stress-test the operating model:

- what qualifies as discordance,
- who triages it,
- how reassessment is conducted,
- what retraining looks like,
- when medical review is required,
- and how the event is documented.

That is what makes a MetALD study inspection-ready and scientifically defensible. It demonstrates that phenotype integrity was not left to retrospective judgement. It was actively governed.

In this indication, lack of control is itself a confounder.

OPERATIONS BRIEF

Trigger → Action → Evidence: Turning ICH E6(R3) into a Control System for Obesity and Metabolic Liver Trials

The most important shift in ICH E6(R3) is not a new checklist. It is a new operating logic.

The guideline moves quality away from broad, retrospective compliance activity and toward a principles-based, risk-proportionate model that asks a more meaningful question: what truly matters to participant safety and reliable results, and how is it being governed?

That question is especially useful in obesity and metabolic liver studies, where trial risk often emerges from interactions between variables rather than isolated site-level mistakes.

In obesity, this may involve:

- baseline instability from background therapies,
- under-delivered counselling,
- home-versus-clinic weight discordance,
- device provenance gaps,
- rescue or switch events,
- or ungoverned discontinuation patterns.

In MetALD, it often includes:

- phenotype misclassification,
- discordance between self-report and objective alcohol data,
- drift over time,
- predefined safety escalation,
- and alcohol trajectory as a covariate of interpretability.

The Trigger → Action → Evidence model turns those risks into a real control system.
For each CtQ factor, sponsors should be able to specify:
Objective — what is being protected
Trigger — what data pattern signals risk
Action — what happens next, by whom, and how quickly
Evidence — what proves the control was executed

This framework makes oversight more targeted, easier to explain, and more defensible under inspection. It also supports hybrid and digital trial models by forcing clarity around data lineage, accountability, and escalation routing.

THE INTEGRITY SHIELD, QUALITY & SECURITY

Quality by Design in Action: Building Inspection-Ready Metabolic Trials

Clinical trial quality is no longer best demonstrated by how much activity occurred after the fact. It is demonstrated by whether the right controls were designed around the right risks before the first predictable problem emerged.

Modern quality systems should be:

- principles-based rather than checklist-driven
- risk-proportionate, scaling controls to what truly matters
- digital-ready, explicitly accommodating decentralized and technology-enabled trials
- compatible with remote and centralized monitoring where these improve quality and efficiency
- built on integrated QMS thinking across protocol design, monitoring, vendor oversight, and data governance

ICH E6(R3) reinforces the shift from a prescriptive E6(R2)-style mindset toward a more risk-based Quality-by-Design approach. For sponsors, that means greater focus on participant safety and reliable data, and less emphasis on low-impact administrative activity.

Key implications include:

- integrated risk-based QMS across the trial lifecycle
- proportionality of controls, with greater attention on high-risk elements
- clearer use of Quality Tolerance Limits in context
- broader compatibility with hybrid and decentralized models, provided systems are validated and governance is clear
- stronger definition of roles across sponsors, CROs, investigators, and vendors

What This Means for Sponsors

- clearer risk rationales
- more efficient resource allocation
- stronger sponsor/CRO/vendor accountability
- and better inspection readiness

PARTNER INSIGHT

Where Metabolic Programs Really Fail: Execution, Not Intention

Most programs do not lose momentum because of one dramatic operational failure. They weaken gradually. A protocol assumption goes unchallenged. A support model is too light for the real burden. A variable that should have been CtQ is treated as background. A dataset becomes harder to interpret than anyone expected.

In obesity and MetALD especially, operational clarity is increasingly what separates resilient programs from fragile ones.

That means:
• knowing which risks truly matter,
• defining how those risks will be detected,
• deciding who acts and how,
• and preserving evidence that the system worked as intended.

Execution is increasingly where scientific value survives - or does not. That is not a secondary function of development strategy. It is part of development strategy.

TALENT & TOMORROW

What Modern Study Teams Need to Execute Obesity and Metabolic Liver Trials Well

Teams now need fluency not only in GCP, but in:

- CtQ thinking
- hybrid and decentralized oversight
- data provenance
- behavioural intervention governance
- vendor management
- patient-centric execution in long-term care settings

In obesity, this means understanding that counselling, adherence, persistence, and source-of-truth decisions affect interpretability directly. In MetALD, it means recognizing that alcohol reporting, biomarker reconciliation, and supportive site communication are not peripheral tasks - they are part of data reliability itself.

CLOSING

Ready to Pressure-Test Your Obesity or MetALD Protocol?

If you are planning or adapting an obesity, MetALD, or metabolic liver program, the best time to identify fragility is before it becomes a timeline, quality, or interpretability problem.

Our approach

- **Obesity protocol review** - baseline stability, counselling governance, endpoint source-of-truth, hybrid control loops
- **MetALD protocol stress test** - target phenotype definition, TLFB + PEth logic, discordance workflow, safety escalation, alcohol-governance controls
- **MASH operational review** - screening funnel, burden reduction, endpoint protection, retention-sensitive design

Let’s identify the single points of failure before they become expensive.