



DRAFT 0.5 INSPECTION-READINESS PACK

**for Type 2 Diabetes /
Cardiometabolic Trials**

A practical pack to translate ICH E6(R3) Quality-by-Design expectations into inspection-ready controls for:

- baseline stability
- rescue / intensification governance
- HbA1c endpoint integrity
- device/data provenance
- and protocol-SAP alignment

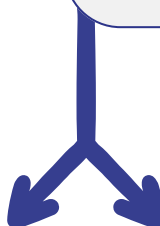
Most expensive rework later is caused by definitions that were:

- implied
- discussed informally
- or never operationalized early

Fixing these after FPI is slower, more expensive, and harder to defend.

Examples

- baseline antihyperglycemic therapy stability not fully written
- rescue vs intensification not clearly defined
- insulin-change handling left ambiguous
- HbA1c source-of-truth not locked
- supportive digital data role unclear
- protocol-SAP alignment deferred too long



Stream 1 — Endpoint

HbA1c
Fasting plasma glucose
Key metabolic/cardiometabolic measures
Safety outcomes

Stream 2 — Treatment / Care Pathway

Background antihyperglycemic therapy
Insulin changes
Rescue therapy
Treatment intensification / de-intensification
Adherence / persistence
Access-driven standard-of-care drift
Device / digital provenance

If teams govern only Stream 1, Stream 2 will govern the results.

The 3-Pillar QbD Defense

Pillar 1 – Baseline Stability / Eligibility Integrity

Do not randomize a moving baseline.

Pillar 2 – Operational Control Loop

Objective → Trigger → Action → Evidence

Pillar 3 – Defensible Endpoints

Protocol ↔ SAP ↔ DMP/CMP aligned before screening



Inspection lens

Inspectors test:

*Where is it defined?
Show me it happened.*

No silent thresholds:

What must be explicitly closed before Final Protocol / SAP

- Stabilization/run-in duration
- Definition of unstable glycemia
- Rescue therapy definition
- Treatment intensification handling
- Insulin-change handling
- HbA1c visit recovery window
- Safety escalation closure expectations
- Digital/device latency or completeness thresholds
- Access drift cut points
- SAP consequences of discontinuation, rescue, missingness, and temporary DCT gaps

If a threshold is not explicitly fixed in the protocol, SAP, plans, or contracts, label it:

TBD — needs confirmation

The risk-graded protocol audit (Red/Yellow scorecard)

Operational check	Priority	Rationale & operational action
Baseline stability / eligibility integrity	●	Check: Protocol defines handling of recent antihyperglycemic therapy change, unstable glycemic baseline, insulin-adjustment history, recent rescue/intensification, and any relevant access or region-level variability. Action: Hardcode eligibility gating, concomitant therapy logic, and stratification/monitoring variables. Any stabilization window = needs confirmation unless protocolized.
Background therapy posture	●	Check: Protocol clearly defines how metformin, SGLT2i, GLP-1 RA, insulin, sulfonylureas, and other relevant therapies are handled (allow/exclude/stabilize/stratify/standardize). Action: Define background-therapy control framework and required capture fields; ensure consistency across regions/sites.
Device/data provenance + vendor oversight	●	Check: If CGM, BGM, ePRO, eCOA, app-enabled adherence, telehealth, or other digital systems are used, chain-of-custody is documented and vendor oversight is operationalized. Action: Define device/app → vendor → sponsor/EDC data flow, audit trail expectations, reconciliation rules, and KPI governance. Vendor thresholds = needs confirmation unless contracted.
Safety escalation workflow	●	Check: Protocol and SMP define hypoglycemia escalation, urgent glycemic deterioration routing, AE-related withdrawal handling, medical review/adjudication responsibilities, and documentation expectations. Action: Implement safety routing and evidence standards; define any protocol-specific urgent review logic. SLA targets = needs confirmation unless protocolized/contracted.
Endpoint defensibility / SAP alignment	●	Check: SAP and protocol jointly define handling of discontinuation, rescue therapy, treatment intensification, missed key visits, missing data, and any supportive device/data outages. Action: Create SAP Log / estimand documentation pack and operational trigger-to-SAP linkage.

[Access the full table >> Download the Playbook](#)

T2D / Cardiometabolic trial reality → protocol control crosswalk

Trial reality	What must be explicitly defined
background therapy affects interpretability	allow/exclude/stabilize/stratify rules
rescue/intensification is expected	capture fields + SAP linkage
HbA1c is operationally fragile	source-of-truth + visit recovery
digital/device data are useful but risky	provenance + vendor oversight

Glycemic Endpoint Integrity

Risk it controls

Loss of endpoint credibility due to missed HbA1c visits, weak fasting standardization, local/central lab inconsistency, source ambiguity, inadequate visit-recovery workflows, or poor linkage between endpoint collection and intercurrent treatment reality.

Objective

Protect the reliability and interpretability of HbA1c and other key glycemic endpoints through standardized source-of-truth rules, key-visit integrity, recovery workflows, and auditable handling of endpoint-impacting events.

Trigger (signal logic)

Minimum trigger families

1. Missed key glycemic visit

A scheduled HbA1c or other key glycemic assessment is missed or falls outside the protocol-defined visit window.

Needs confirmation:

- key visit windows
- out-of-window tolerances
- allowable recovery window



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2. Source-of-truth inconsistency

Unclear or conflicting endpoint source, for example:

- local vs central lab ambiguity
- endpoint result recorded without clear hierarchy
- duplicate or conflicting source entries
- undocumented substitution of one source for another

3. Fasting-condition documentation concern

Required fasting or collection-condition data are incomplete, inconsistent, or absent for endpoint-relevant measurements.

Needs confirmation:

- what qualifies as acceptable collection-condition documentation
- whether repeat collection is required under specific deviations

4. Endpoint-impacting intercurrent event near assessment

Rescue therapy, insulin initiation/major adjustment, treatment intensification, discontinuation, or access-driven interruption occurs near the endpoint visit and may affect interpretation.

5. Repeat site pattern

Repeated missed key visits, repeated source inconsistencies, or repeated collection-condition failures at site or region level.

Action (workflow)

Visit recovery workflow

When a key HbA1c or glycemic endpoint visit is missed or compromised:

1. Determine whether recovery within the protocol-defined allowance is permitted
2. Rebook the visit where allowed
3. Document the reason for the miss or deviation
4. Confirm source-of-truth hierarchy
5. Assess whether associated intercurrent events require SAP-linked capture
6. Route repeated site-level patterns to Data Integrity governance
7. Open CAPA if drift is systemic

Source-of-truth workflow

Where endpoint source ambiguity is detected:

1. Confirm protocol/SAP-defined primary source
2. reconcile lab/source discrepancy
3. document why one source is valid and the other is supportive, excluded, or non-primary
4. ensure no silent substitution occurs
5. record any analysis-impacting consequence through controlled SAP governance

Intercurrent event bridge

If rescue, discontinuation, insulin change, or treatment intensification occurs near endpoint collection:

- confirm event capture in operational systems
- ensure event is linked to SAP handling
- route to Biostatistics / DM / ClinOps where protocol/SAP requires it

Evidence (inspection trail)

Minimum evidence should include:

- visit tracker
- lab records and lab manual cross-reference
- source documentation
- fasting-condition documentation where relevant
- deviation log where applicable
- query trail
- reconciliation worksheet where source ambiguity exists
- SAP Log entry if analysis-impacting
- governance minutes if escalated
- CAPA and retraining records for repeated site/region issues

Owner / RACI

Sponsor (A) | Data Management (R) | Accelsiors (R) | Site (R) | Vendor (C, if digital/lab interface contributes) | Biostatistics (C/A for SAP-linked consequences)

Where defined

Protocol §[Endpoints + procedures] | SAP §[endpoint handling + intercurrent-event linkage] | DMP §[source hierarchy / reconciliation] | CMP §[missed-visit and drift triggers] | Lab Manual §[] | SOM §[site workflow]



INSPECTION LENS (FDA/EMA)

Inspectors commonly test:

- Which source was primary for HbA1c?
- What happened when the key visit was missed?
- How was the recovery handled?
- How were rescue or treatment changes near endpoint assessment governed?
- Can the Sponsor reconstruct the event-to-decision chain?

If answers differ across Protocol, SAP, lab operations, and monitoring records, glycemic endpoint integrity is weakened.

Case study — “The trigger existed, but no one owned it”

Scenario:

A key HbA1c visit is missed. The site notes it locally, the dashboard reflects the missed visit a week later, but no one can show who was responsible for initiating recovery or deciding whether SAP handling was required.

Old way (reactive):

The issue is discussed retrospectively during data review. Documentation is fragmented, and the missed visit becomes an avoidable analysis dispute.

Playbook way (proactive):

T06 — Missed key HbA1c visit routes directly to **Accelsiors** as triage owner. The visit recovery workflow is initiated, the reason is documented, outreach evidence is captured, and if the visit is not recoverable, the event routes to **T25 — SAP-triggered analysis set change** logic where applicable.

Outcome:

The study can prove signal → action → closure → analysis governance.

A SAP Log / endpoint defensibility example

Topic	Sponsor ClinOps	Data Management	Biostatistics	Safety / Medical Monitor	Accelsiors
Endpoint source-of-truth rules	A	R	C	C	C
Trigger implementation and evidence trail	A	R	C	C	R
SAP Log governance	A	R	A/R	C	C
Temporary DCT gap handling	A	R	C	C	R

Hybrid / device evidence excerpt

participant/device/app

→

vendor

→

Sponsor/Accelsiors

→

EDC

→

analysis

Checklist



- device ID
- timestamps
- transfer logs
- mapping validation
- audit trail extractability
- vendor incident/CAPA evidence

What this pack helps you stress test

- Is baseline stability defined?
- Is rescue/intensification operationalized?
- Is HbA1c source-of-truth explicit?
- Are digital/vendor boundaries provable?
- Are SAP-relevant intercurrent events captured and governed?



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- [Book a 30-minutes stress-test with our team](#)

Any numeric threshold, timing window, or analysis consequence not explicitly fixed in the final protocol, SAP, or study plans must remain marked as:

TBD — needs confirmation