

DRAFT 0.5
INSPECTION-READINESS PACK
for CKD / DKD Trials

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

- baseline renal stability
- background therapy governance
- eGFR / UACR endpoint integrity
- acute kidney event reassessment
- laboratory / provenance discipline
- and protocol-SAP alignment

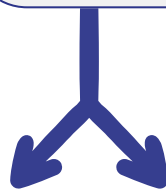
Most expensive rework later is caused by definitions that were:

- implied
- discussed informally
- or never operationalized early

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

Examples

- baseline renal stability not fully written
- RAASi / SGLT2i / GLP-1 / diuretic handling left broad
- acute kidney event reassessment rules not operationalized
- eGFR source-of-truth not locked
- UACR collection-condition rules not locked
- central vs local lab hierarchy not fully defined
- protocol-SAP alignment deferred too long



Stream 1 — Endpoint

eGFR
 serum creatinine and renal labs
 UACR / albuminuria
 key renal endpoint visits
 safety outcomes
 renal and cardiorenal outcomes where applicable

Stream 2 — Treatment / Care Pathway

RAASi
 SGLT2 inhibitor use
 GLP-1 therapy where relevant
 diuretic and volume-management changes
 acute kidney events
 reassessment pathways
 treatment interruption / discontinuation
 access-driven standard-of-care drift
 central vs local lab realities

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 renal 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 / lookback duration before randomization
- definition of unstable renal baseline
- what counts as meaningful RAASi / SGLT2i / GLP-1 / diuretic change
- acute kidney event definition and reassessment timing
- eGFR key-visit recovery window
- UACR collection-condition tolerances
- repeat / confirmatory renal sample handling
- safety escalation closure expectations
- central vs local lab hierarchy exceptions
- laboratory / vendor latency or completeness thresholds
- access-drift cut points
- SAP consequences of treatment change, AKI-like events, discontinuation, and missingness

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 renal stability / eligibility integrity rules are explicit	●	Check: Protocol defines handling of recent RAASi / SGLT2i / GLP-1 / diuretic change, unstable renal baseline, unresolved or recent acute kidney event, 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 is operationalized	●	Check: Protocol clearly defines how RAASi, SGLT2 inhibitors, GLP-1 therapies, diuretics, MRAs, antihypertensives, 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.
eGFR source-of-truth + renal lab visit recovery logic are explicit	●	Check: Protocol/SAP specify source-of-truth for eGFR and other key renal laboratory endpoints, with visit-window rules, missed-visit recovery workflow, repeat/retest logic, and local/central lab hierarchy. Action: Define endpoint source-of-truth, visit rescue process, and evidence requirements. eGFR should not be treated as routine/implicit.
UACR / albuminuria collection conditions + source hierarchy are explicit	●	Check: Protocol/lab manual define sample type, collection conditions, confirmation/repeat logic, source hierarchy, and handling of collection-condition deviations. Action: Define the operational rules that preserve repeatability and defensibility. Numeric tolerances or repeat logic = needs confirmation unless protocolized.
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](#)

CKD / DKD trial reality → protocol control crosswalk

Trial reality	What must be explicitly defined
Background therapy affects interpretability	allow / exclude / stabilize / stratify rules
Acute kidney events are expected	reassessment workflow + treatment-path handling + SAP linkage
eGFR is operationally fragile	source-of-truth + visit recovery + repeat-handling
UACR is operationally fragile	collection conditions + source hierarchy + confirmation logic
Local and central lab use creates ambiguity	lab hierarchy + reconciliation workflow
Discontinuation and missingness affect endpoint meaning	controlled intercurrent-event capture + SAP handling



eGFR / Renal Lab Endpoint Integrity

Risk it controls

Loss of endpoint credibility due to missed eGFR visits, weak timing discipline, local/central lab inconsistency, source ambiguity, inadequate visit-recovery workflows, repeat-handling ambiguity, or poor linkage between renal endpoint collection and intercurrent treatment reality.

Objective

Protect the reliability and interpretability of eGFR and other key renal laboratory endpoints through standardized source-of-truth rules, key-visit integrity, recovery workflows, repeat-handling governance, and auditable handling of endpoint-impacting events.

Trigger (signal logic)

Minimum trigger families

1. Missed key renal endpoint visit

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

Needs confirmation:

- key visit windows
- out-of-window tolerances
- allowable recovery window
- whether different rules apply for eGFR, creatinine, and other renal measures



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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. Collection / timing documentation concern

Required timing or collection-condition documentation is incomplete, inconsistent, or absent for endpoint-relevant renal measurements.

Needs confirmation:

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

4. Repeat / reassessment sample ambiguity

Repeated renal sample exists, but its role is unclear:

- endpoint-valid repeat
- safety-only reassessment
- confirmatory repeat
- clinically obtained local value
- unscheduled repeat near endpoint window

Needs confirmation:

- classification logic
- hierarchy rule
- SAP relevance if repeat sample affects endpoint interpretation

5. Endpoint-impacting intercurrent event near assessment

Acute kidney event, treatment discontinuation, RAASi / SGLT2i change, diuretic escalation, or hospitalization occurs near the endpoint visit and may affect interpretation.

6. Repeat site / region pattern

Repeated missed key visits, repeated source inconsistencies, repeated timing failures, or repeated repeat-sample ambiguity at site or region level.

Action (workflow)

Visit recovery workflow

When a key eGFR or renal endpoint visit is missed or compromised:

- determine whether recovery within the protocol-defined allowance is permitted
- rebook the visit where allowed
- document the reason for the miss or deviation
- confirm source-of-truth hierarchy
- assess whether associated intercurrent events require SAP-linked capture
- route repeated site-level patterns to Data Integrity governance
- open CAPA if drift is systemic

Source-of-truth workflow

Where endpoint source ambiguity is detected:

- confirm Protocol / SAP-defined primary source
- reconcile lab/source discrepancy
- document why one source is valid and the other is supportive, excluded, safety-only, or non-primary
- ensure no silent substitution occurs
- record any analysis-impacting consequence through controlled SAP governance

Repeat-sample workflow

Where repeated renal samples exist:

- classify each sample under protocol-defined hierarchy
- distinguish endpoint-valid repeat from safety-only reassessment
- document the rationale for inclusion, exclusion, or supportive-only status
- escalate any unresolved ambiguity to Data Management + Biostatistics + ClinOps governance



Intercurrent-event bridge

If acute kidney event, treatment change, discontinuation, or access-driven interruption occurs near endpoint collection:

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

Owner / RACI

Sponsor (A) | Data Management (R) | Accelsiors (R) | Site (R) | Lab/Vendor (C) | 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 eGFR?
- What happened when the key renal visit was missed?
- How was the recovery handled?
- How were acute kidney events or treatment changes near endpoint assessment governed?
- How were repeated renal samples classified?
- Can the Sponsor reconstruct the event-to-decision chain?

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

Case study — “The missed Week 24 eGFR”

Scenario:

A participant misses the Week 24 visit because of a travel/access issue. A local creatinine value is later obtained outside expected visit timing, and an unscheduled repeat is performed after a recent acute renal deterioration.

Old way (reactive):

Teams debate informally whether the delayed local result or the reassessment value can “fill the gap,” with inconsistent documentation.

Playbook way (proactive):

The missed key renal visit trigger fires. The visit recovery workflow is applied. The protocol-defined source-of-truth is confirmed. The reason for the missed visit is documented. The repeat/reassessment value is classified under the defined hierarchy. If the event has SAP consequences, it is routed into the controlled SAP Log.

Outcome:

Endpoint handling remains prospective, repeatable, and auditable.

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 hybrid / lab execution gap handling	A	R	C	C	R

SAP Log / endpoint defensibility example

participant / specimen



site



local lab and/or central lab



Sponsor / Accelsiors / EDC



analysis

Checklist



- specimen/source ID
- collection timestamp
- local vs central designation
- transfer logs
- mapping validation
- reconciliation worksheet
- incident / CAPA evidence
- audit trail extractability

What this pack helps you stress test

- Is baseline renal stability explicitly defined?
- Is RAASi / SGLT2i / GLP-1 / diuretic handling operationalized?
- Are eGFR and UACR source-of-truth rules explicit?
- Is acute kidney event reassessment governed?
- Are central vs local lab boundaries provable?
- Are discontinuation, treatment change, and missingness linked to SAP handling?
- Is governance auditable?



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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