C1C - Generative Artificial Intelligence in QSP

Agentic Orchestration · Auditable Guardrails · Adaptive Calibration

CHAIRS

Weirong Wang, PhD
Johnson & Johnson

Aleksander S. Popel, PhD
Johns Hopkins University

TODAY'S SPEAKERS

Priyata Kalra, PhD Simulations Plus

Model-in-the-Loop as a New Paradigm for Quantitative Systems Pharmacology Modeling

Joel Eliason, PhD Johns Hopkins University

LLM-Enabled Data Mining for QSP Model Calibration and Validation

Sudheer Rani, PhD, MBA Johnson & Johnson

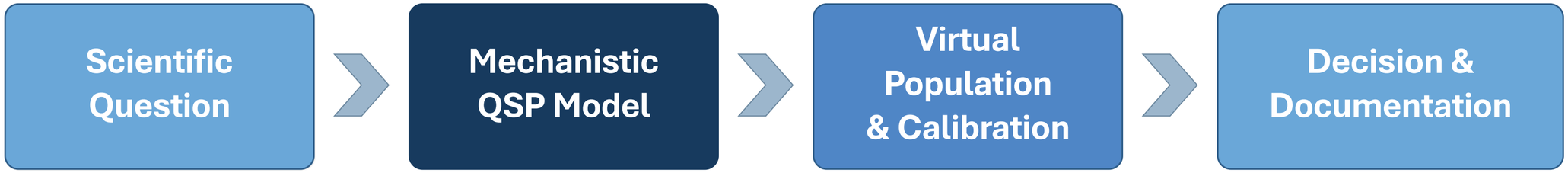
GenAI-Driven Adaptive Virtual Population Calibration for QSP

PANEL DISCUSSION

Menglun Wang, PhD FDA

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QSP Workflow: Where Can AI Help?



01 **Orchestrate the workflow**
Natural-language interaction with validated modeling and data tools

02 **Structure the evidence**
Literature extraction, model mapping, uncertainty, and parameter inference

03 **Accelerate virtual population exploration**
Efficient VPop generation, sensitivity analysis, and calibration

Agentic Orchestration · Auditable Guardrails · Adaptive Calibration

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AI-ENABLED MIDD · 2026

Modelling-in-the-loop as a new paradigm for quantitative systems pharmacology

MODELS TO MEDICINES

Actual intelligence, thoughtfully integrated

PRESENTER

Priyata Kalra, PhD
Senior scientific product manager
Simulations plus

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THE PROBLEM

Bespoke, manual and time intensive

GUIs and click-paths of various tools in your workflow; manual hand offs

MANY MANUAL HAND OFFS AND DECISION REEXPLAINATION

Data	Curating the dataset	4–8 wks
Papers	Finding parameters in papers	2–4 wks
Models	Choosing the model	2–6 wks
Runs	Running scenarios by hand	1–3 wks
Reports	Writing it up and QC	2–4 wks

SOURCE · SIMULATIONS PLUS MIDD SCIENTIFIC ENGAGEMENT DATA

80%

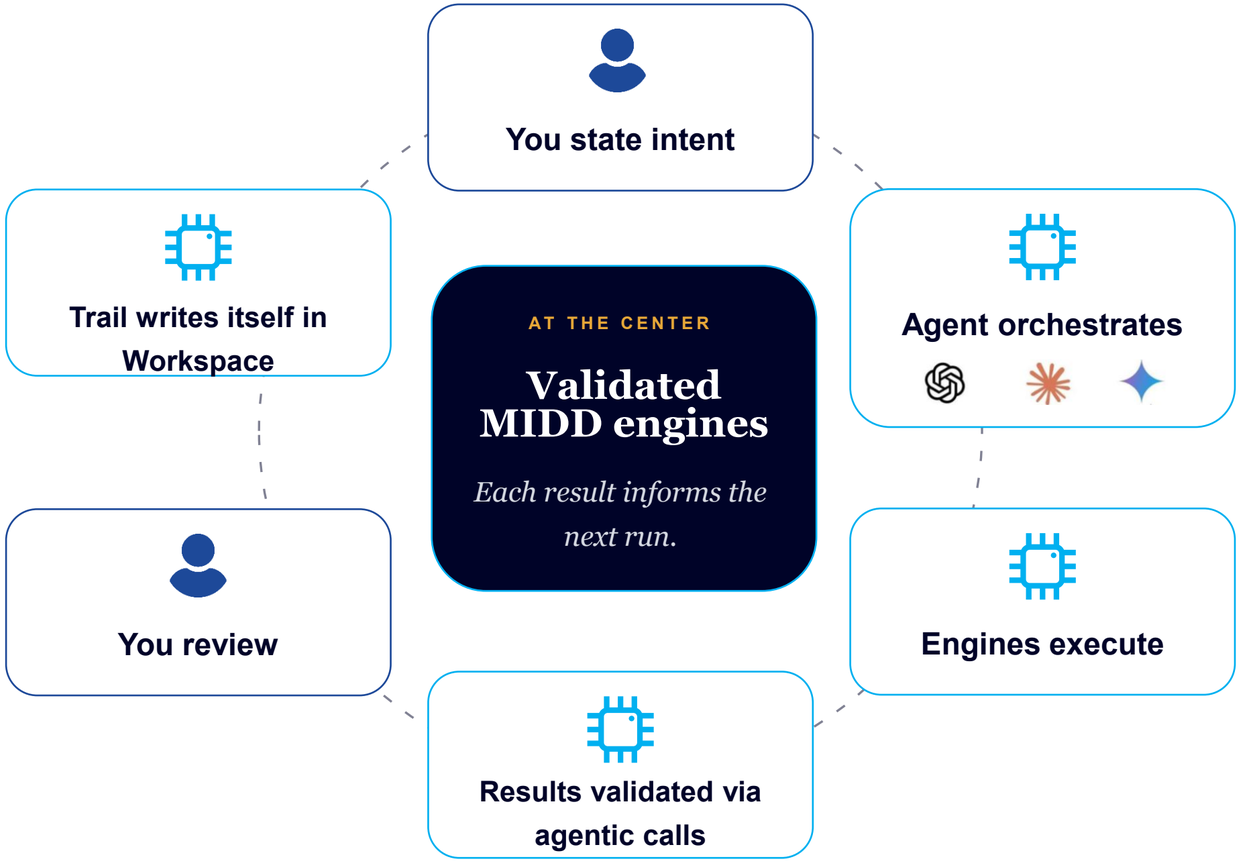
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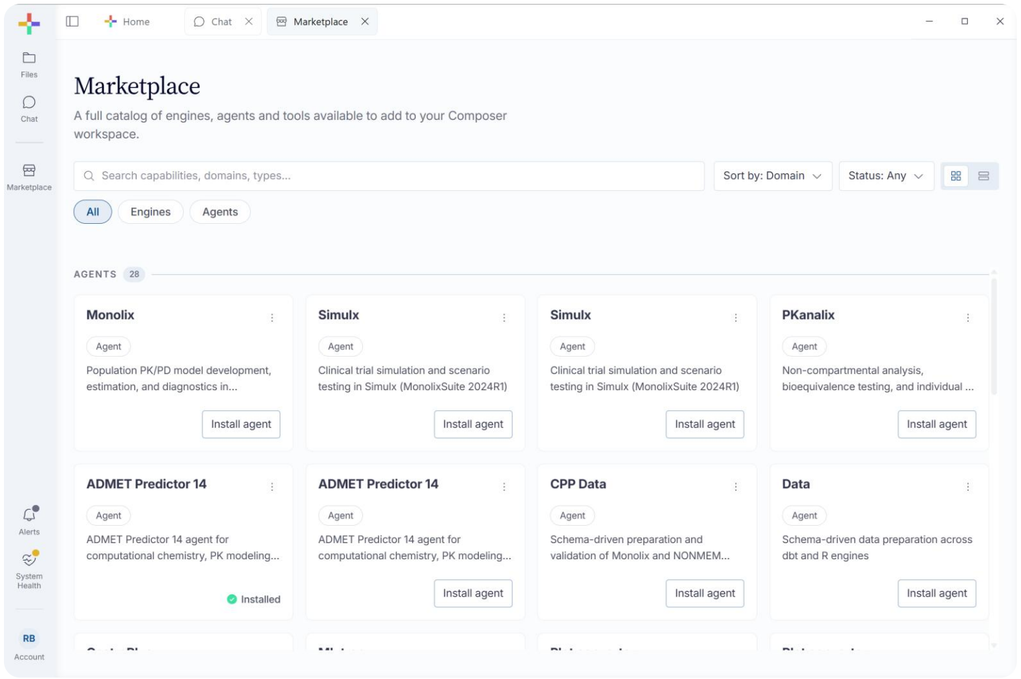


- Assembly work
- Modelling Scientist judgement

THE SOLUTION

A loop you work inside





Human

AI

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THE FRAMEWORK

Modelling-in-the-loop

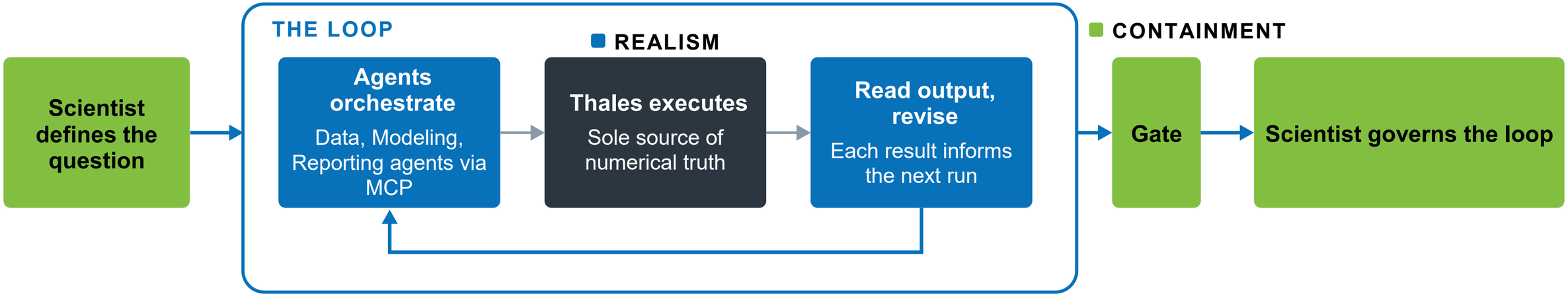
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BEFORE The model was in the loop; the act of modelling was not.

Decide | Model, by hand | **Decide** | Model, by hand | **Decide**

Episodic and artisanal: a scientist operating tools by hand between decisions.

NOW Modelling itself runs continuously inside a loop: an agent executes an engine, reads its output, and revises.

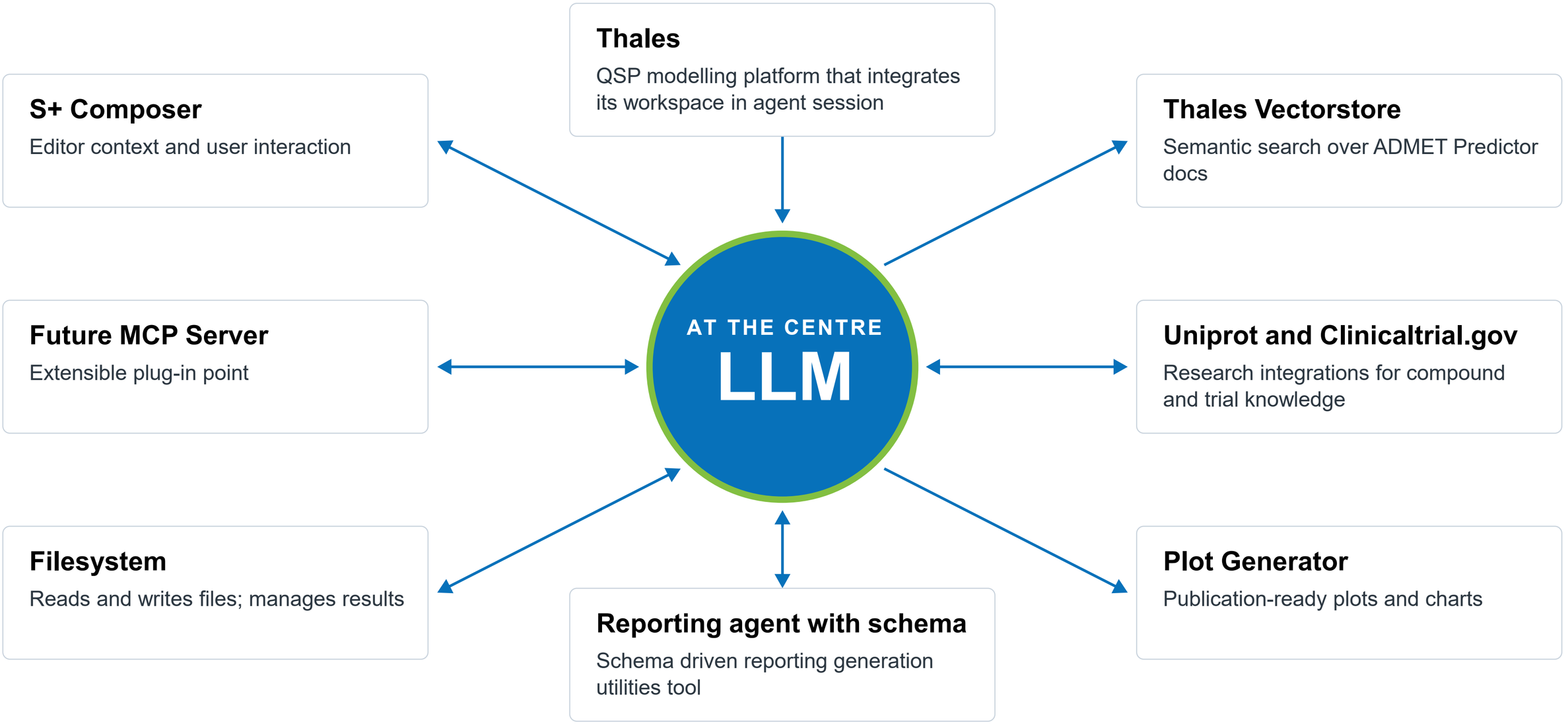


THE SHIFT **The scientist moves outward, from operating the tools to governing the loop.**

THE ARCHITECTURE

How the thales-agent is built

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Crohn’s Disease QSP From Raw Data to Report

WS 1

Data Agent

Agentic time taken ~25 min

Raw UNITI trial data → validated, model-ready datasets with audit trail

WS 2

Modelling agent

Agentic time taken for 3 prompts ~10 min

Onboard a new scientist to a Crohn’s QSP model in minutes, not weeks

WS 3

Modelling agent

Agentic time taken ~30 min

Create a novel combination therapy parameter input for Thales from natural language

WS 4

Reporting agent

Agentic time taken ~45 min

Generate QC summary professional documentation automatically

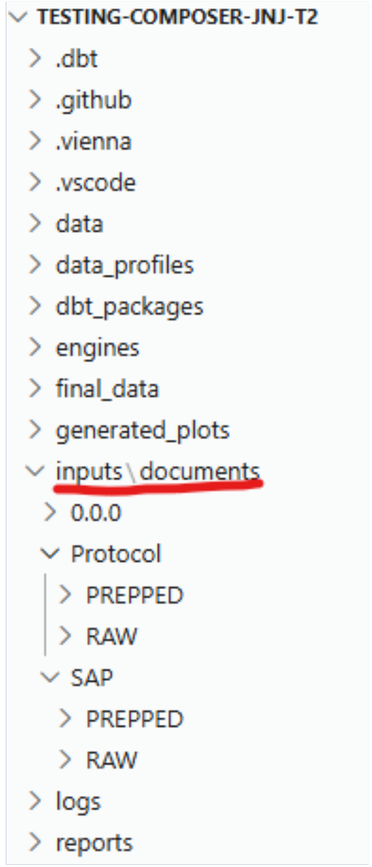
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WS 0

Setting project context

Ingest proprietary documents in your setup workspace to create context

PROMPT **Prepare and setup documents for ingestion into a vectorstore**



Prepare and setup documents for vectorstore ingestion into a vectorstore for all SAPs in inputs\documents\SAP

Used 1 reference

Checked SAP directory and analyzed project structure

I'll help you prepare the SAP documents for vectorstore ingestion. Let me first examine the current structure and existing files to understand what needs to be updated.

Ran List Directory – filesystem-testing-composer-jnj-t1 (MCP Server)

Ran Read Text File – filesystem-testing-composer-jnj-t1 (MCP Server)

Ran Read Text File – filesystem-testing-composer-jnj-t1 (MCP Server)

Now I'll use the MCP knowledge base tools to prepare and ingest the SAP documents. First, let me prepare the data directory, then ingest it into a vectorstore.

Ran `prepare_data` – knowledgebase-generator-testing-composer-jnj-t1 (MCP Server)

Ran `ingest_data` – knowledgebase-generator-testing-composer-jnj-t1 (MCP Server)

Perfect! I've successfully prepared and ingested the SAP documents into a vectorstore. Now let me update the existing project structure to include SAP documents in the main document preparation workflow as well.

Exploration of the data trust

PROMPT

Give a summary of one trial ADaM data and SAP, e.g. UNITI/CNTO1275CRD3001: what studies are included, how many patients, key primary & secondary endpoints, biomarkers in these studies? Induction or maintenance phase?

Biomarkers Available in ADaM Datasets

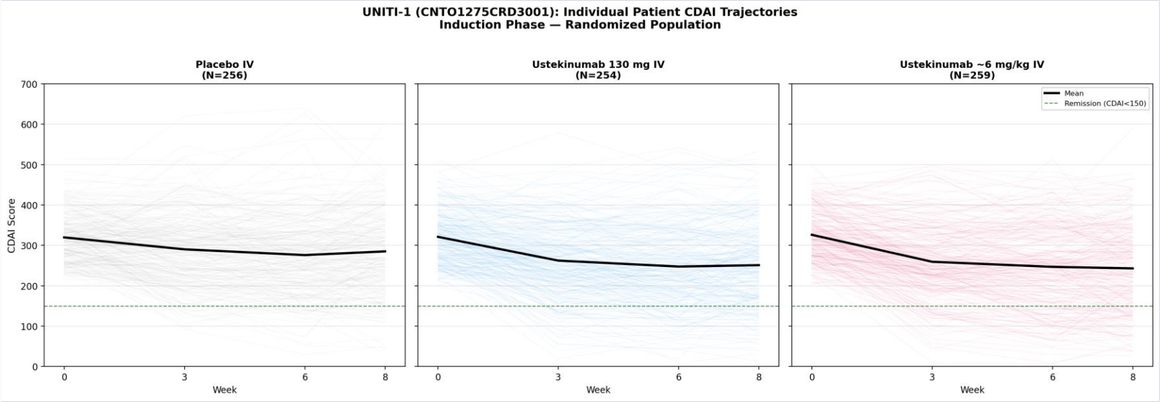
Dataset	Key Biomarkers / Parameters
ADLBEF (lab/efficacy biomarkers)	**CRP** (C-reactive protein), **fecal calprotectin**, **fecal lactoferrin** — continuous values, normalization flags, and LOCF/treatment-failure variants
ADPC (pharmacokinetics)	**Serum ustekinumab concentration** (CNTO 1275 PK MSD assay, µg/mL)
ADXA (immunogenicity)	**Anti-drug antibodies (ADA)** — sample/subject ADA status, NAb status, titer, specificity-inhibition
ADCDAI (CDAI components)	Total CDAI, individual CDAI sub-scores (stool frequency, abdominal pain, well-being, extra-intestinal manifestations, etc.)
ADEF (efficacy flags)	Binary response/remission flags at each timepoint
ADCDAICP	CDAI component-level data
ADVSCDAI	CDAI visit-specific data

Key Takeaway

UNITI-1 is an 8-week IV induction study in a TNF-antagonist-refractory Crohn's population (N = 769 randomized). It provides CDAI-based efficacy endpoints, inflammatory biomarkers (CRP, calprotectin, lactoferrin), PK drug levels, and immunogenicity data. Responders flowed into the IM-UNITI maintenance study (CRD3003).

PROMPT

Plot each individual patient CDAI trajectory (a.k.a Spaghetti plot) with different panels per arm in this trial



WS1- Data Trust

Raw AdaM data to model ready dataset

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PROMPT **Prepare the UNITI-1 trial data for Thales(PLAN)**

✓ Compiled output plan and saved to file

✓ Managed and tracked todo items for planning

Written to output-plan.md. Key sections:

- **Project context** — trial design, baseline definition, TF/LOCF handling, SOC, all sourced from SAP/protocol via project-knowledge
- **Arm mapping** — 3 pooled arms → existing scenario tuples
- **Analyte mapping** — CDAI + 3 proposed components with value derivations
- **Source → target column mapping** — every individual_targets column traced to its ADaM source field
- **Open questions** — 4 items needing your input before build

Please review and let me know your answers on the open questions (especially component analyte names and weighted vs unweighted), and I'll proceed to Phase 1 → Phase 2 build.

1.) Those proposed component analyte names work well. They will actually only be used for exploratory purposes.
2.) Please use the unweighted subscores.
3.) Include data for all subjects who were randomized. See if you can identify those pre-restart subjects in source data though.
4.) Correct. Use the values in the ADaM datasets.

› Used 1 reference

✓ Answered open questions and updated build plan

✓ Starting: *Phase 1: Data Understanding* (5/8)

Let me verify the unweighted component data and investigate pre-restart subjects.

✓ Ran Query files – data-explorer-composer-2026-02-12 (MCP Server)

✓ Ran Query files – data-explorer-composer-2026-02-12 (MCP Server)

✓ Ran Query files – data-explorer-composer-2026-02-12 (MCP Server)

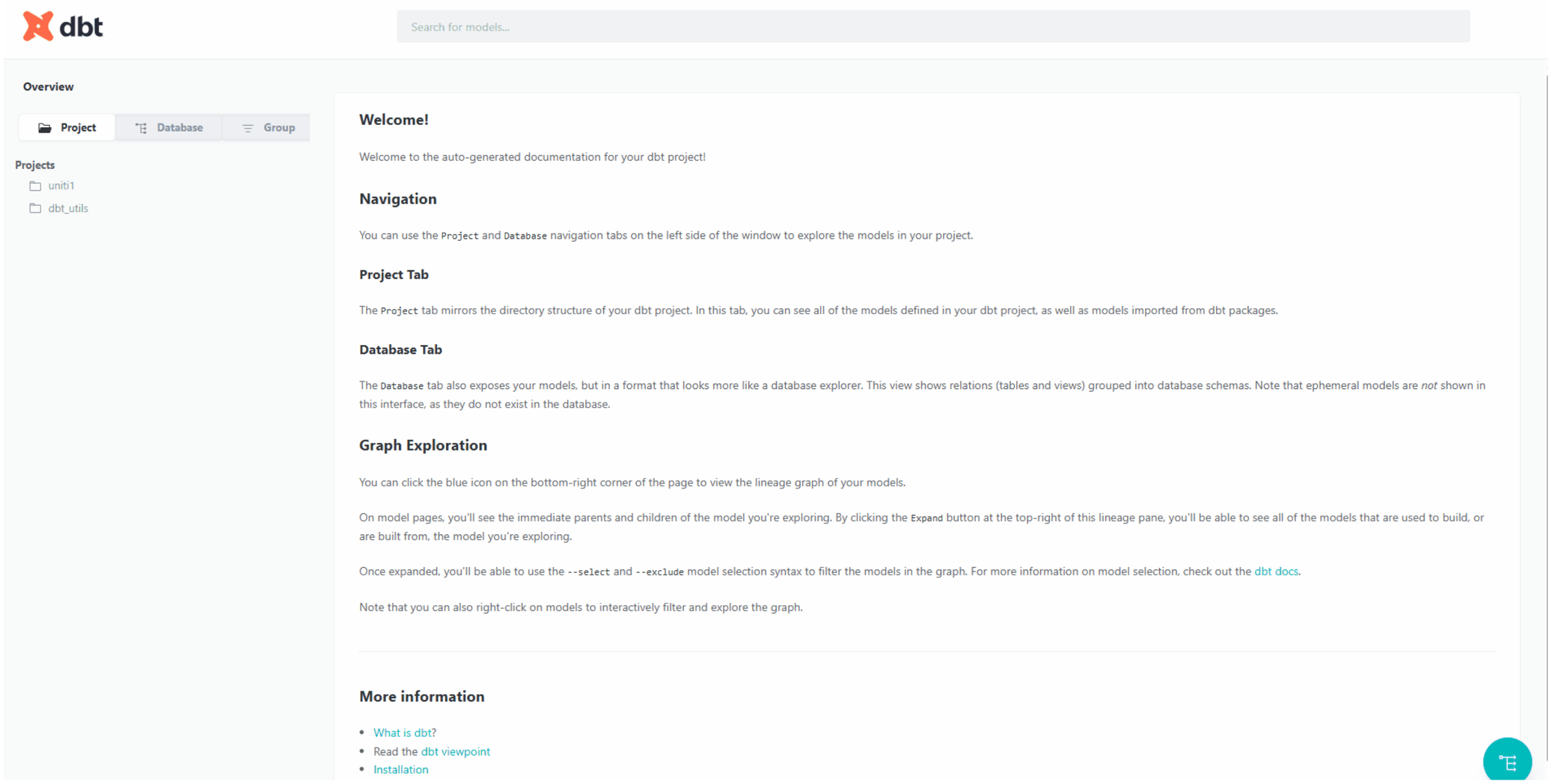
output-plan.md

output-plan.md › abc # Output Plan — UNITI-1 (CNTO1275CRD3001) › abc ## Project Context

```
1   # Output Plan — UNITI-1 (CNTO1275CRD3001)
88  ## individual_targets.csv
153 ### Expected Row Counts
156 ~4 analytes x ~769 patients (baseline) + ~4 analytes x ~722 patients (Week 8)
157 ≈ 3,076 + 2,888 = ~5,964 rows (exact count depends on component data availability)
158 ```
159
160 ---
161
162 ## Open Questions
163
164 1. **Component analyte names**: `CDAI_AP` (pain), `CDAI_SF` (stool frequency), `CDAI_WB` (well-being)
165    are PROPOSED names — not yet in the existing model endpoints.md. Do these match what the
166    modeler expects? Different naming conventions?
167
168 2. **Weighted vs unweighted components**: Plan uses CDAI-weighted contributions (so components
169    approximately add up toward the total CDAI). The weighted values are:
170    - Pain: sum of 7 daily ratings x 5 (range 0–105)
171    - Stool freq: sum of 7 daily counts x 2 (range 0–322 observed)
172    - Well-being: sum of 7 daily ratings x 7 (range 0–196)
173    Is this the correct representation for the model, or should we use unweighted subscores?
174
175 3. **Pre-restart subjects (28)**: SAP §5 excludes them from efficacy analyses. Need to verify
176    whether they are already excluded from the ADaM dataset or require explicit filtering.
177    Will check in Phase 1 via SQL query on RANDFL and subject counts.
178
179 4. **adcdaicp TF-adjusted data**: Plan uses raw observed from adcdai (no TF imputation).
180    The adcdaicp dataset has LVCF/TF-adjusted weighted components. Confirm this is correct
181    for individual_targets (Thales handles its own scoring).
182
183 ---
```

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Documentation of databuild with tests



Human augmented GenAI decision

Please help to compare human-made "data/Gus_Uste_megafile_timezeroSoC_plus_8hr24hr48hr_110824.csv" with the AI-generated "final_data/thales_individual_targets.csv".

AGENTS.md:14

- Used 1 reference
- Optimizing tool selection...
- Loaded and examined CSV files for structure
- Created 5 todos
- Ran Generate data profiles – data-explorer-testing-composer-jnj-t2 (MCP Server)
- Ran List source data files – data-explorer-testing-composer-jnj-t2 (MCP Server)
- Queried files to understand schemas and compared

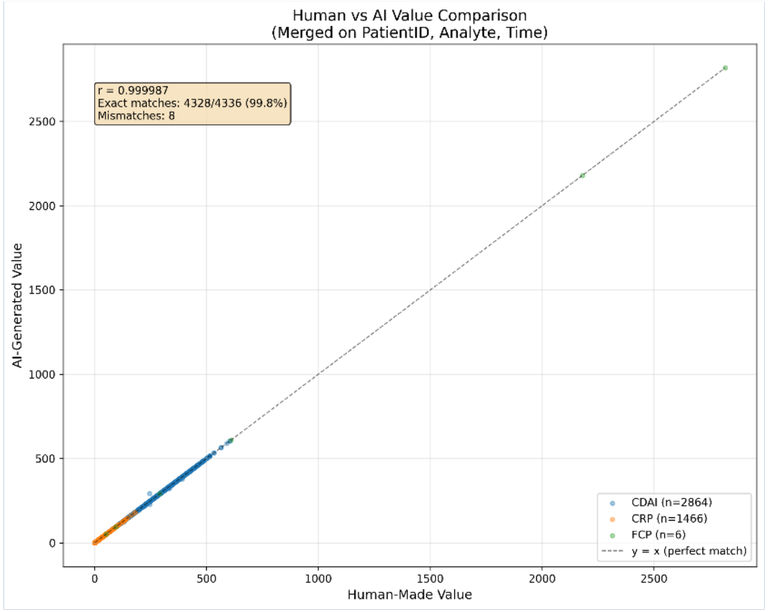
Show me records that did not have exact match

- Used 1 reference
- Viewed records with value mismatches
- Ran Query files – data-explorer-testing-composer-jnj-t2 (MCP Server)

Here are all 8 mismatched records:

PatientID	Analyte	Time	Human Value	AI Value	Diff
CNTO1275CRD3001-35334	CDAI	8	246	293	**-47**
CNTO1275CRD3001-19049	CDAI	60	247	229	+18
CNTO1275CRD3001-41121	CDAI	8	391	378	+13
CNTO1275CRD3001-76218	CDAI	8	334	322	+12
CNTO1275CRD3001-18845	CDAI	8	132	126	+6
CNTO1275CRD3001-04055	CDAI	8	224	218	+6
CNTO1275CRD3001-37258	CDAI	60	435	436	-1
CNTO1275CRD3001-37258	CDAI	8	413	414	-1

All 8 are **CDAI** only, all from patients with prefix `CNTO1275CRD3001-*`. Notably, the human file assigns these patients to trial `CNTO1275CRD3003` while the AI file maps them to `Feagan 2016 (UNITI-1)` (which is CRD3001). That trial mismatch may indicate these patients were handled differently between the two pipelines, which could explain the value discrepancies. The two smallest diffs (±1) could be rounding; the larger ones (6–47) likely reflect a different source record or calculation path.



adcdai from 3001:

	A	B	C	D	AK	AL	AM	AN	AO
1	STUDYID	USUBJID	AVISIT	AVISI	PARAMCI	PARAM	PARAMT	PARAN	AVAL
42514	CNTO1275CRD3001	CNTO1275CRD3001-35334	WEEK 0	2	CDAI	Total CDAI score	DERIVED	439	352
51912	CNTO1275CRD3001	CNTO1275CRD3001-35334	WEEK 3	3	CDAI	Total CDAI score	DERIVED	439	177
64568	CNTO1275CRD3001	CNTO1275CRD3001-35334	WEEK 6	4	CDAI	Total CDAI score	DERIVED	439	215
79612	CNTO1275CRD3001	CNTO1275CRD3001-35334	WEEK 8	5	CDAI	Total CDAI score	DERIVED	439	293

adcdai from 3003:

	A	B	C	D	E	AL	AM	AN	AO	AP
1	STUDYID	USUBJID	AVISIT	AVISITN	ADT	PARAMCD	PARAM	PARAMTYP	PARAMN	AVAL
8060	CNTO1275CRD3003	CNTO1275CRD3001-35334	WEEK 0	2	18611	CDAI	Total CDAI score	DERIVED	439	352
38186	CNTO1275CRD3003	CNTO1275CRD3001-35334	WEEK 3	3	18831	CDAI	Total CDAI score	DERIVED	439	177
56610	CNTO1275CRD3003	CNTO1275CRD3001-35334	WEEK 6	4	18853	CDAI	Total CDAI score	DERIVED	439	215
80826	CNTO1275CRD3003	CNTO1275CRD3001-35334	WEEK 0 MAINTENANCE	9	18871	CDAI	Total CDAI score	DERIVED	439	246
89778	CNTO1275CRD3003	CNTO1275CRD3001-35334	WEEK 0 MAINTENANCE	9	18871	CDAI	Total CDAI score	DERIVED	439	246

WS2

Tool Intelligence

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PROMPT

Can you help me understand the config.yml file? Explain the fit_pipeline structure and how simulation stages are connected for drug trials.

fit_pipeline Architecture

The `fit_pipeline` in `!config.yml` defines a hierarchical structure for running QSP model simulations with multiple treatment scenarios. Here's how it works:

1. Pipeline Components

Pipeline Elements:

- `!PipelineSequence`: Stages run sequentially (one after another)
- `!PipelineBranch`: Stages run in parallel branches (different treatment arms)

Key Pipeline Stages:

- `pre_healthy`: Initialize to healthy steady-state
- `healthy`: Confirm healthy baseline
- `pre_disease`: Progress to diseased steady-state
- `disease`: Confirm diseased state
- `standard_of_care`: Apply background medications (steroids, etc.)
- **Drug Trial Stages**: Various treatment scenarios

2. Hierarchical Structure

```
fit_pipeline:
  - !PipelineSequence
      elements:
        - !PipelineBranch  # Healthy vs Disease paths
            elements:
              - !PipelineSequence  # Healthy path
                  elements: [pre_healthy, healthy]
              - !PipelineSequence  # Disease path
                  elements:
                    - pre_disease
                    - !PipelineBranch
                        elements:
                          - attempt_healing
                          - disease
                          - !PipelineBranch  # Treatment arms
                              elements:
```

3. Drug Trial Connection Pattern

Sequential Treatment Pattern (for drugs with induction + maintenance):

```
- !PipelineSequence
    elements:
      - uste_6mgkg_wk0  # Induction dose
      - !PipelineBranch  # Maintenance options
          elements:
            - uste_90mg_Q8W    # Maintenance arm 1
            - uste_90mg_Q12W   # Maintenance arm 2
            - placebo_maint    # Placebo maintenance
```

Parallel Treatment Arms:

```
- !PipelineBranch
    elements:
      - placebo
      - adalimumab_40mg
      - adalimumab_80mg
      - ustekinumab_90mg
```

4. Stage Definitions in `!stages.yml`

Each stage referenced in the pipeline is defined in `!stages.yml`:

```
- !SimulationStage
    name: uste_90mg_Q8W
    scenario: ['Ustekinumab 90mg Q8W 40 taper 10', 'Ustekinumab', '90mg SC Q8W']
    use_stage_criteria: CDAIchangeResponderEntranceCriterion
    post_sim_transform:
        - PredictorOutputs
        - CalculateCustomClinicalOutputs
    trajectory_filter: *WEEKLY_FILTER
    abort_criteria: null
```

5. prediction_pipeline vs fit_pipeline

fit_pipeline: Used for parameter estimation against clinical trial data

- Includes all treatment arms from historical trials
- Runs parallel simulations for each dosing regimen
- Estimates model parameters via optimization

prediction_pipeline: Used for forward simulation/prediction

- Focuses on specific scenarios of interest
- Many fit scenarios are commented out
- Includes validation scenarios and new predictions

6. Clinical Trial Simulation Flow

1. **Baseline**: `pre_healthy` → `healthy` → `pre_disease` → `disease`
2. **Standard Care**: Apply background medications
3. **Treatment**: Branch into drug vs placebo arms
4. **Dosing Pattern**:
   - Single stage (simple dosing)
   - Sequential stages (induction → maintenance)
5. **Data Collection**: Weekly filter captures CDAI, biomarkers, clinical endpoints
6. **Analysis**: Compare treatment arms against placebo reference

7. Key Features for Drug Development

Multi-arm Studies:

- Parallel comparison of multiple doses
- Placebo controls for each treatment sequence

Real-world Complexity:

- Background medications (steroids, immunosuppressants)
- Patient heterogeneity via population parameters

WS2

Model Intelligence

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PROMPT

Can you list all mechanisms modelled for IL-23 in this model.

IL-23 Mechanisms in the CrohnsDisease-clean-Vienna Model

1. IL-23 Production

- **APC-mediated IL-23 production**: Antigen Presenting Cells (APCs) produce IL-23
- **Modulated by multiple factors**:
  - IL-10 monocyte inhibition
  - Aminosalicylate inhibition
  - Steroid inhibition
  - APC cell activation state
  - TNF enhancement (M1 polarization)
  - IL-23 production limits
  - JNJ2113 inhibition

2. IL-23 Signaling & Effects

- **Th17 cell differentiation enhancement**: IL-23 promotes Th17 cell differentiation through Hill kinetics
- **Normalized IL-23 signaling**: IL-23 concentration is normalized against physiological upper bounds for modeling purposes

3. IL-23 Pharmacological Inhibition

- **Small molecule JAK inhibitors** affecting IL-23 signaling:
  - **Tofacitinib** (tofa_il23_effect_inhibition)
  - **Filgotinib** (filgot_il23_effect_inhibition) - both prodrug and metabolite effects
  - **Upadacitinib** (upa_il23_effect_inhibition)

4. IL-23 Direct Binding & Neutralization

Multiple monoclonal antibodies directly bind and neutralize IL-23:

- **Guselkumab**: Forms guselkumab-IL23 complexes with reversible binding kinetics
- **Mirikizumab**: Forms miri-IL23 complexes with reversible binding kinetics
- **Ustekinumab**: Binds IL-23 (and IL-12) forming uste-IL23 complexes
- **Risankizumab**: Forms risan-IL23 complexes with reversible binding kinetics
- **Brazikumab**: Forms brazi-IL23 complexes with reversible binding kinetics

5. IL-23 Complex Dynamics

- **Reversible binding**: All IL-23-antibody complexes can dissociate back to free drug and free IL-23
- **Molecular balance**: Complex formation and dissociation are tracked using molar balancing
- **Tissue distribution**: IL-23 binding occurs primarily in tissue compartments

6. IL-23 Normalization & Effective Concentration

- **IL-23 normalization**: Raw IL-23 levels normalized to physiological bounds
- **Effective IL-23**: Accounts for all inhibitory factors (JAK inhibitors) affecting IL-23 signaling
- **Formula**: `il23_normalized_effective = il23_normalized × tofa_il23_effect_inhibition × filgot_il23_effect_inhibition × upa_il23_effect_inhibition`

This comprehensive IL-23 modeling captures both the biology of IL-23 production/signaling and the pharmacological interventions targeting this pathway in Crohn's disease treatment.

Based on my analysis of the model files, here are all the **IL-23 mechanisms** modeled in the CrohnsDisease-clean-Vienna model presented as a table:

Mechanism Category	Specific Mechanism	Description	Key Components
Production	APC IL-23 Production	Antigen Presenting Cells produce IL-23	`apc_cell_il23_production`
Production Modulation	IL-10 Inhibition	IL-10 from monocytes inhibits IL-23 production	`il10_mono_inh`
Production Modulation	Aminosalicylate Inhibition	5-ASA drugs inhibit IL-23 production	`aminosalicylate_inh`
Production Modulation	Steroid Inhibition	Corticosteroids inhibit IL-23 production	`steroid_inh`
Production Modulation	TNF Enhancement	TNF enhances IL-23 production (M1 polarization)	`tnf_enh_M1`
Production Modulation	APC Activation Effect	APC activation state affects IL-23 production	`apc_cell_activation`
Production Modulation	Production Limit	Upper bound on IL-23 production capacity	`il23_limit`
Production Modulation	JNJ2113 Inhibition	Experimental inhibitor of IL-23 production	`inh_JNJ2113`
Signaling Effects	Th17 Differentiation	IL-23 enhances Th17 cell differentiation	`th17_cell_differentiation_effect_il23_normalized_effective`
Normalization	IL-23 Normalization	Normalizes IL-23 levels to physiological bounds	`il23_normalized`
Effective Concentration	JAK Inhibitor Effects	Multiple JAK inhibitors reduce IL-23 signaling	`il23_normalized_effective`
JAK Inhibition	Tofacitinib Effect	Tofacitinib inhibits IL-23 signaling	`tofa_il23_effect_inhibition`
JAK Inhibition	Filgotinib Effect	Filgotinib (prodrug + metabolite) inhibits IL-23	`filgot_il23_effect_inhibition`

Agentic modelling

Read the projectID: 996, lauch a simulation job with fit pipeline in it and sync the job with the project workspace after it is finied. Use plan mode to execute all these steps

Used 1 reference

Read project ID 996 and launched simulation job

let me start by understanding the available actions and the project structure.

Created 6 todos

Ran `list_thales_actions` – thales-testing-composer-jnj-t2 (MCP Server)

Starting: *Read project 996* (2/6)

Running `call_thales_action_http` – thales-testing-composer-jnj-t2 (MCP Server)

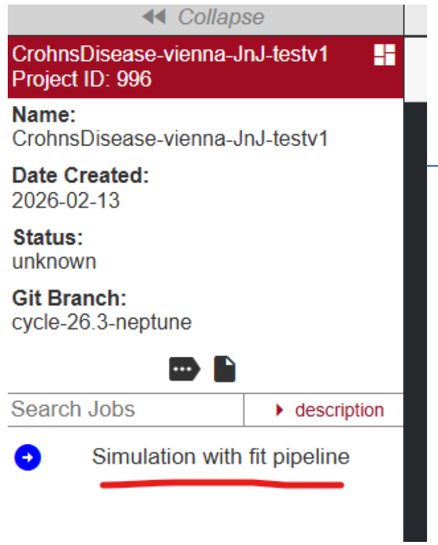
Todos (2/6)

- Explore Thales actions
- Read project 996
- Sync workspace to project
- Launch simulation with fit pipeline
- Wait for job completion
- Sync job with workspace

Ran `call_thales_action_http` – thales-testing-composer-jnj-t2 (MCP Server)

Job launched — **ID 89415**. Now let me poll its status:

Starting: *Wait for job completion* (5/6)



Ran `call_thales_action_http` – thales-testing-composer-jnj-t2 (MCP Server)

Job completed! Now let me sync the results to the workspace:

Starting: *Sync job with workspace* (6/6)

Step	Action	Result
1. Read project	Retrieved project 996	`CrohnsDisease-vienna-JnJ-testv1` (owner: priyata.kalra)
2. Sync workspace → project	Pushed local files	Already up to date
3. Launch simulation	`ThalesProjectOwnerViewSet.run` with `mode=simulate`, fit pipeline	**Job 89415** created (SGE 143651)
4. Wait for completion	Polled status ~35 times	Status: **completed** ✅
5. Sync job → workspace	Downloaded job results	**50+ files** synced to jobs/89415/

WS3-Param Intelligence

Design, build and validate new therapy scenarios

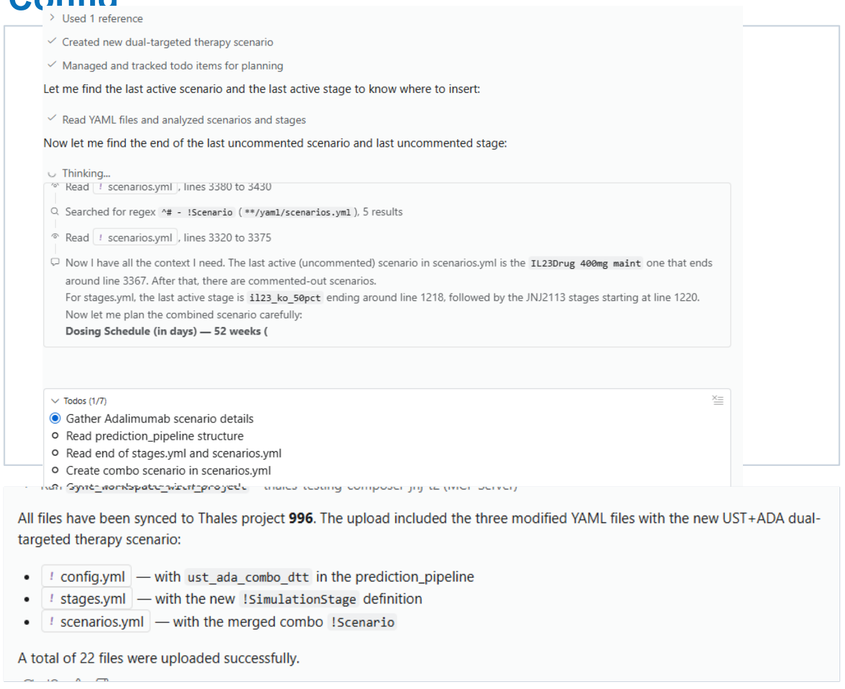
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PROMPT

Create a new dual-targeted combination therapy scenario based on the He et al. 2025 study (DOI: 10.1007/s10238-025-01731-x) for refractory Crohn's disease:
USTEKINUMAB: 6 mg/kg IV at week 0, 90 mg SC Q8W maintenance

ADALIMUMAB: 160 mg SC wk 0, 80 mg SC wk 2, 40 mg SC Q2W maintenance

Config



Config

```
                - ['anti_MAdCAM 25mg
    - !PipelineSequence
      elements:
        - amadcam_75mg_Q4W
        - !PipelineBranch
          elements:
            - pbo_20taper10:
                label: ['Placebo M 20 taper 10 post 75mg', 'placebo', 'none']
                groups:
                  - ['Placebo M 20 taper 10', 'placebo', 'none']
            - amadcam_75mg_Q4W_maint:
                label: ['anti_MAdCAM 75mg Q4W 20 taper 10 post 75mg', 'anti_MAdCAM',
                groups:
                  - ['anti_MAdCAM 25mg Q4W 20 taper 10', 'anti_MAdCAM', '25mg Q4W'
- amadcam_225mg
- amadcam_75mg
- secu_10mgkg
- UST_ADA_combo_DTT


tprodstop')
```

Scenarios

```
# Dual-Targeted Combination Therapy based on He et al. 2025 (DOI: 10.1007/s10238-025-01731-x)
# Refractory Crohn's disease: UST + ADA combination
- !Scenario
  key_tuple: ['UST_ADA_combo_DTT', 'UST+ADA', 'UST 6mgkg IV wk0 then 90mg Q8W + ADA 160-80mg wk0-2 then 40mg Q2W']
  times: !FloatRange
    start: 0
    end: 364
    step: 1
  overrides_namespace:
    {
      'Intestine:ada_convergence_assurance': 1.0
    }
  event_specs:
    - !ScheduledEventSpec
      description: UST_ADA_ComboTreatment
      map_time_to_set_expressions:
        0:
          Intestine___aminosalicylate_inh: Intestine___aminosalicylate_effectiveness * Intestine___placebo_effectiveness
          Intestine___sterold_inh: Intestine___sterold_effectiveness * Intestine___placebo_effectiveness
          <<: *40MG_TAPER10_startWK12
      map_time_to_add_expressions:
        # Week 0: UST 6 mg/kg IV + ADA 160 mg SC
        0:
          Intestine___ustekinumab_serum: 6.0*Intestine___patient_weight*Intestine___g_per_mg/Intestine___uste_mol_wt*Intestine___fmole_per_mole
          Intestine___adalimumab_sc: 160.0*Intestine___g_per_mg/Intestine___ada_mol_wt*Intestine___fmole_per_mole
        # Week 2: ADA 80 mg SC
        14:
          Intestine___adalimumab_sc: 80.0*Intestine___g_per_mg/Intestine___ada_mol_wt*Intestine___fmole_per_mole
        # Week 4: ADA 40 mg SC Q2W maintenance begins
        28:
          Intestine___adalimumab_sc: 40.0*Intestine___g_per_mg/Intestine___ada_mol_wt*Intestine___fmole_per_mole
        # Week 6: ADA 40 mg SC
        42:
          Intestine___adalimumab_sc: 40.0*Intestine___g_per_mg/Intestine___ada_mol_wt*Intestine___fmole_per_mole
        # Week 8: UST 90 mg SC Q8W maintenance begins + ADA 40 mg SC
        56:
          Intestine___ustekinumab_sc: 90.0*Intestine___g_per_mg/Intestine___uste_mol_wt*Intestine___fmole_per_mole
          Intestine___adalimumab_sc: 40.0*Intestine___g_per_mg/Intestine___ada_mol_wt*Intestine___fmole_per_mole
        # Week 10: ADA 40 mg SC
        70:
```

Stages

```
# Dual-targeted combination therapy stage for refractory Crohn's disease
- !SimulationStage
  name: UST_ADA_combo_DTT
  scenario: ['UST_ADA_combo_DTT', 'UST+ADA', 'UST 6mgkg IV wk0 then 90mg Q8W + ADA 160-80mg wk0-2 then 40mg Q2W']
  use_stage_criteria: null
  post_sim_transform:
      - PredictorOutputs
      - CalculateCustomClinicalOutputs
  trajectory_filter: *WEEKLY_FILTER
  abort_criteria: null
```

SimulationsPlus

Product human reviewed by SME

ACoP 2026

PROMPT

Generate a comprehensive QC Summary Report using the approved QC template. Populate all sections with accurate and traceable information derived from the following sources:

project-workspace **logs directory** **generated_plot folder**

- ✓ Listed templates and gathered workspace context
- ✓ Created 5 todos
- ✓ Ran `list_templates` – document-gen-testing-composer-jnj-t2 (MCP Server)
- Thinking...
  - Read SAP
  - Read csvs
  - Read logs-dataagent.md, lines 200 to 449
  - Read Protocol
  - Read SAP
  - Read dbt.log, lines 1 to 50

Todos (1/5)

- (●) List templates & gather context
- ( ) Create schema from template
- ( ) Initialize document & fill sections
- ( ) Generate final markdown
- ( ) Export to PDF/DOCX

QC Report: UNITI-1 (CNTO1275CRD3001) — Crohn's Disease QSP Model Data Preparation & Pipeline Configuration

Purpose and Scope

This Quality Control (QC) report documents the data preparation, pipeline configuration, and simulation readiness for the UNITI-1 (CNTO1275CRD3001) clinical trial dataset within the Crohn's disease Quantitative Systems Pharmacology (QSP) model hosted on **Thales Project ID 996** (`CrohnsDisease-vienna-JnJ-testv1`). The primary objective of this workstream was to transform raw ADaM clinical data from the UNITI-1 Phase 3 induction study (ustekinumab in moderate-to-severe Crohn's disease, TNF-failure population) into a Thales-compliant `individual_targets.csv` suitable for model calibration. In addition, a dual-targeted combination therapy (DTT) scenario based on He et al. 2025 (DOI: 10.1007/s10238-025-01731-x) was configured into the prediction pipeline for prospective simulation.

The scope of this QC effort covers: (1) data extraction and transformation from the UNITI-1 source ADaM dataset, (2) dbt-based pipeline construction and automated testing, (3) QA visualization and manual inspection, (4) scenario configuration changes to the Thales YAML files, and (5) synchronization to the Thales cloud platform. This report does not cover model fitting or parameter estimation results, as the simulation job has not yet been executed with the new DTT scenario.

Thales Project Context

Project ID: 996 — `CrohnsDisease-vienna-JnJ-testv1`

Objective: Develop and calibrate a QSP model of Crohn's disease incorporating 15+ drug programs across anti-TNF, anti-IL-12/23, anti-IL-23, anti-integrin, JAK inhibitor, and anti-IL-17A mechanisms of action. The model supports mechanistic exploration of treatment response heterogeneity, dose optimization, and prospective prediction of novel combination therapies.

Dataset Intended Use: The UNITI-1 individual targets dataset (16,295 rows, 769 patients) is intended as individual patient-level calibration data for the fit pipeline. CDAI total score and three sub-components (CDAI_SF, CDAI_AP, CDAI_WB) provide detailed response trajectories, while CRP and fecal calprotectin (FCP) biomarkers provide objective inflammatory endpoints for multi-analyte fitting.

Scenario Origins: The existing model configuration contains calibration scenarios sourced from published Phase 2/3 clinical trials (CLASSIC, CHARM, GEMINI-2, ADVANCE/FORTIFY, UNITI/IM-UNITI, U-EXCEL/U-ENDURE, PANES, GALAXI, SERENITY/VIVID, SONIC, CAIN457F2349). Each scenario encodes dosing schedules, steroid tapers, and PK/PD expressions derived from registered trial protocols and published PK models.

level fitting.

Note: QC Process Summary: All automated tests passed (dbt run: 4/4 models OK, dbt test: 25/25 PASS across 3 separate execution runs). Zero errors were encountered in the entire 5,205-line dbt execution log. Two benign warnings were logged (DuckDB transaction cleanup, dbt syntax deprecation) — neither affects data integrity or test validity. All 10 data quality and configuration findings above are resolved or by-design. The QC process is **complete** for the data preparation and pipeline configuration scope defined above.

Warning: This QC report is limited to data preparation and pipeline configuration activities. Model fitting, parameter estimation, sensitivity analysis, and calibration/validation results are not yet available for this specific dataset. Sections addressing those topics are marked as pending. The DTT combo scenario (He et al. 2025) is a prediction-only scenario and has not been fitted to clinical data.

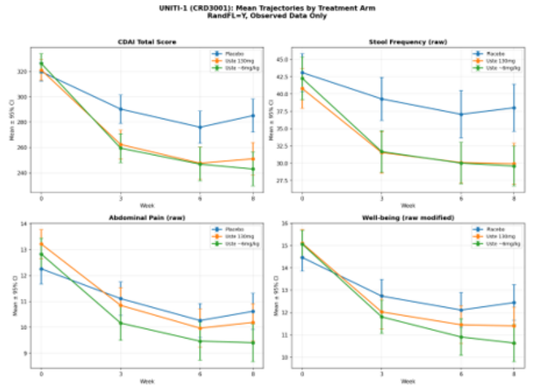


Figure 30: Mean ± 95% CI trajectories for CDAI and 3 component analytes (CDAI_SF, CDAI_AP, CDAI_WB) by treatment arm across Weeks 0–8 in UNITI-1. QC Purpose: Validates that arm-level treatment separation and dose-response are consistent with published UNITI-1 efficacy results (Feagan et al. 2016). Expected: ustekinumab arms should show greater CDAI reduction than placebo by Week 6.

SimulationsPlus

The scientist defines, decides and interprets.

Find what works. Faster.

Thank You

Weirong Wang
Lu Huang
Nash Delcamp
Paul Barger
Nicole Parish
Tao Peng
Sudheer Rani
Wes Jourdan
Vlad Chupakin
Christina Battista
Dawei Song
Jonathan Chauvin
Rafal Bachorz
John Bartels
Pallavi Bhargava
Jin Niu
Grant Fowler
Brian Rossi
Steve Chang
Erik Guffrey



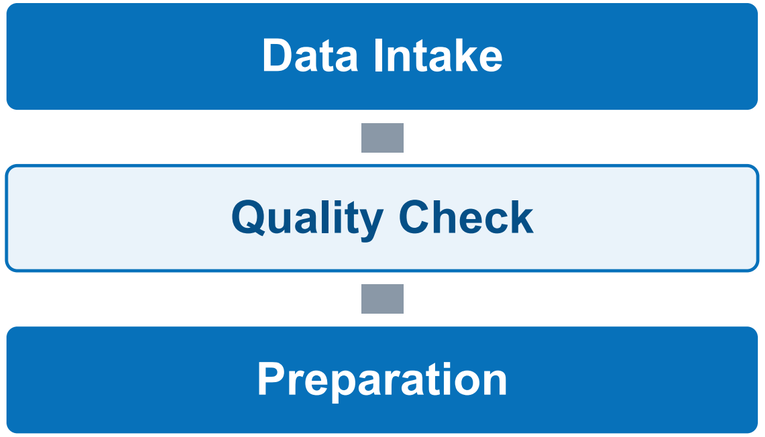
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WS1

Data Trust

- Explore clinical trial inventory and endpoints
- Extract CDAI time courses and summarize by arm
- Analyze visit windows and missing values
- Prepare aligned datasets for Thales ingestion



PROMPTS

Give a summary of one trial Adam data and SAP, e.g. UNITI/CNTO1275CRD3001: what studies are included, how many patients, key primary & secondary endpoints, biomarkers in these studies? Induction or maintenance phase?

Plot each individual patient trajectory (a.k.a Spaghetti plot) with different panels per arm in this trial

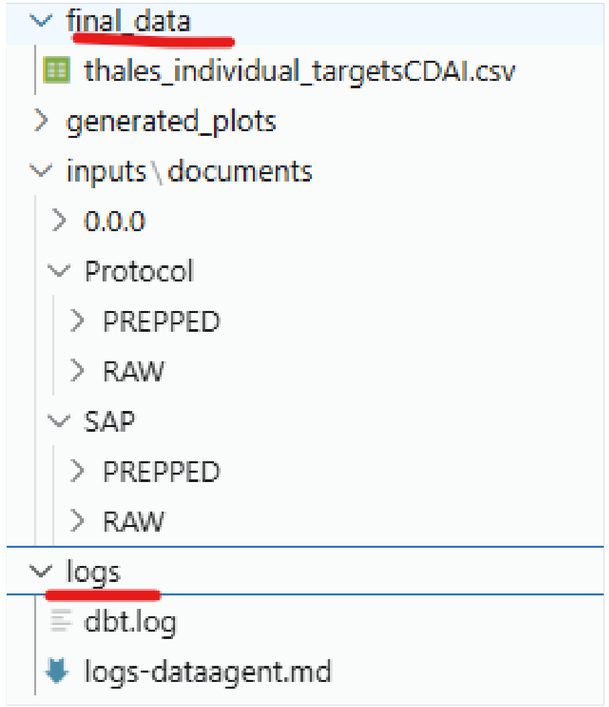
Prepare the UNITI-1 trial data for Thales platform calibration. I need:

- Time-aligned CDAI at baseline and week 8
- Include CDAI components (pain, stool frequency, well-being)
- Apply ICE handling rules from the SAP (exclude post-ICE data)
- Create constraint file format with sigma_measure=10, sigma_trust=0

Show me the mapping from source ADaM fields to individual_targets columns [Source, Trial, PatientID, Arm, Drug, Dose, Time, Analyte, Value]

product – Thales input file

Confirmed with SME on the structure of individual targets. The Analytes FCP and CRP can also be added with a good plan upfront



	A	B	C	D	E	F	G	H	I	J	K	L	M
1	Source	Trial	Arm	Drug	Dose	Analyte	Time	Value	PatientID	Fitlog	sigma_mea	sigma_trust	
2	JnJ	Feagan 20	Ustekinum	Ustekinum	6 mg_kg IV	CDAI	3	383	CNTO1275CRD3001-(		10	0	
3	JnJ	Feagan 20	Ustekinum	Ustekinum	6 mg_kg IV	CDAI	6	390	CNTO1275CRD3001-(		10	0	
4	JnJ	Feagan 20	Ustekinum	Ustekinum	6 mg_kg IV	CDAI	8	366	CNTO1275CRD3001-(		10	0	
5	JnJ	Feagan 20	soc	soc	std	CDAI	60	452	CNTO1275CRD3001-(		10	0	
6	JnJ	Feagan 20	Ustekinum	Ustekinum	6 mg_kg IV	CDAI_AP	3	11	CNTO1275CRD3001-(		10	0	
7	JnJ	Feagan 20	Ustekinum	Ustekinum	6 mg_kg IV	CDAI_AP	6	9	CNTO1275CRD3001-(		10	0	
8	JnJ	Feagan 20	Ustekinum	Ustekinum	6 mg_kg IV	CDAI_AP	8	10	CNTO1275CRD3001-(		10	0	
9	JnJ	Feagan 20	soc	soc	std	CDAI_AP	60	11	CNTO1275CRD3001-(		10	0	
10	JnJ	Feagan 20	Ustekinum	Ustekinum	6 mg_kg IV	CDAI_SF	3	93	CNTO1275CRD3001-(		10	0	
11	JnJ	Feagan 20	Ustekinum	Ustekinum	6 mg_kg IV	CDAI_SF	6	86	CNTO1275CRD3001-(		10	0	
12	JnJ	Feagan 20	Ustekinum	Ustekinum	6 mg_kg IV	CDAI_SF	8	89	CNTO1275CRD3001-(		10	0	
13	JnJ	Feagan 20	soc	soc	std	CDAI_SF	60	104	CNTO1275CRD3001-(		10	0	
14	JnJ	Feagan 20	Ustekinum	Ustekinum	6 mg_kg IV	CDAI_WB	3	16	CNTO1275CRD3001-(		10	0	
15	JnJ	Feagan 20	Ustekinum	Ustekinum	6 mg_kg IV	CDAI_WB	6	16	CNTO1275CRD3001-(		10	0	
16	JnJ	Feagan 20	Ustekinum	Ustekinum	6 mg_kg IV	CDAI_WB	8	14	CNTO1275CRD3001-(		10	0	
17	JnJ	Feagan 20	soc	soc	std	CDAI_WB	60	14	CNTO1275CRD3001-(		10	0	
18	JnJ	Feagan 20	placebo	placebo	none	CDAI	3	228	CNTO1275CRD3001-(		10	0	
19	JnJ	Feagan 20	placebo	placebo	none	CDAI	6	264	CNTO1275CRD3001-(		10	0	
20	JnJ	Feagan 20	placebo	placebo	none	CDAI	8	186	CNTO1275CRD3001-(		10	0	
21	JnJ	Feagan 20	soc	soc	std	CDAI	60	239	CNTO1275CRD3001-(		10	0	
22	JnJ	Feagan 20	placebo	placebo	none	CDAI_AP	3	7	CNTO1275CRD3001-(		10	0	
23	JnJ	Feagan 20	placebo	placebo	none	CDAI_AP	6	11	CNTO1275CRD3001-(		10	0	
24	JnJ	Feagan 20	placebo	placebo	none	CDAI_AP	8	9	CNTO1275CRD3001-(		10	0	

Product human reviewed by SME

From analysis results to professional, auditable documentation

REVIEWER COMMENT

I suggest giving two options such as “ [ ] Passed/Verified [ ] Needs Revision or Pending Fixes”. Eventually, when all the fields are Passed, the QC process is completed.
Do Data Completeness mean non-missing data? And what does Data Quality column mean? I think if they have the same meaning, we can remove the Data Quality. But I would be interested in knowing whether the trial data are aggregated (e.g., response rate, mean+/-SD) or individual (measurements from each patient).

- **PDF**: qc-report-uniti1.pdf
- **DOCX**: qc-report-uniti1.docx
- **Markdown**: qc-report-uniti1.md

Stats: 10 sections, 19 tables, 28 figures, 0 unresolved references. Would you like to review any section conten
or mark sections as approved?

Claude Opus 4.6 •

yes I want to review

Used 1 reference

Reviewed updated sections and checked available files.

Let me pull up the current section files so you can review them.

Ran `list_sections` – document-gen-testing-composer-jnj-t2 (MCP Server)

All 10 sections are in **draft** status. Here are the direct links to review each section file:

#	Section	Status	File
0	Purpose and Scope	draft	qc_overview.json
1	Data Sources and Data Types	draft	qc_data_sources.json
2	Parameter Table Summary	draft	qc_parameter_table.json

Todos (6/6)

dbt Build: 3/3 models OK (exit code 0) — [ ] Passed/Verified [ ] Needs Revision or Pending Fixes

dbt Tests: 25/25 PASS (exit code 0), covering not_null (10 columns), accepted_values (8 columns), unique composite key, time precision, sigma constraints, SOC row validation, scenario tuple validation, expected row counts, unmapped arm detection — [ ] Passed/Verified [ ] Needs Revision or Pending Fixes

Sensitivity Analysis QC Checklist

- ☒ **Passed / Verified** — Sigma context assessed: {{fig:fig_sigma}} generated comparing observed SD vs. sigma_measure=10 across all analytes and timepoints. Visual assessment completed; formal statistical comparison pending.
- ☒ **Passed / Verified** — Outlier prevalence assessed: {{fig:fig_outliers}} generated showing |z|>2/3/4 proportions. No analyte-timepoint combination exceeds critical outlier thresholds.
- ☐ **Pending** — Formal sensitivity analysis: Local or global sensitivity analysis (e.g., Sobol indices, Morris screening) has not been conducted. Should be performed after parameter estimation against UNITI-1 individual targets.

Limitation: Formal sensitivity analysis (local or global) has not been conducted against the UNITI-1 individual patient data. The QA plots above (Figure 35 and Figure 36) are provided as informational context only and should not be interpreted as substitutes for systematic sensitivity analysis.