Building a regulatory framework for precision clinical trials in neuroscience

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- This presentation reflects the views of the presenter and should not be construed to represent the views or policies of the U.S. Food and Drug Administration.
- Examples are provided for scientific and regulatory discussion in the context of precision clinical trials; they are not prescriptive approaches for any specific program.
- Determinations of evidentiary adequacy (including biomarkers, enrichment strategies, and endpoints) are context-dependent and made on a case-by-case basis.

How precision neuroscience changes the 3 pillars of clinical trials

Precision neuroscience makes each pillar more biology- and measurement-driven

Population (Who?)

Define who has the biology of interest

- Biomarker/genotype-confirmed cohorts
- Enrichment and stratification to manage heterogeneity
- Labeling and generalizability become key questions

Design and duration (How?)

Match design to disease

- Follow long enough to observe a meaningful change
- Adaptive features and interim analyses (if pre-specified)
- Efficiency via platform designs and expedited pathways

Outcomes (What?)

Improve sensitivity and interpretability

- COU-specific biomarkers as endpoints (e.g.: surrogate endpoints when appropriate or confirmatory evidence to support effectiveness)

Precision neuroscience for population inclusion

Enrichment across a spectrum of precision

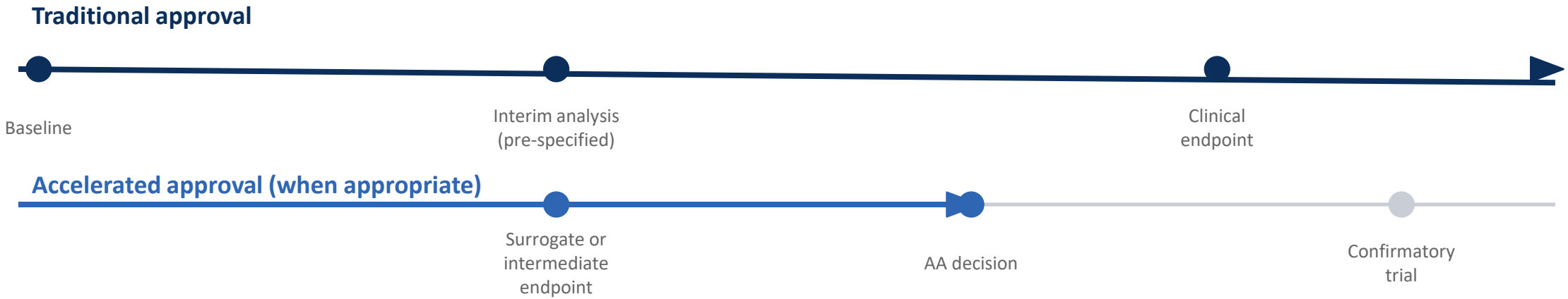
Individualized / ultra-rare (single gene)	Neurodegeneration (pathology-defined)	Psychiatry (phenomenology; high heterogeneity)

Successful enrichment precedents	Emerging examples
• Alzheimer disease: confirm amyloid-β pathology prior to initiating therapy • Lecanemab and donanemab programs illustrate pathology-based enrollment and subgroup analyses	• Parkinson disease: diagnostic/enrichment tools entering biomarker qualification • Huntington disease: genetically defined population; growing biomarker toolkit for monitoring and prognosis

Discussion question: What are the labeling implications of biomarker-based enrichment (e.g., required testing, subgroups, and generalizability)?

Trial design and duration

Long enough to observe meaningful change — or shorten the path with fit-for-purpose endpoints



Principle

- Follow participants as long as needed to observe a clinically meaningful change.
- Time can be shortened when a fit-for-purpose surrogate/intermediate endpoint supports an expedited pathway.

Example (DN1)

- Tofersen (Qalsody) in SOD1-ALS: accelerated approval based on plasma neurofilament light chain (NfL) as a surrogate endpoint reasonably likely to predict clinical benefit.
- Confirmatory study required to verify clinical benefit.

Precision neuroscience for outcomes

Biomarkers as endpoints and as confirmatory evidence

Clinical benefit

How patients feel, function, or survive

Intermediate clinical endpoint

Measured earlier; not yet clinically meaningful but likely predicts clinical benefit

Validated surrogate endpoint

Strong evidence that effect predicts clinical benefit

Reasonably likely surrogate endpoint

Mechanistic/epidemiologic rationale + supportive clinical data

Biomarkers can serve multiple contexts of use

- Patient selection / enrichment / stratification
- Target engagement and pharmacodynamic response
- Dose optimization
- Safety monitoring and risk identification
- Primary endpoints (when appropriate: surrogate endpoints)
- Confirmatory evidence to support efficacy interpretability

Key concept: context of use (COU) + evidence chain (analytical validation → clinical validation → regulatory interpretation)

Precision psychiatry: a roadmap toward precision trials

Psychiatry lags behind neurology — biological hypotheses and actionable biomarkers must be built stepwise

Today	Next	Future
DSM/ICD phenotypes High heterogeneity	Biotypes from multimodal data (EEG, imaging, digital)	Biology-informed diagnoses and enrichment

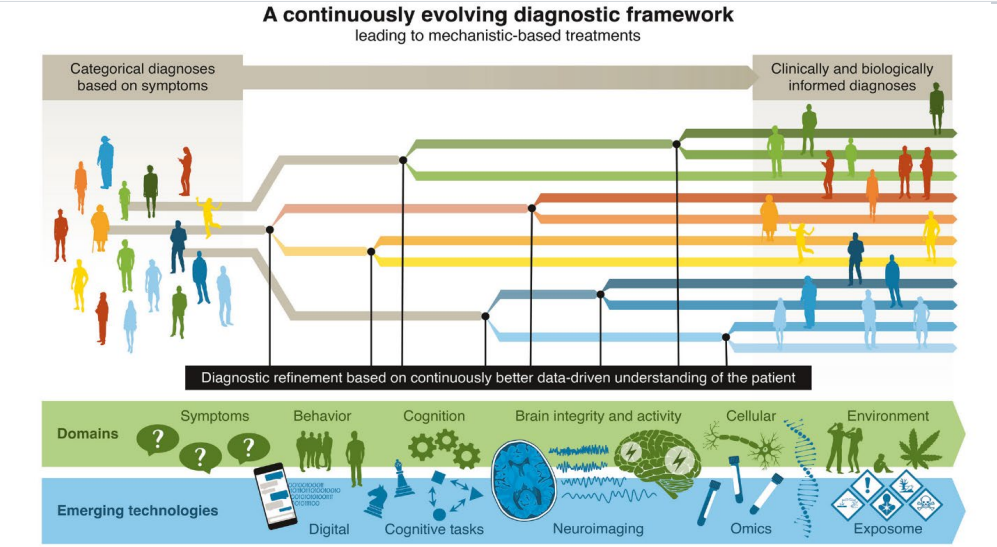


Fig. 1 The vision of bringing precision to psychiatry requires both a continuously evolving framework incorporating scientific an

- 1) Discover and prioritize biological hypotheses
- 2) Build quantitative measures/biomarkers; define Context of Use
- 3) Generate evidence for biomarker validation
- 4) Run prospective, biology-stratified trials; iterate the framework

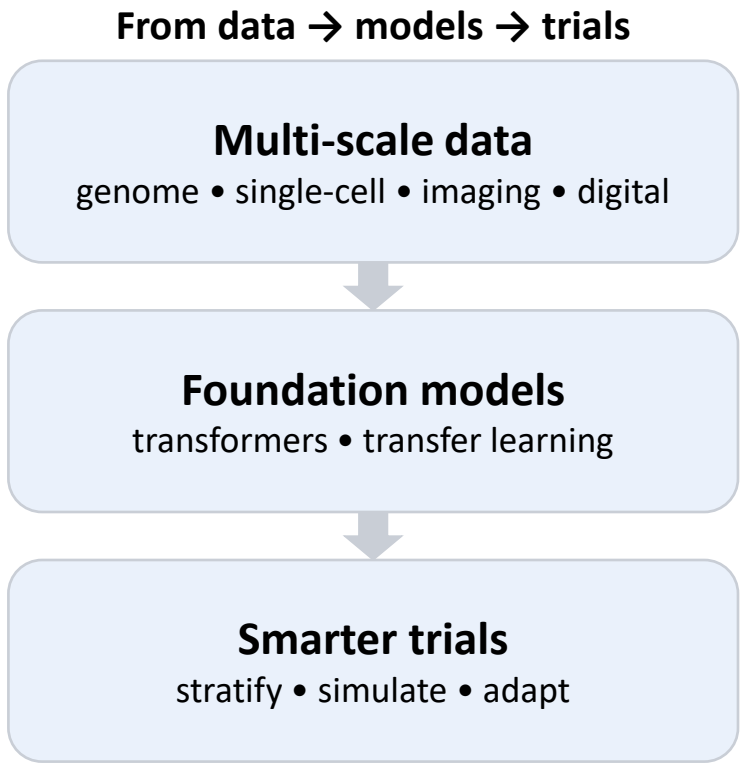
Takeaway: Psychiatry is a roadmap today — a regulatory framework once biology-defined populations and validated measures emerge.

Embrace complexity: precision neuroscience in the AI era

Homogeneity is a development need. Heterogeneity is biology.

Foundation models are learning the “grammar” of biology across scales:

- Genomics transformers for promoter/variant effects and beyond
- Single-cell models (e.g., scGPT) for cell typing, multi-omics integration, and perturbation prediction
- Next step: translate these representations into better hypotheses, biomarkers, and trial designs



Don’t erase heterogeneity—measure it, model it, and design for it.

Conclusions

- Precision trials start with a clear biological hypothesis and a fit-for-purpose population definition (COU-driven enrichment).
- Trial duration should match the disease course, with efficiency gains from adaptive features and (where appropriate) expedited pathways.
- Outcome strategies should be planned as an evidence chain—linking target engagement → biomarker change → clinically meaningful benefit.
- Early, iterative engagement with regulators helps identify evidence gaps and align on endpoints, analyses, and confirmatory plans.
- In the AI era the goal of precision neuroscience is not to erase heterogeneity, it is to measure it, model it, and design for it.

Prompt for discussion: Where are the biggest friction points today—population definition, endpoints, or bridging Phase 2→3?

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