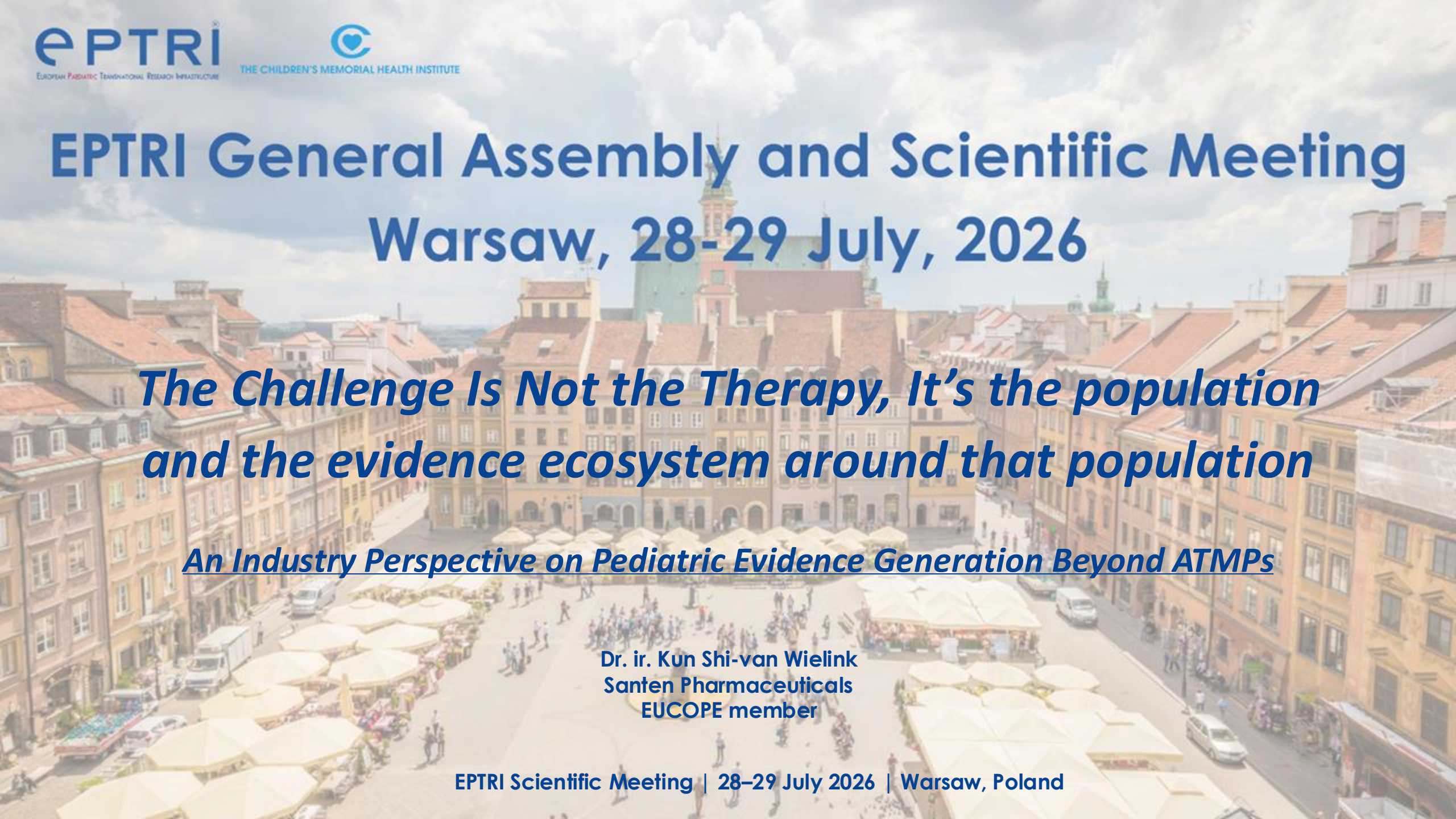

The Challenge Is Not the Therapy, It's the population and the evidence ecosystem around that population

An Industry Perspective on Pediatric Evidence Generation Beyond ATMPs

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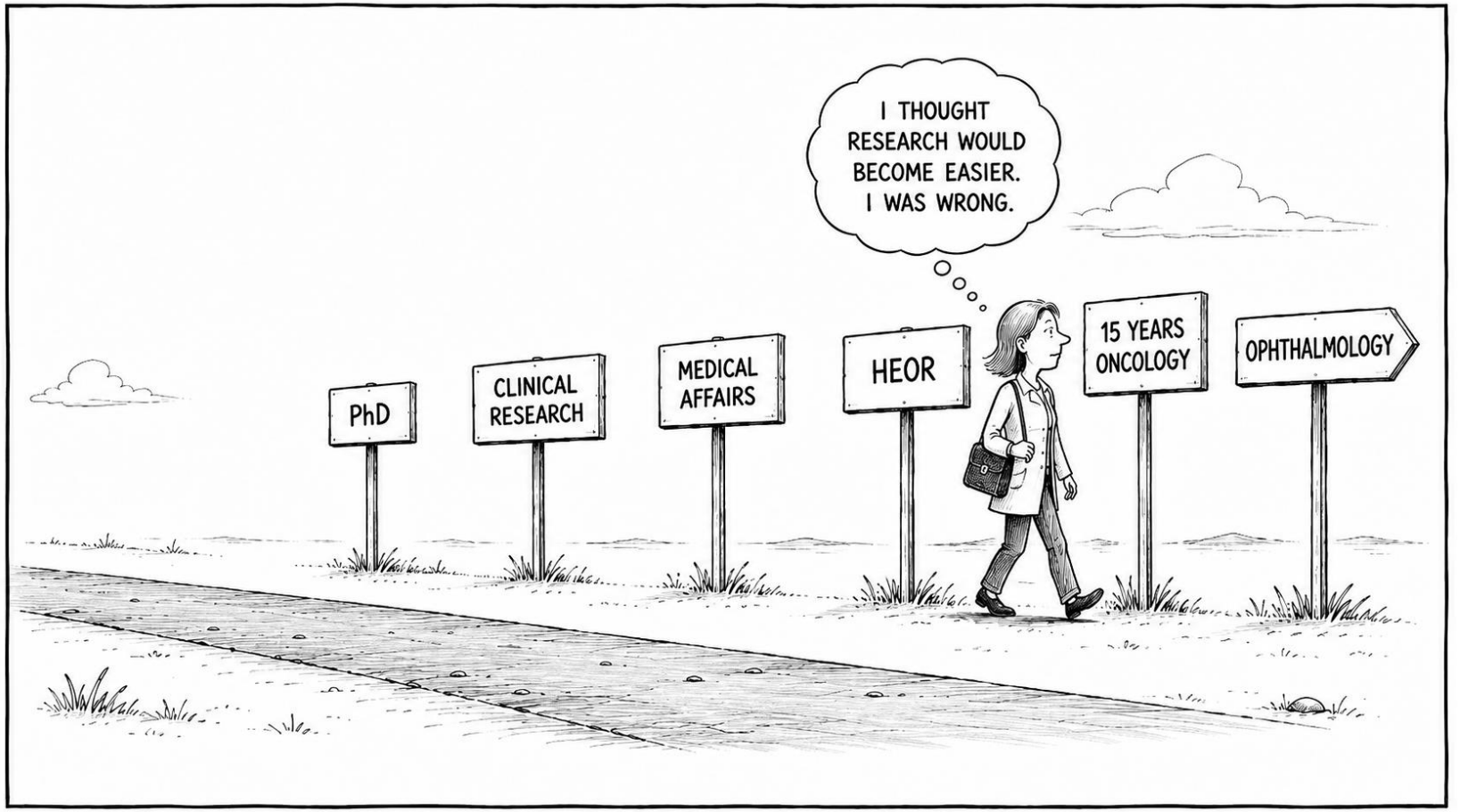
How I got here…

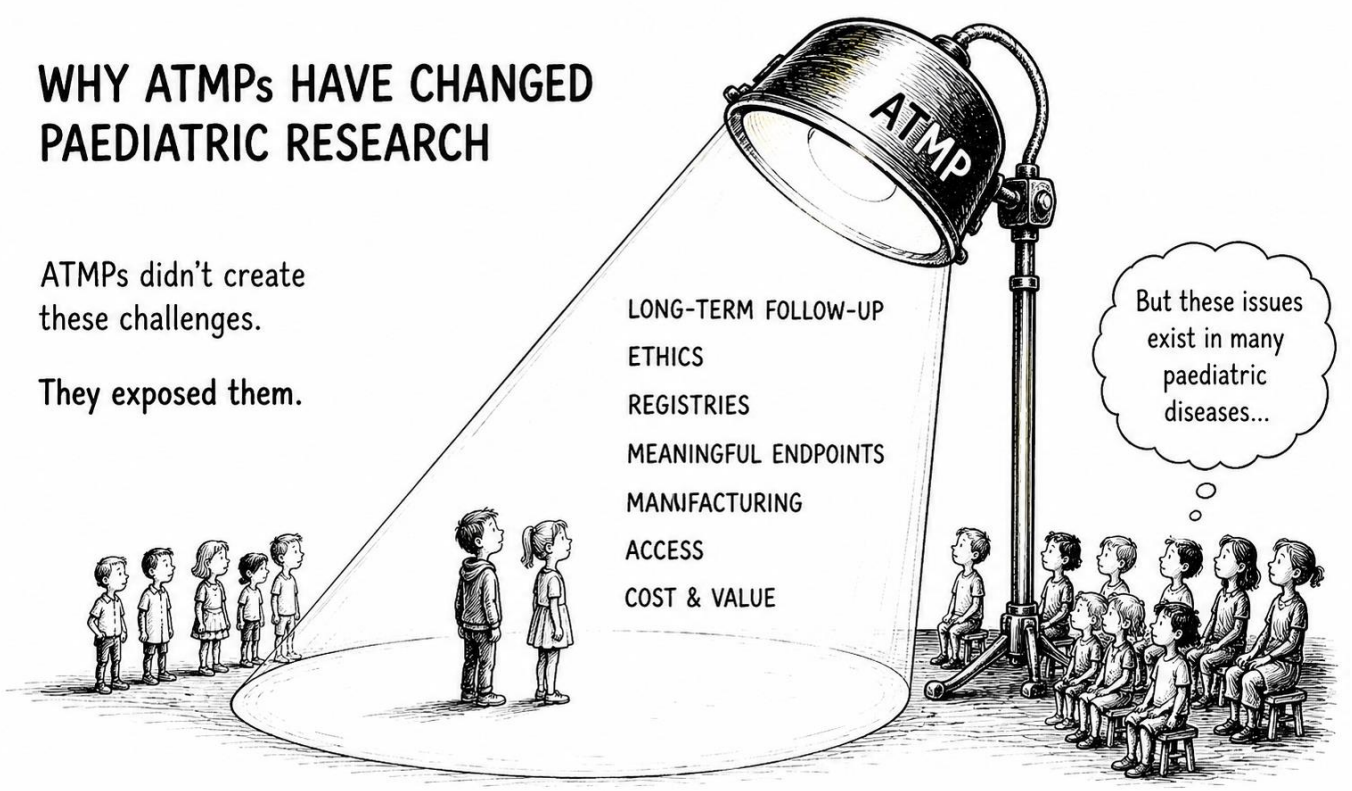
From oncology to ophthalmology, and an unexpected lesson about evidence.



The difficulty was not only biology.
It was the absence of the evidence scaffolding that oncology spent decades building.

ATMPs did not create these challenges.

They **exposed** them.



The same evidence problems appear across paediatric diseases: follow-up, ethics, registries, meaningful endpoints, access, cost and value.

So, the "industry perspective"
is not: build a better vector.
It is: build a development path that can survive uncertainty.

Before I continue…

Who here works with HEOR, HTA or market-access evidence?

HEOR = Health Economics & Outcomes Research — the evidence that decides whether a therapy is worth paying for.

I work with it regularly

Health economics, HTA, market access

I've heard of it

Some exposure, not my day-to-day

It's new to me

Does it even matter?

HTA: Health technology assessment
HEOR: Health economics & outcome research

HEOR at a glance

Why development evidence determines access.

Clinical development asks:
Is the therapy sufficiently safe and effective?

→

HTA / HEOR asks:
Compared with current care, how meaningful, durable and uncertain is the benefit?

→

Reimbursement asks:
At what price and conditions is access justified?

Evidence inputs that matter early

Comparator / natural history
Validated endpoints
Durability and uncertainty
Quality of life
Patient and caregiver burden

ICER is one common tool: additional cost ÷ additional QALYs

QALY combines length and quality of life. England/NICE uses an explicit threshold range; the Netherlands varies by disease burden; Germany focuses on added benefit; Sweden applies severity-based judgement.

The point for scientists:

stronger evidence → less uncertainty → stronger access proposition.

Weak evidence does not only weaken a paper. It weakens investment, price negotiation and routine patient access.

HTA: Health technology assessment
HEOR: Health economics & outcome research
ICER: Incremental Cost-Effectiveness Ratio
QALY: Quality-Adjusted Life Year
NICE: National Institute for Health and Care Excellence

Paediatric ATMPs can do the impossible

Kymriah

CAR-T for paediatric relapsed B-cell ALL — the first approved gene therapy.

Zolgensma

One-time gene therapy for spinal muscular atrophy in infants.

Upstaza

Gene therapy infused into the brain for AADC deficiency in children.

THE NEWEST HEADLINES · LIQUID & SOLID TUMOURS

BE-CAR7

Base-edited "universal" CAR-T — relapsed/refractory T-cell leukaemia

9 children — all in remission by day 28

Chiesa et al., NEJM 2025 (GOSH/UCL).

TAA-T · ReMIND

Autologous multi-antigen T cells — DIPG & recurrent CNS tumours

1 complete response + 3 long-term responders

Hont/Bollard et al., Nat Med 2026 · phase 1.

ALL: Acute lymphoblastic leukemia
AADC: Aromatic L-amino acid decarboxylase
DIPG: Diffuse Intrinsic Pontine Glioma
CNS: Central Nervous System

But approval ≠ access

Clinical success starts the access journey; it does not finish it.

EU marketing authorisations withdrawn

Zynteglo — β-thalassaemia gene therapy

Skysona — early cerebral ALD in boys

Withdrawn at company request for commercial reasons; reimbursement and launch viability were central to the commercial reality.

The second valley of death

High cost × tiny population × long-term uncertainty × fragmented national reimbursement

A harder case

If a common paediatric disease with millions of children — myopia — still cannot generate clean, comparable evidence…

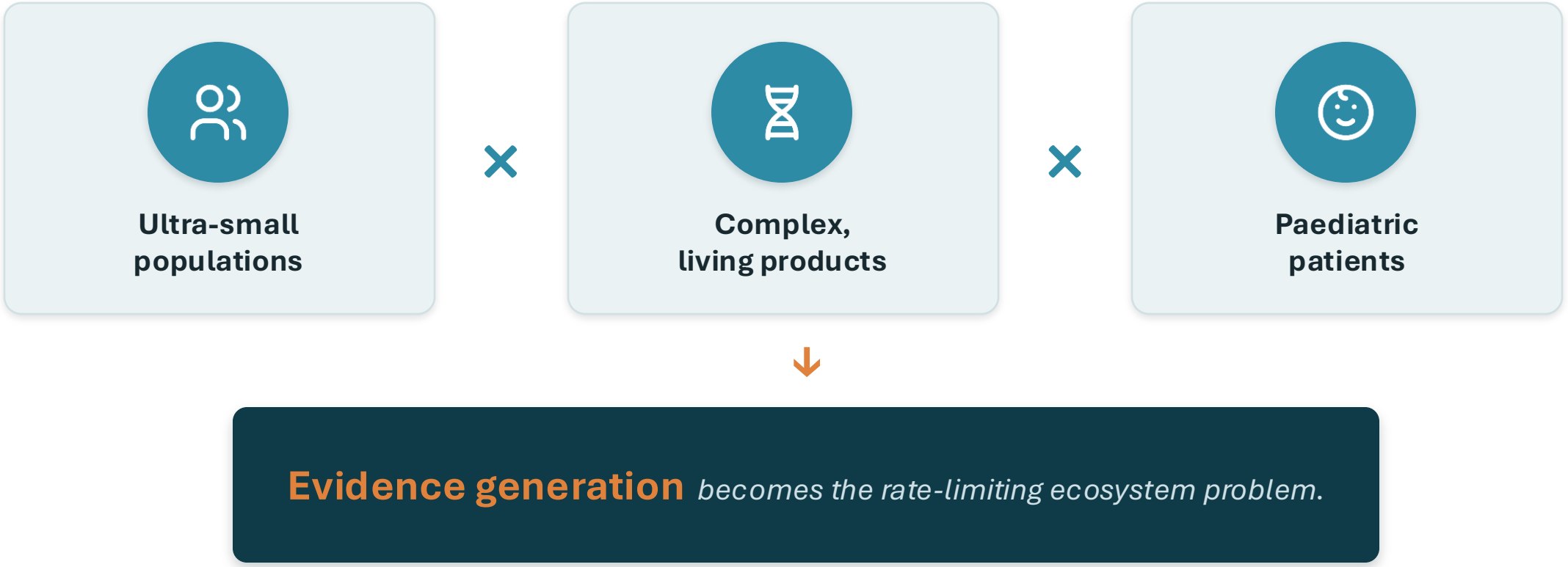
…imagine a one-time therapy for a handful of children, where durability, comparison and value must be credible for years.

For paediatric ATMPs, the evidence problem is not smaller.
It is existential.

ALD: Adrenoleukodystrophy

One triad drives everything downstream

Evidence uncertainty multiplies where all three overlap.



Operational feasibility is wider than manufacturing

Manufacturing is visible and critical; population logistics are just as decisive.

Starting material	**Comparability**	**Release testing**	**Cold chain**	**Qualified centre**
Find the child	**Cross borders**	**Coordinate families**	**Capture clean data**	**Retain for years**

Practical developer's view

Operational feasibility is not only "can we make the product?" It is also "can the child and family move through the system without the evidence falling apart?"

The less visible bottleneck: interpretable, durable, reimbursement-relevant evidence.

The real bottleneck: evidence generation

ATMP-specific problems are real; broader paediatric evidence problems are longer and shared.

ATMP-specific	Generic paediatric — longer, harder
• Durability of a one-time therapy • Potency-to-clinical bridging • Risk-based long-term follow-up, sometimes for many years	• Natural history and external controls • Validated, age-appropriate endpoints • Biomarkers accepted by regulators and payers • Dose rationale and extrapolation • Trial feasibility at N-of-few • Clean data capture: QoL, adherence, retention

Because these problems are shared across modalities, the rational answer is shared infrastructure — not every sponsor rebuilding the same scaffolding.

QoL: Quality of Life

Evidence, part 1 · design

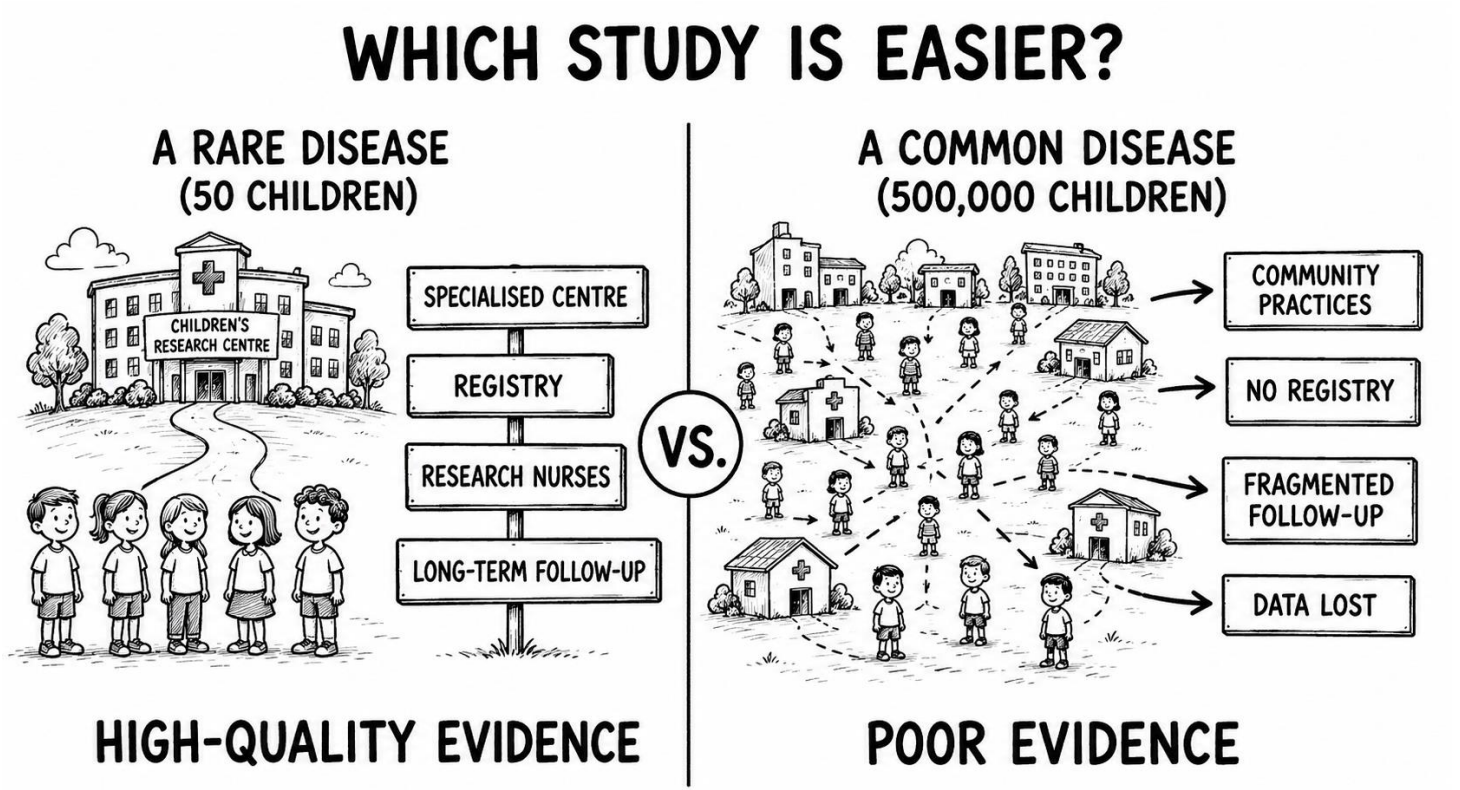
Can you even interpret the study?

No natural history	No external control → an uninterpretable single-arm trial or weak counterfactual, very large uncertainty.
No agreed endpoints	Few validated, age-appropriate outcomes accepted by regulators and payers.
Feasibility & ethics	Assent, invasive administration, sham-control dilemmas, cross-border recruitment.
Shaky dose rationale	Weight/age dosing, extrapolation, model-informed development.

None of this is hypothetical. A common disease I work in (myopia) shows that even a huge patient population cannot rescue a fragmented evidence ecosystem.

Population size is not the same as evidence quality

Concentrated care can beat fragmented care.



The point is not that rare disease is easy.
The point is that evidence quality follows the pathway, not the headcount.

Case study · myopia

A common paediatric disease : we can't even agree what to measure

≈ Half the world myopic by 2050 (~5 billion); ~1 billion high myopia. Common — yet the evidence base stays thin.

SER
spherical equivalent refraction

- Defines the disease (≤ −0.50 D); the metric regulators & legacy trials know
- Measured by cycloplegic autorefraction
- But: accommodation, lens changes — and atropine's own cycloplegia — can flatter the effect

AL
axial length

- The structural driver of sight-threatening pathology; robust, no cycloplegia
- Many clinicians call it the gold standard
- But: needs an optical biometer many settings lack; thresholds (≥ 26 mm) miss much pathology

So trials now report both. Pick SER and a clinician says AL is the gold standard; pick AL and you've excluded every site without a biometer. There is no settled endpoint.

Case study · real-world data

Myopia: the data will not come clean.

One child, many doors

Optician, optometrist, GP or ophthalmologist — who sees a myopic child differs by country and even locally. No single owner of the record.

Siloed, often private

Community optometry / optician data usually sit outside the health-system EHR — hard to access, link, or standardise.

Variable quality

Community refraction is often non-cycloplegic, with wide variance; big-data studies must discard invalid or aberrant records.

AL barely captured

Outside specialist clinics, axial length is rarely measured at all — the endpoint clinicians prefer is missing from the real-world data.

A common disease — and still no clean, comparable dataset. **Shrink the population to a few hundred children, hand it to a one-time gene therapy, and every problem here gets harder.**

Evidence, part 2 · execution

Even when you run it: getting clean data out.

We didn't build QoL capture into the pivotal trial — so we paid for it twice: **a separate QoL study, more money, more time.** ***What you don't build in up front, you pay for later.***

Proxy vs. self-report

Young children can't reliably self-report; parent-proxy scores diverge; the reliable reporter changes with age.

Adherence → retention

Chronic care loses data through daily adherence. One-time therapy escapes that, but the risk migrates to long-term retention.

Patient & caregiver burden

Visits, travel, invasive sampling, missed school and work. Burden is a design parameter, not an afterthought.

For paediatric ATMPs, QoL and economic endpoints may be impossible, or much weaker to reconstruct later.
Front-loading is costly; omitting it can be fatal to the evidence package.

QoL: Quality of Life

Regulatory & Policy Uncertainty

The ground is shifting — both ways

EASES SOME PATHS

- Iterative Paediatric Investigation Plans
- A regulatory sandbox open to ATMPs
- Shorter marketing-authorisation assessment
- Platform / master-file thinking

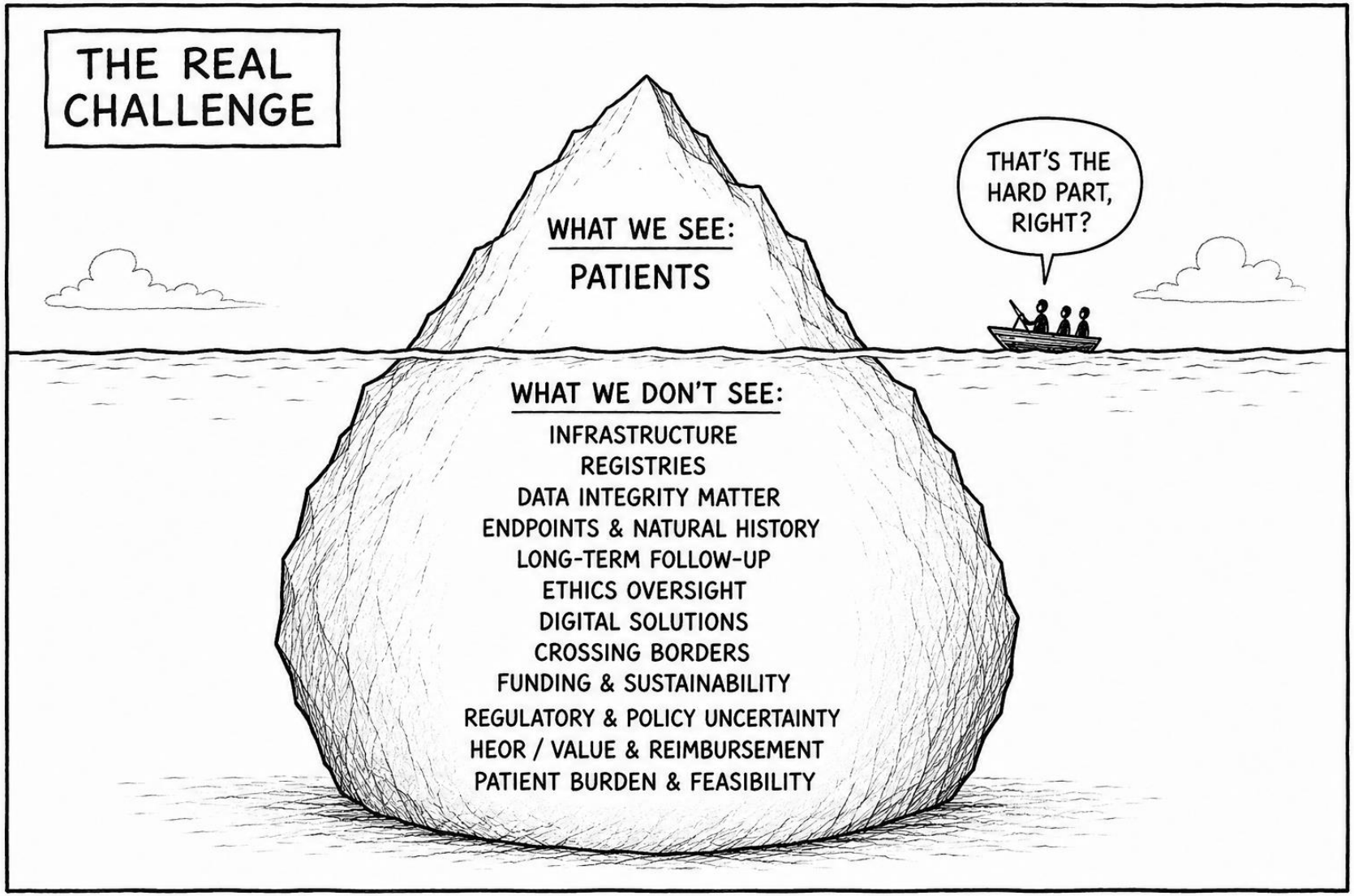
RAISES THE EVIDENCE BAR

- Joint Clinical Assessment (JCA, EU HTA) — live for ATMPs since Jan 2025 — demands comparative evidence
- New hospital-exemption reporting obligations
- Uncertain future of the Committee for Advanced Therapies (CAT)

Practical developer's problem: uncertainty itself has a cost. If nobody can say what "yes" requires, the programme is priced as risk — or not started.

EU pharma reform: political agreement reached Dec 2025; adopted acts expected to enter into force in 2026 with transition to 2028.

The Invisible Part Of Evidence Generation



What would make development predictable — and attractive

Predictability is not a comfort. It is the precondition for investment: an unpredictable programme is priced as a risk, and often simply isn't started.

Endpoints agreed before we start	Pre-qualified, age-appropriate endpoints and biomarkers that regulators AND payers accept — so a positive trial isn't re-litigated at HTA.
Natural history we can point at	Ready-made external controls. The single biggest de-risker for a single-arm programme in a tiny population.
Trial-ready sites, already connected	A standing paediatric network beats standing up sites country by country for a handful of children.
Follow-up someone else can carry	Shared registries that discharge a 15-year obligation, instead of each sponsor funding a bespoke cohort alone.
An early, honest read on value	Joint scientific advice with HTA and payers up front — so the economic evidence is designed in, not discovered too late.

Every one of these is infrastructure, not chemistry. **Make the path predictable and the programmes will come.**

Where EPTRI is the critical path

EPTRI DOMAIN		THE EVIDENCE GAP IT CLOSES
Biomarkers	→	Validated, age-appropriate biomarkers
Paediatric pharmacology	→	Dose rationale & model-informed dosing
Formulation science	→	Age-appropriate administration & adherence
Underpinning studies	→	Natural history, endpoints, methodology & networks
Medicines discovery	→	Early de-risking & translational readiness

None of this is ATMP-specific. All of it is what stalls my programmes. **This shared layer is the difference between a viable paediatric programme and a dead one.**

Neither side can do this alone

Industry brings

- Portfolio & candidates
- GMP & manufacturing
- Regulatory experience
- Funding & real-world execution

Infrastructure brings

- Patients & care pathways
- Natural history
- Validated methodology & standardisation
- Cross-border reach

Oncology took decades to build its evidence scaffolding.
We do not have decades — and we do not need them, if industry and infrastructure actually meet.

For your attention!

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Sources & caveats

BE-CAR7 (T-cell ALL)	Chiesa et al., NEJM 2025 — 9 children + 2 adults; 7 of 11 in remission at 3–36 months. GOSH/UCL.
Earlier CRISPR CAR-T (B-ALL)	Universal CRISPR-edited CAR19, 2022 — 4 of 6 children into remission (Sci Transl Med).
EU market withdrawals	Zynteglo & Skysona withdrawn from the EU over reimbursement, not efficacy (Bluebird bio, 2021–22).
EU pharma reform	Political agreement Dec 2025; compromise texts Mar 2026; entry into force expected 2026, transition to 2028.
Joint Clinical Assessment	EU HTA Regulation — JCA operational for ATMPs & oncology since Jan 2025.
Trial network	conect4children Stichting (c4c-S) — pan-European paediatric trial network, 220+ sites / 21 countries.
Myopia — evidence base	Prevalence: Holden et al., Ophthalmology 2016 (~half the world by 2050). Endpoints (AL vs SER): IMI clinical trials report, IOVS 2019; systematic review, Ophthalmology 2026.
CT-179 (medulloblastoma)	Modality-agnostic example — small-molecule OLIG2 inhibitor, NOT an ATMP; preclinical (mouse), now early-phase. Li et al., Nat Commun 2025 (Emory / QIMR Berghofer).