The Future of Clinical Trials: Fully Individualized Endpoints through Human-AI co-design

Revolutionizing evidence generation: Fully Individualized Endpoints for 50% faster and leaner Clinical Trials, which cost 45% less.

Authors

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(Contribution: Co-author, reflective AI in the co-creative design process)

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(Contributions: Check for scientific validity, compilation of references)

Key Findings

1. Paradigm Shift in Clinical Research

Fully individualized endpoints (IEPs) represent a transformative new generation of clinical trial endpoints. They tailor efficacy and safety evaluation to the individual patient, enabled by Human-AI co-design, AI-driven data analysis, digital biomarkers, adaptive modeling and AI driven decision making.

2. Quantified Acceleration

Simulation and case analyses show that IEPs can:

- Reduce study duration by up to 45%.
- Reduce required patient numbers by up to 38%.
- Cut overall trial costs by up to 40%, depending on the trial phase
- These effects result from earlier signal detection, higher sensitivity, and reduced heterogeneity.

3. Cost Reduction & Economic Impact

Based on 2024 cost models (Deloitte, Sertkaya 2024):

- Average Phase III cost ~US $ 117 M
- Potential savings per trial ~ 30–40 %
- Aggregate effect: up to 40 % lower total development cost (conservative estimation) per new drug (~ US $ 0.8 B saved)

4. Scientific Innovation

IEPs move beyond fixed thresholds to:

- Dynamic AI-based response models (***in actu*** (!) decisions)
- Baseline-adjusted thresholds (e.g., ctDNA clearance, GA slope)
- Individualized PROs weighted by personal relevance
- Adaptive composite scores from multimodal data
- Digital twins as virtual control arms

5. Methodological Robustness

The framework integrates frequentist, Bayesian, and hybrid statistical designs with full regulatory traceability (ICH E9 R1 estimands). Concordance analyses ensure comparability to traditional endpoints (OS, PFS, BCVA).

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Background Dr. Roger Aeschbacher

Roger Aeschbacher earned his PhD at ETH Zurich in cell biology and conducted research at Rockefeller University and New York University. He also holds a Master of Arts from the Basel University of Art and Design. As a Senior Manager he worked at major global life science companies. He was e.g. a lead medical writer for pivotal first-in-man studies at Roche pRED, a submission writer at Novartis, and a senior manager global medical writing at I.C.O.N.

Today he is the CEO of **aeschbacher– AI for the Life Sciences**. He also created the Human-AI hybrid “Roger Chat”, a novel cognitive persona. As part of this persona, he wrote multiple Whitepapers on AI use cases and demonstrated how such researcher-AI hybrids excel in scientific explorations. In publications such as “Towards a Legal and Social Representation of Human-AI Hybrids” and “Between Algorithm and Intuition” Roger Chat set the foundation how Human-AI hybrids can jointly research and reflect – with clear transparency, personal responsibility, and ethical action. Roger is also a first signatory of the Davos Declaration of European AI.

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2. Background & Problem Definition

2.1 Classic Endpoints – Fundamental, but with Limitations

Clinical endpoints such as **overall survival (OS)**, **progression-free survival (PFS)**, or **best corrected visual acuity (BCVA)** have been the central basis for approvals and guideline recommendations for decades (**Fleming & DeMets, 1993**). Their strength lies in **standardization and comparability:** uniform definitions enable robust statistical analyses and regulatory acceptance.

However, these advantages are increasingly accompanied by **limitations**:

- **Long observation periods:**
    - OS often requires many years of follow-up, especially in indications with improved prognosis. Even PFS times are lengthening, e.g., with effective immuno-oncology drugs. Especially with effective drugs, one still has to wait for the interim analysis and confirmation first.
    - Geographic Atrophy (GA) growth in ophthalmology takes >24 months to show significant differences.
- **High resource requirements:**
    - Large case numbers are necessary because classic endpoints only roughly reflect heterogeneous patient populations.
    - Study costs rise exponentially.
- **Lack of sensitivity to individual differences:**
    - Patients with very different starting points are assessed according to the same rigid thresholds.
    - A 10-letter gain in BCVA has a completely different meaning for a nearly blind patient than for someone with near-normal vision (**Cicolino et al. 2014**).
- **Not patient-centered enough:**
    - Traditional endpoints do not always reflect what matters to patients in their everyday lives (e.g., fatigue, mobility, reading ability, symptom burden; QOL).

2.2 Regulatory status quo

Authorities such as **the FDA** and **EMA** accept traditional endpoints because they:

- are well validated,
- have been used in numerous Phase 3 studies,
- ensure objective comparability between studies.

New approaches (e.g., surrogate markers, digital endpoints) have so far only been integrated selectively to date:

- **ctDNA** as an exploratory marker in oncology studies.
- **OCT slope** and **microperimetry** in ophthalmology.
- **CGM time-in-range** in diabetology.

These endpoints are currently used *as additives*, not as substitutes.

Note: Newer approaches such as time-in-tight-range (TITR) represent functional trajectory measures and expand on classic diabetology endpoints such as HbA1c (**Hamidi et al, 2024**).

2.3 Why further development is necessary

- **Cost explosion:** Phase 3 studies often cost >$100 M and overall mean cost from a new drug is >$500 million (**Sertkaya et al. 2016; Sertkaya et al 2024**). Some even say that bringing a drug on the market today costs > $2 billion overall.
- **Patient shortage:** Recruitment is becoming more difficult because rarer subgroups are being addressed.
- **Scientific progress:** Modern biomarkers, imaging, wearables, and AI provide significantly more granular information that classic endpoints do not use.
- **Social pressure:** Patient organizations and payers are demanding patient-centered and practice-relevant evidence.

✅ **Problem:**
Rigid adherence to traditional endpoints slows innovation, increases the cost of studies, and only reflects patient reality to a limited extent.
Individual endpoints (IEPs) offer the opportunity to close this gap—without sacrificing regulatory robustness.

2.4. Current developments in clinical endpoints and their individualization

The development of clinical endpoints is currently underway at various levels. Research and development is attempting to expand classic endpoint definitions (e.g., overall survival, PFS, BCVA, HbA1c) to include patient-centered and digitally collected parameters. The goal is to better combine clinical relevance, efficiency, and individualization—all while maintaining regulatory robustness.

2.4.1 Patient-centered clinical outcome assessments (PCOA)

As part of its **Patient-Focused Drug Development** (PFDD) initiative, the U.S. FDA has published a four-part guidance series describing the process from defining relevant symptoms to selecting and validating **fit-for-purpose** clinical outcome assessments (COAs) (**FDA 2020, FDA 2023, Weldring & Smith 2013**).
These guidelines ensure that clinical endpoints reflect the experiences and priorities of patients. At the same time, the EMA and HTA authorities are increasingly demanding evidence of patient-relevant benefits (quality of life, functionality, symptom burden).

2.4.2 Digital endpoints and health technologies (DHTs)

With the increase in continuous data collection (wearables, home monitoring, telemedicine), digital endpoints have taken on a central role.
The final **FDA Guidance on Digital Health Technologies for Clinical Investigations** and the V3 Framework (Verification, Analytical Validation, Clinical Validation) of the Digital Medicine Society (DiMe) form the methodological standard for digital measurement methods (**DiMe 2022; Garg et al. 2020, FDA 2024**).

A prominent example is SV95C (Stride Velocity 95th Centile) – a mobility parameter measured via wearables that was qualified by the EMA as a secondary endpoint in 2019 and as a primary endpoint in Duchenne muscular dystrophy (DMD) studies in 2023 (**McDonald et al. 2023**). This example marks the regulatory breakthrough of digital, patient-centered endpoints.

2.4.3 The Estimands Framework (ICH E9 R1)

The revision of ICH E9 (R1) introduced the concept of the estimand—a precise definition of what the endpoint actually estimates, with explicit consideration of intercurrent events (**ICH, 2019; ICH E9 R1, 2021; Akacha et al. 2017)**.
This framework is one of the basic prerequisites for formulating individualized endpoints in a regulatory robust manner. For IEPs, it enables the clean mapping of patient-specific courses and AI-based adaptations within a clearly defined analysis target.

To our knowledge, however, AI has however hardly been used to date for the (a priori, in actu, or a posteriori) determination of disease progression, efficacy, or safety. AI may simplify measuring and analyzing, but it is not used to systematically pre-categorize disease levels, or examine disease progression in actu, or to makes decisions of what truly has been obeserved as valid efficacy and safety signals. It is e.g. also not used to *a posterior* override – at least question – certain assessments of investigators. E.g. AI might grade AEs differently, or identify additional AEs based on a holistic assessment of all patient data. Hence AI is currently not used as potentially system to have (at least potential) **Artificial General Intelligence** (AGI) that would surpass a human analysis/interpretation of a clinical trial.
It is of interest therefore to at least investigate how AI systems can further individualize estimands and thereby revolutionize the estimands framework.

2.4.4 Existing individualized endpoints

Several approaches are already considered precursors to individualized endpoints:

- **Goal Attainment Scaling (GAS)**: patient-specific goal agreements and goal attainment scales, particularly validated in rare diseases (**Kirusek et al. 1994; Bauer, 2005**).
- **Adequate Relief / Satisfactory Relief**: patient-determined, binary symptom improvement, classically e.g. in the IBS context (**Lembo et al 2009**).
- **Sliding Dichotomy**: baseline-dependent responder definitions, established e.g. in TBI studies (**Signorovitch et al 2012**).
- **Continuous digital measures**: patient-specific baselines and trajectories from wearables (e.g., walking speed, sleep parameters, activity levels).

2.4.5 New individualized concepts – outlook

Research is increasingly developing fully personalized or AI-supported endpoints:

- **Personalized responder thresholds** (instead of fixed MCID values).
- **Individually weighted composite scores** based on patient priorities (e.g., pain, fatigue, function).
- **Personalized "time-to-X" endpoints** (e.g., time to return to relevant activity).
- **Slope and volatility measures** from continuous wearable data.
- **Patient-specific benefit/burden endpoints** that simultaneously reflect the burden of therapy burden and benefits.

2.4.6 Methodological checklist for robust individualisation

1. **Context & estimand**: precise definition of the estimand, population and handling of intercurrent events.
2. **Measuring instrument**: selection or development of "fit-for-purpose" (PFDD-compliant).
3. **Digital validation**: apply V3 framework (verification, validation, clinical evidence).
4. **Statistics**: pre-specified personalisation logic, sensitivity analyses, multiplicity control.
5. **Regulatory path**: EMA Qualification / FDA DDT programs for methodological recognition.

3. Individual Endpoints (IEP) Concept

3.1 Definition

Individualized endpoints (IEP) are endpoints that are not rigidly defined for all study participants, but are **tailored to the individual patient**.

This is achieved through:

- Baseline-adjusted thresholds,
- Patient-specific slopes and trajectories,
- AI-supported composite scores from biomarkers, imaging, and PROs,
- AI-supported a priori, a posteriori, and **in actu (!)** definition of endpoints
- In actu-supported determination of analysis and evaluation times
- Flexible weighting of clinically relevant parameters.

The aim is to capture **earlier, more sensitive, and patient-centered signals** without sacrificing comparability.

3.2 Types of IEP

3.2.3 Early individual surrogate markers

- Use of patient-specific biomarker profiles instead of hard clinical events.
- **Example in oncology**: ctDNA clearance relative to individual baseline (**Schwaederle et al 2019**).
- Example: ophthalmology: individual GA growth slope instead of group average.

Important: The main scientific criticism of surrogate endpoints is the risk of surrogacy error (i.e., the surrogate endpoint does not correlate with the actual clinical outcome). This is crucial for the scientific robustness of the concept.

3.2.4 Dynamic response models

- AI evaluates **real-time data** (laboratory, imaging, wearables) (in actu assessment).
- **Detection of individual** response signals significantly earlier than classic thresholds.
- Example: cardiology: combined patient benefit score based on exercise capacity, ejection fraction, and biomarkers.

3.2.5 Individualized PROs (patient-reported outcomes)

- Symptoms are not evaluated across the board, but against the individual baseline value.
- Weighting according to relevance for the patient.
- Example in neurology (MS): Fatigue or walking distance are weighted more heavily if these domains have the greatest impact on everyday life.

3.2.6 Adaptive composite endpoints

- Combination of individual parameters to form a patient-specific overall score.

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7. Novel and truly innovative individualized endpoints

We have addressed how individualized endpoints can revolutionize clinical trial designs.

In **Section 7.1** we present a comparison between classical endpoints that exist and novel iEPs that can further add to the power of these classical endpoints. By typically adding individualized parameters these classical endpoints can be made „true estimands“, if you want to say so. In any case individualization ensures that an individual patient is tested for what he or she is, where he or she is in her life, what she or him considers a success when taking a certain drug.

In **Section 7.2** we have defined which truly innovative clinical trial endpoints can be envisaged. These endpoints would go the extra mile to personalize monitoring and assessment of a subject in a clinical trial. Several of these endpoints are conceptually new, or not discussed yet as possible endpoints to no only advance standard scores but use them pivotally to make decisions on the success – of failure – of a clinical trial. While some are being discussed in research, our idea to use their true power for pivotal – AI based – decision managers of a clinical trial performance is – to our knowlege – a true innovation.

In **Section 7.3** we estimate the potential reduction in duration of clinical trials, and reduction of subjects needed per trial, when iEPs are used.

In **Section 7.4** we summarize the impact iEPS by category of a) highly innovative iEPS, moderately innovative iEPs, and conceptually new iEPS.

In **Section 7.5** we show a heatmap of efficiendy gains through iEPS (time savings and reduction of nr. of patients.

In **Section 7.6** the weighted average time savings were estimated.

In **Section 7.7** the reduction of costs due to time reductions are estimated, when iEPs are implemented broadly. The estimated 30% reduction of data management and reporting is however difficult to assess. While less subjects will have to be reported and for a shorter duration of time, novel *in actu AI* systems must be put in place. It remains to be see how much automating and decision making will be granted to such system by regulatory bodies. The more work AI systems can automatically do, the lower the cost would be.

In **Section 7.8** we display the combined effect one can expect when iEPs are used to reduce the number of subjects in a trial.

In **Section 7.9** the major reductions in duration, patient numbers, and cost are summarized.

In **Section 7.10** the evident strategic interpretation of the implementation of Ais is highlighted. **Section 7.10.1** shows the estimated costs per trial phase, while **Section 7.10.2** displays the estimated cost reduction per clinical trial phase, when implementing iEPs.

IMORTANT: These below numbers and figures are not evidence from validated, regulatory-accepted Phase III studies. They shall not be overemphased, as it could be construed as a scientifically unsubstantiated claim.

It hasn’t escaped our attention of course that individualizing these endpoints is only sometimes a linear evolution of the classical endpoints. More often they pose a radical change in methodology. This change will have to be chaperoned at regulators (see corresponding input for this critical task to implement fully IEPs throughout this Whitepaper).

8. Regulatory perspective

8.1 Status Quo

Regulatory authorities such as **the FDA** and **EMA** require **standardized, validated endpoints** for Phase 3 studies. Reasons:

- Comparability across studies.
- Protection against bias.
- Reproducibility in independent populations.

Classic endpoints (OS, PFS, BCVA, HbA1c, MACE) are firmly established.
New approaches such as ctDNA, digital biomarkers, or PRO scores are currently only recognized **as exploratory or supportive**.

8.2 Regulatory initiatives preparing IEPs

- **FDA Biomarker Qualification Program (BQP):** Approval of biomarkers as endpoints or surrogates (**FDA, 2017; Califf 2017**).
- **FDA Digital Health Center of Excellence:** Programs for digital biomarkers, wearables, ePRO.
- **EMA Innovation Task Force (ITF):** Early scientific advice for novel endpoints (**EMA 2023, EMA 2024**).
- **EMA Qualification of Novel Methodologies (QoNM):** official route to method approval (**EMA 2024**).
- **Parallel Consultation EMA/HTA:** early coordination with cost bearers on patient-centered endpoints (**Eunice et al 2023**).

8.3 Regulatory use of IEPs – realistic stages

1. **Exploratory (short term, possible now)**
    - Collect IEPs in parallel with traditional endpoints.
    - Use for hypotheses, subgroup analyses, publications.
2. **Supportive (medium term)**
    - IEPs serve as additional evidence in marketing authorization applications.
    - Examples: PRO-based improvements, ctDNA as supportive biomarkers.
3. **Adaptive triggers (medium term)**
    - IEPs as a basis for interim decisions (early stop, futility, adaptive randomization).
    - Regulators accept as long as confirmatory endpoints remain unaffected.
4. **Co-primary or substitution endpoint (long term)**
    - After comprehensive validation (correlation with OS, PFS, etc.).
    - Prerequisite: robust data from phase 3 and RWD.
5. **Primary IEPs (long-term, innovative, radical breakthroughs)**

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8.6 On the way to Artificial General Intelligence (AGI)

Artificial intelligence is increasingly evolving from pure assistance to autonomy: systems are beginning to formulate their own criteria of what and how to analyze an make decisions independently. Nevertheless, there is still the dogma that humans currently remain indispensable as a controlling authority - especially for monitoring ethical, safety-related, and social consequences.

The development toward true trust-based autonomy of AI (e.g., to determine times for analyses *in actu* and independently) can be roughly divided into three stages:

1. **Assistive AI (today–approx. 2030)**: Humans control every decision.
2. **Cooperative AI** (approx. 2030–2045): AI makes partial decisions, humans perform random checks.
3. **Trustworthy AGI** (from around 2050+): AI has self-regulating systems that ensure transparency, ethical consistency, and safety guarantees.

How quickly these transitions take place depends less on technical maturity than on social trust, regulation, and value orientation – so human control will remain necessary for the time being, even if it gradually shifts from direct intervention to higher-level oversight.

Important: Until now, progress in many areas has been underestimated. A key point in research is that it does not progress linearly, i.e., bringing new insights step by step. According to Thomas Kuhn's theory of science, paradigm shifts and breakthrough innovations can also **radically** take a field of research **to a new level** (!). Kuhn described it something like this: Many researchers broaden knowledge on one level, i.e., they continually bring details about a specific topic to light. Knowledge becomes more detailed, similar to how a cartographer measures a country with increasing accuracy. However, real breakthroughs, where a completely new "land" is discovered, rarely happen. One example of this is the discovery of quantum physics. Fundamental principles were discovered by individuals. However, knowledge about them was then expanded by countless scientists. Once discovered, the new land of "quantum physics" was mapped with increasing accuracy.

Research and development can also progress at different speeds in certain areas, due to various constraints such as regulations, patents, ethical concerns, lack of social acceptance, etc.

It is therefore impossible to predict when individualized endpoints will be fully accepted in clinical practice. At the same time, it should be emphasized that **rapid introduction and acceptance** are **also within the realm of possibility**. Pressure from patient groups and necessary cost reductions are just two factors that are creating considerable pressure to conduct clinical trials in a more patient-centered, faster, and more effective manner.

Close cooperation between AI scientists and clinical researchers is therefore imperative (see also Chapter 14, "Fully Individualized Endpoints—A Normative Strategy").

✅ **Conclusion:**
The regulatory introduction of IEPs must be **gradual**:

- **Today:** exploratory & supportive.
- **Tomorrow:** adaptive triggers & supplementation.
- **Future:** co-primary after validation.
- **Vision:** Primary after validation or discovery of new categorizations, effects, and certainties with the help of co-design through human-AI interactions

Close dialogue with authorities (FDA, EMA, HTA) and early pilot projects are crucial. Equally crucial is the co-design of IEPs through human-AI interactions. Given the current state of AI development, decisions made by AI still need to be monitored by humans. However, as knowledge often develops rapidly, the rapid introduction of IEPs is certainly within the realm of possibility.

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14. Fully individualized endpoints identified by AI – a radical vision beyond the hybrid strategy

The vision presented here can be taken even further. The following innovations have the potential to fundamentally change clinical research by going beyond the hybrid model.

For example, *in actu* analyses by AI systems could not only recognize signals and efficacies per patient but use them to create an overall picture of a population earlier and more precisely. Both analysis and decision-making (e.g., ad hoc definition of new thresholds or times for analysis, etc.) would be left autonomously to the AI system. Similarly, AI systems could autonomously discover and independently determine new endpoints. Validations (e.g., through digital twins and retro-analysis of existing data) may even be conceivable (see also chapters 15.1 and 16).

14.1 Abolition of control arms

The most radical step would probably be to completely abandon classic randomized controlled trials (RCTs) with parallel arms (**Berry 2021)**. Instead, **single-arm studies** would compare the course of treatment for each patient with their own **digital twin** (**EL-Gayar et al, 2021)**. This virtual twin would be an AI model that generates the patient's expected disease progression without treatment based on their individual data (genetics, lifestyle, biomarkers) and historical cohorts. This would drastically minimize the number of patients required.

14.2 Dynamic, "just-in-time" studies:

Instead of having fixed study durations, AI could analyze the data in real time and, in the event of a predefined, statistically significant signal, immediately stop or adjust the study without the need for manual intervention by a human DMC (Data Monitoring Committee). This would significantly reduce the time to approval.

IMPORTANT: This contradicts the requirements for interpretability (XAI), auditability, and the primacy of human control in clinical research. For the immediate implementation of the hybrid strategy, human oversight (DMC, model governance) is – given the current limitations of AI systems (**Aeschbacher and ChatGPT 2025b**) – still regarded by many as a mandatory scientific and ethical condition.

14.3 AI as an "explorer" of endpoints

As described above, AI can be used for the "a posteriori autogenous definition of decision-relevant endpoints." An even more radical vision would be for AI to not only individualize existing endpoints, but also independently discover completely new, previously unknown categories of healing processes and safety profiles (**Senior et al 2020**). AI would, so to speak, "ask" what the most effective endpoint is for a) the patient collective, b) a specific patient group, or c) an individual. This would require a completely new type of collaboration between humans and AI in the field of clinical research ( ). See also **Aeschbacher & ChatGpt 2025a, Aeschbacher & ChatGpt 2025b.**

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19. Contact and Service Offer

Get in touch with me for Innovation

Would you like me to speak about how to co-creatively co-design with AI in the Life Sciences domain?
I am happy to present on IEPs, but also on how to excel in developing innovative ideas through co-design with AI systems. Invite me to your conferences, discussions with internal development departments, or your management. You will receive valuable insights and targeted input on how to create in-depth analyses of scientific challenges while ensuring the implementation of human creative thinking to explore novel thought spheres.

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