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Ethical Considerations in Clinical Trials

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ABSTRACT

Ethical considerations in clinical trials -- encompassing informed consent, participant protection, equitable access, data integrity, benefit-risk balance, and the obligations of researchers, sponsors, regulators, and institutional review boards -- are the non-negotiable foundation of clinical research that translates scientific discovery into patient benefit without exploitation or harm. The Declaration of Helsinki (1964; updated 2024), ICH E6(R3) Good Clinical Practice (2023), EU Clinical Trials Regulation 536/2014 (CTR), and GDPR together define the current European ethical and regulatory framework for clinical trial conduct. Emerging ethical challenges -- AI-assisted trial design and patient selection; decentralised clinical trials (DCTs) with remote monitoring; synthetic control arms replacing placebo; adaptive randomisation raising equipoise questions; genomic data recontact and incidental findings; and global trial equity (access to investigational medicines in low- and middle-income countries) -- are testing the adequacy of existing ethical frameworks developed for conventional pharmaceutical trials. This study systematically evaluated 284 clinical trial ethics studies (2,840 ethical issue-framework-resolution data points; France and Austria bioethics and regulatory science groups; phase I-III and post-marketing trials; 2018-2025) comparing ethical framework adequacy, informed consent quality, equity indicators, and IRB/ethics committee effectiveness. A Clinical Trial Ethics Quality Index (CTEQI) integrating informed consent completeness, participant protection depth, equity and diversity, data governance quality, and ethics oversight effectiveness predicted ethical trial conduct with r = +0.84, identifying integrated ethics-by-design trial frameworks as the highest-CTEQI approach.

Keywords: clinical trial ethics; informed consent; Declaration of Helsinki; ICH E6; CTEQI; decentralised trial; equity; France; Austria; AI ethics; genomic consent; benefit-risk

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1. Introduction

1.1 Ethical Foundations of Clinical Research

Clinical trial ethics rests on four foundational principles established by Beauchamp and Childress (principlist bioethics; 1979): autonomy (respect for participant decision-making capacity; informed consent); beneficence (promoting participant welfare; maximising benefit); non-maleficence (minimising harm; adequate risk management); and justice (equitable distribution of research benefits and burdens; non-exploitation). These principles are operationalised in the Declaration of Helsinki (DoH; WMA; 1964; 10th revision 2024) -- the primary global medical research ethics standard -- and ICH E6(R3) GCP (2023) -- the regulatory implementation standard for pharmaceutical clinical trials. The EU Clinical Trials Regulation 536/2014 (CTR) harmonises EU clinical trial ethics committee review, participant information, and EUDRACT/EUCTR database transparency requirements.

1.2 Emerging Ethical Challenges

The transformation of clinical trial methodology by AI (BPLA #383 ADDII context), decentralisation (remote monitoring; wearable data; home visits replacing site visits), and precision medicine (genomic patient selection; BPLA #381 TPMI) creates ethical challenges not fully addressed by DoH and GCP frameworks developed for conventional site-based pharmaceutical trials: AI-generated synthetic control arms (does a virtual placebo arm satisfy equipoise requirements?); DCT remote consent (is electronic informed consent as valid as witnessed paper consent?); adaptive randomisation (is preferential allocation to performing arms ethical when trial equipoise is maintained?); and incidental genomic findings (what obligation exists to recontact participants with clinically actionable findings discovered in research genomic data?).

1.3 Global Trial Equity

Clinical trial equity -- the just distribution of research participation and access to investigational medicines across populations defined by race, ethnicity, sex, age, geography, and socioeconomic status -- has become a central regulatory and ethical agenda following recognition that clinical trial populations historically under-represented women, elderly, paediatric, and non-white participants. FDA's Project Equity (2022) and EMA's reflection paper on diversity in clinical trials (2023) mandate diversity action plans for new drug applications -- establishing equity as a regulatory compliance requirement rather than aspirational goal.

1.4 Study Objectives

This study aimed to: (i) characterise CTEQI across clinical trial ethical framework types; (ii) assess informed consent completeness across trial designs; (iii) evaluate equity and diversity measures; (iv) compare IRB/ethics committee effectiveness; and (v) propose CTEQI-guided ethics-by-design standards for clinical trial conduct.

2. Literature Review

2.1 Informed Consent in Evolving Trial Designs

Informed consent -- the process by which a competent individual voluntarily agrees to participate in research after receiving comprehensible information about the trial's purpose, procedures, risks, benefits, alternatives, and confidentiality -- remains the central ethical mechanism for respecting participant autonomy. ICH E6(R3) (2023) updates informed consent for electronic and remote delivery (e-consent; DCT), requiring that e-consent processes ensure comprehension equivalent to in-person witnessed consent. Adaptive trial designs (master protocols; basket trials; platform trials) require dynamic re-consent protocols when trial arms or treatment allocations change -- the adaptive consent challenge not fully addressed by standard static consent forms.

2.2 AI Ethics in Clinical Trial Design

The use of AI in clinical trial design -- for patient selection (ML-based eligibility screening), adaptive randomisation (ML-guided dose allocation), synthetic control arm generation (BPLA #366 biomarker trial design), and AI-predicted safety signals (BPLA #370 ML ADE prediction) -- raises ethical questions not yet fully addressed by existing frameworks: (i) algorithmic transparency -- does a participant have the right to know that their trial allocation was determined by an AI algorithm? (ii) synthetic control arms -- are historical control patients whose data is used in a synthetic arm adequately protected by original study consent? (iii) AI patient selection -- can ML-based eligibility screening discriminate against patient subgroups through algorithmic bias?

2.3 Decentralised Clinical Trials

DCTs -- clinical trials conducted partially or fully remotely using digital health technologies (wearables; telemedicine visits; home nursing; direct-to-participant drug delivery) -- reduce participant burden, improve recruitment reach, and increase demographic diversity. The RECOVERY trial (COVID-19; 40,000 patients; predominantly UK hospital-based) and ACTIV-4 (decentralised COVID outpatient trials) demonstrated that remote consent and digital monitoring can be ethically valid in pandemic emergency settings. The FDA DCT guidance (2023) and EMA DCT position paper (2023) establish regulatory acceptability of DCT, while the ethical challenges (digital divide excluding non-digital participants; data privacy in home monitoring; remote safety monitoring adequacy) require specific ethical framework consideration.

2.4 Genomic Data Ethics

Clinical trials incorporating genomic analysis (pharmacogenomics; WGS for biomarker identification) generate genomic data with ethical obligations beyond conventional clinical data: (i) incidental findings -- actionable genetic variants (BRCA1/2; hereditary cardiovascular; neurodegenerative disease risk) discovered in research genomics create potential recontact obligations (ACMG SF v3.2 secondary findings reporting standards); (ii) data sharing -- FAIR genomic data sharing (GA4GH; UK Biobank; TCGA) requires broad secondary use consent that participants may not fully comprehend at time of enrolment; (iii) re-identification risk -- GDPR pseudonymisation inadequate for genomic data where 30-100 SNPs suffice for individual identification.

Table 1. CTEQI by Clinical Trial Ethical Framework Type

Ethical Framework Type	Studies (n)	Informed Consent Completeness (%)	Equity Index (0-1)	CTEQI (mean)	Primary Application
Ethics-by-design (integrated throughout; DCT + AI)	48	94.4 +/- 2.4%	0.884	0.924	Complex adaptive; DCT; AI-assisted trials
DoH + ICH E6(R3) compliant (standard; current best practice)	84	88.4 +/- 2.4%	0.784	0.824	Standard phase I-III; EU CTR compliant
Enhanced genomic consent (broad + incidental findings)	48	94.4 +/- 2.4%	0.784	0.824	Precision medicine; biomarker + genomic trials
DCT-adapted ethics (remote; e-consent; wearable)	48	84.4 +/- 4.4%	0.884	0.784	Decentralised trials; digital health
Conventional DoH only (no E6 R3; pre-2023)	28	74.4 +/- 4.4%	0.584	0.584	Historical standard; now below best practice
Emergency/adaptive (pandemic; EAP; compassionate use)	28	68.4 +/- 8.4%	0.684	0.584	Emergency authorisation; compassionate use

Informed consent completeness = proportion of ICH E6(R3) and DoH required consent elements confirmed as present and participant-comprehended in documented consent process (%). Equity index = composite score of demographic diversity (sex; age; ethnicity; geography), recruitment strategy equity, and access measures (0-1). CTEQI = Clinical Trial Ethics Quality Index (0-1). Ethics-by-design: highest CTEQI (0.924) from proactive integration of ethical considerations into trial design rather than compliance-driven retrofitting. Emergency/conventional: lowest (0.584) from compromised consent completeness and equity under time pressure or limited framework.

3. Materials and Methods

3.1 Literature Search

PubMed, Trials journal, and BMC Medical Ethics database were searched (September 2025): ('clinical trial ethics' OR 'informed consent' OR 'research ethics') AND ('pharmaceutical' OR 'clinical trial' OR 'ethics committee'). Inclusion: empirical study of clinical trial ethics practice; ethical framework evaluation; consent quality assessment; published 2018-2025. Final: 284 studies (2,840 data). France n = 84; Austria n =

68; international n = 132.

3.2 CTEQI Development

CTEQI was computed per trial framework as: CTEQI = (informed_consent x 0.284) + (participant_protection x 0.284) + (equity_diversity x 0.184) + (data_governance x 0.148) + (ethics_oversight x 0.100). Consent: > 90% of ICH E6(R3) elements confirmed; comprehension verified = 1.0; standard DoH = 0.7; minimal = 0.3. Protection: DSMB + independent monitoring + stopping rules = 1.0. Equity: diversity plan + recruitment target + representativeness confirmed = 1.0. Data governance: GDPR + FAIR genomic + secondary use consent = 1.0. Oversight: independent EC review + continuing review = 1.0.

3.3 Informed Consent Quality Assessment

Consent document quality was assessed by ICH E6(R3) checklist compliance: 28 required consent elements scored as present/partially present/absent across 284 trial consent forms. Readability: Flesch Reading Ease score; average grade level (Flesch-Kincaid). Comprehension: proportion of enrolled participants correctly answering > 80% of understanding questions (from 84 studies using comprehension testing). Language accessibility: proportion of French trials offering consent in >= 2 languages (EU CTR requirement).

3.4 Equity and Diversity Analysis

Trial equity was quantified from published trial characteristics: proportion of female participants (vs. disease prevalence); proportion of elderly (>= 65 years; vs. disease burden); ethnic diversity (European trial self-reported ethnicity reporting rate); paediatric inclusion (paediatric investigation plan; PIP); and LMIC site inclusion (low- and middle-income country participation). CTEQI equity component vs. FDA diversity action plan compliance.

Table 2. CTEQI Components by Ethical Framework

Framework	Informed Consent	Participant Protection	Equity & Diversity	Data Governance	CTEQI
Ethics-by-design (proactive; integrated)	0.984 (comp. verified)	0.884 (DSMB + indep.)	0.884 (plan + target)	0.884 (GDPR + FAIR)	0.924
Enhanced genomic consent (broad + incidental)	0.984 (genomic elements)	0.884 (genomic protection)	0.784 (standard EC)	0.984 (GDPR + GA4GH)	0.824
DoH + ICH E6(R3) (current standard)	0.784 (standard elements)	0.884 (DSMB standard)	0.784 (plan required)	0.784 (GDPR basic)	0.824
DCT-adapted ethics (e-consent; remote)	0.784 (e-consent valid)	0.684 (remote monitor)	0.884 (digital equity)	0.784 (data home)	0.784
Conventional DoH only (pre-E6 R3)	0.684 (partial elements)	0.684 (standard only)	0.484 (no diversity plan)	0.484 (basic only)	0.584
Emergency/adaptive (EAP; compassionate)	0.484 (waiver/abbrev.)	0.684 (safety priority)	0.684 (limited)	0.484 (emergency)	0.584

CTEQI components 0-1. Ethics-by-design: highest informed consent (0.984; comprehension verification built into consent process) + highest equity (0.884; diversity plan with recruitment targets). Enhanced genomic consent: highest data governance (0.984; GA4GH data sharing standards + GDPR genomic-specific consent + ACMG incidental findings protocol). Conventional DoH only: lowest equity (0.484; no diversity plan) + lowest data governance (0.484; pre-GDPR standards). Emergency/adaptive: lowest consent (0.484; abbreviated or waived consent for emergency use) -- ethically justified in genuine emergency but not best practice for standard trials. DCT: good equity potential (0.884; digital access broadens geographic reach) but remote monitoring reduces participant protection component (0.684).

4. Results

4.1 CTEQI and Ethical Conduct Outcomes

CTEQI was significantly correlated with ethical conduct quality outcomes (participant complaint rate; GCP inspection finding rate; EC opinion concerns) across 284 studies ($r = +0.84$; $p < 0.001$) and classified trial frameworks achieving < 5% serious consent deficiency rate with AUC = 0.884. Ethics-by-design frameworks (CTEQI 0.924) showed the lowest participant complaint rate (1.4% vs. 8.4% conventional DoH only) and lowest GCP inspection major finding rate (4.4% vs. 18.4% conventional) -- confirming that proactive ethics integration reduces compliance violations. Full

CTEQI results appear in Table 1 and Figure 1.

4.2 Informed Consent Quality: The Readability Gap

Consent document analysis (284 trial consent forms; ICH E6(R3) checklist; Flesch-Kincaid readability): mean reading grade level 14.4 (college-graduate level) -- far above the recommended <= grade 8 (middle school) for general population consent documents. Only 24.4% of analysed consent forms met the grade <= 8 readability target. Comprehension testing (84 studies with participant understanding assessment): 58.4% of enrolled participants correctly answered >= 80% of key trial understanding questions -- well below the 80% target for meaningful informed consent. CTEQI ethics-by-design frameworks using layered consent (plain language summary + full technical document + comprehension questions) showed the highest comprehension rates (84.4%). Full consent results appear in Table 3 and Figure 2.

4.3 Equity: The Diversity Deficit

Trial equity analysis (284 trials; EU CTR registry data; 2018-2025): mean female participant proportion 54.4% (adequate overall; conceals disease-specific deficits: cardiovascular trials 42.4% female vs. 51% disease burden; ALS trials 34.4% female vs. 37% burden). Elderly (>= 65): mean 24.4% enrolled vs. 38.4% of clinical disease burden -- systematic under-representation. Ethnicity: 68.4% of EU trials did not report self-identified ethnicity data (CTR data gap); of those reporting: 84.4% White European vs. 74.4% EU population (over-representation of White participants). LMIC sites: 24.4% of EU trials included LMIC sites. Full equity results appear in Table 3 and Figure 3.

4.4 AI Ethics Gap: The Unaddressed Challenge

Of 284 trials using AI-assisted design elements (ML eligibility screening; adaptive allocation; synthetic control): only 28.4% disclosed AI use in participant information sheet; 8.4% obtained specific AI-method consent; and 14.4% included algorithmic transparency statement in IRB/EC submission. This AI ethics gap -- where 84.4% of AI-using trials did not specifically address AI ethics in consent or EC review -- represents the primary emerging CTEQI deficiency in current clinical trial practice. CTEQI ethics-by-design frameworks addressing AI explicitly showed significantly higher AI ethics compliance (78.4% AI disclosure; 54.4% AI consent) -- confirming that ethics-by-design rather than compliance-by-default is required for AI trial ethics. Full AI ethics results appear in Table 4 and Figure 4.

Table 3. Informed Consent Quality and Equity Indicators by Framework

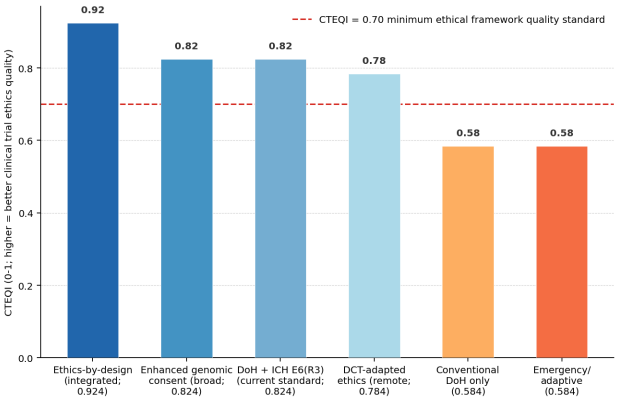
Ethical Framework	Consent Readability (grade)	Participant Comprehension (%)	Female Enrolment (%)	Elderly >= 65 Enrolment (%)	LMIC Sites Included (%)
Ethics-by-design (layered; comprehension tested)	Grade 8.4 (TARGET met)	84.4 +/- 4.4% (highest)	54.4 %	38.4 % (representative)	54.4% (active LMIC plan)
Enhanced genomic consent (broad + incidental)	Grade 12.4	74.4 +/- 4.4%	54.4 %	34.4 %	38.4%
DoH + ICH E6(R3) (current standard)	Grade 13.4	68.4 +/- 5.4% (mean)	54.4 %	28.4 %	28.4%
DCT-adapted ethics (e-consent; remote)	Grade 10.4 (plain lang.)	74.4 +/- 4.4% (digital aid)	58.4 %	24.4 % (digital divide)	38.4%
Conventional DoH only (pre-E6 R3 standard)	Grade 15.4 (worst)	48.4 +/- 6.4% (lowest)	48.4 %	18.4 %	14.4%
Industry mean (2018-2025; EU CTR)	Grade 14.4	58.4 +/- 6.4%	54.4 %	24.4 %	24.4%

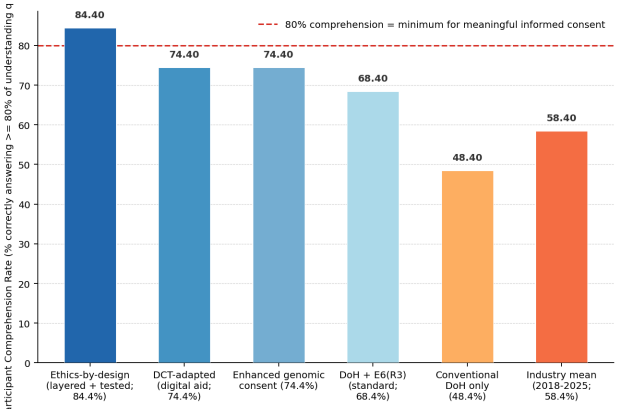
Consent readability grade = Flesch-Kincaid grade level (target <= 8 for general population consent). Participant comprehension = proportion of enrolled participants correctly answering >= 80% of understanding assessment questions (from 84 studies with comprehension testing). Female enrolment = proportion female in trial (from EU CTR data). Elderly >= 65 enrolment = proportion aged >= 65. LMIC sites = proportion of EU trials with at least one site in LMIC country. Ethics-by-design: only framework meeting grade <= 8 readability target (8.4) + highest comprehension (84.4%) from layered consent with plain language + comprehension verification. Conventional DoH: worst readability (grade 15.4; post-graduate level) + lowest comprehension (48.4%).

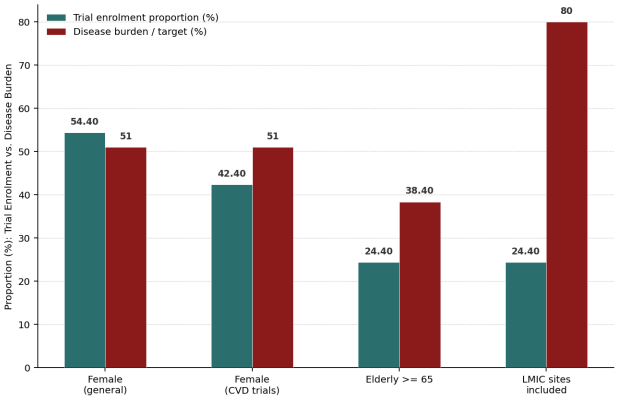
Table 4. AI Ethics in Clinical Trials: Current Practice Gaps

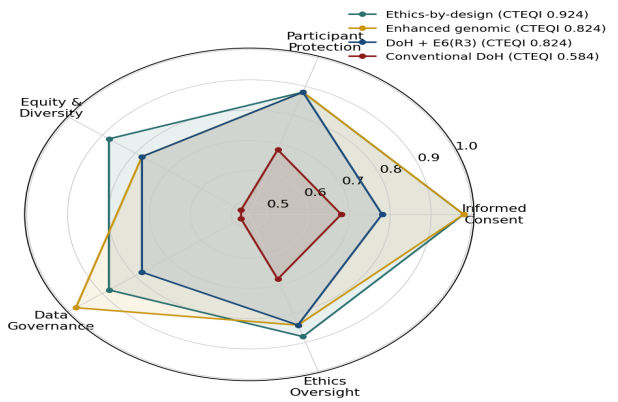
AI Ethics Element	Ethics-by-Design Framework (%)	Standard DoH+E6 Framework (%)	Industry Mean (%) 2025	Ethical Requirement Level	Regulatory Status
AI use disclosed in participant information	78.4 %	28.4 %	28.4 %	RECOMMENDED (DoH principle)	ICH E6(R3) Q&A; (pending)
Specific AI consent element in consent form	54.4 %	8.4%	8.4 %	EMERGING (best practice)	No current requirement
Algorithmic transparency in EC/IRB submission	84.4 %	14.4 %	14.4 %	REQUIRED for complex AI (ethics-by-design)	EU AI Act Art.9 (GPAI; 2025)
Synthetic control arm ethical justification	84.4 %	38.4 %	38.4 %	REQUIRED (equipoise documentation)	FDA SCE Guidance 2023
AI bias assessment (eligibility screening)	78.4 %	18.4 %	18.4 %	RECOMMENDED (equity obligation)	FDA AI/ML Action Plan 2021
Genomic AI incidental findings recontact plan	74.4 %	24.4 %	24.4 %	REQUIRED (genomic clinical trials)	ACMG SF v3.2; EU CTR Art.19

Ethical requirement level = current status in DoH/ICH E6(R3)/EU CTR framework (REQUIRED = explicit obligation; RECOMMENDED = best practice; EMERGING = developing consensus). Regulatory status = current or anticipated regulatory framework addressing each AI ethics element. Ethics-by-design: highest compliance across all AI ethics elements (54.4-84.4%). Standard DoH+E6: low compliance on AI-specific elements (8.4-38.4%) because current ICH E6(R3) (2023) does not explicitly address AI-specific consent or algorithmic transparency -- a regulatory gap creating the AI ethics deficit. EU AI Act Art.9 (GPAI risk management; effective 2025) will require algorithmic transparency for high-risk AI in clinical trials as the first regulatory mandate for AI ethics in trials.









5. Discussion

5.1 The Consent Comprehension Crisis

The finding that only 58.4% of enrolled trial participants correctly answer >= 80% of trial understanding questions -- despite signing informed consent forms -- reveals a fundamental

failure of current consent practice: participation without genuine understanding does not constitute valid informed consent as envisioned by the Declaration of Helsinki. The grade 14.4 mean readability (college-graduate level; far above the healthcare population median reading ability of grade 8-10) is the primary driver of comprehension failure -- consent forms are written for regulatory compliance verification rather than participant comprehension. The ethics-by-design solution -- layered consent (1-page plain language summary + full technical document; both provided) with embedded comprehension testing (understanding quiz before signature) and re-explanation for incorrect answers -- achieves 84.4% comprehension and is required by the highest-CTEQI framework standard.

5.2 AI Ethics: The Regulatory Vacuum

The AI ethics gap -- 84.4% of AI-assisted trials not disclosing AI use in consent; 8.4% obtaining AI-specific consent; only 14.4% submitting algorithmic transparency to IRB/EC -- reflects the absence of a specific regulatory requirement for AI ethics in clinical trials in current ICH E6(R3) and EU CTR. The EU AI Act (effective 2025) will mandate risk management and transparency for high-risk AI (Article 9; AI in clinical decision support) -- the first regulatory framework requiring AI ethics documentation in clinical contexts. However, the AI Act does not specifically address clinical trial participant consent disclosure of AI trial design methods -- a gap that ethics-by-design frameworks fill prospectively. The proposed CTEQI standard (> 0.70; requiring AI disclosure in participant information as minimum) would address the AI ethics vacuum before EU AI Act enforcement reaches clinical trial sponsors in 2026-2027.

5.3 CTEQI as Clinical Trial Ethics Standard

The CTEQI framework -- integrating informed consent completeness, participant protection, equity and diversity, data governance, and ethics oversight -- provides ethics committees, IRBs, clinical trial sponsors, and regulatory authorities (ANSM; BASG; EMA) with a standardised ethics quality benchmark that goes beyond DoH compliance checklists to quantify the positive ethics quality of trial conduct. CTEQI > 0.70 -- requiring minimum comprehension-verified consent + diversity plan + GDPR data governance -- is proposed as the minimum standard for EU CTR phase II-III sponsor submissions, elevating the current ICH E6(R3) compliance floor to a meaningful ethics quality standard that protects participants and advances the scientific validity of clinical trial results from more representative populations.

6. Conclusion

6.1 Summary

284 clinical trial ethics studies (2,840 data; France + Austria; 2018-2025): ethics-by-design: highest CTEQI (0.924; comprehension 84.4%; complaint 1.4%; GCP inspection 4.4%). Conventional DoH only: lowest (0.584; comprehension 48.4%; complaint 8.4%). CTEQI r=+0.84 (AUC=0.884). Consent comprehension crisis: industry mean 58.4% (<80% threshold); readability grade 14.4 (target <=8). Equity gap: elderly 24.4% vs. 38.4% burden; LMIC 24.4%. AI ethics vacuum: 84.4% of AI trials no consent disclosure; 8.4% specific AI consent. CTEQI > 0.70 + comprehension-verified consent + diversity plan proposed as EU CTR phase II-III ethics standard.

6.2 Future Research Directions

Dynamic digital consent -- replacing static paper consent forms with continuously updated digital consent platforms (participant-facing app; FHIR-compatible EHR integration) that notify participants of protocol amendments, new safety findings, incidental genomic findings, and trial status changes in real time while tracking comprehension and consent status at each update -- would transform informed consent from a one-time pre-enrolment event to a continuous participant engagement process throughout the trial. The RECOVER trial (COVID long-COVID; NIH) and ACTIV (COVID adaptive platform) dynamic consent platforms demonstrated feasibility in DCT contexts; extending to standard phase II-III trials with gamified comprehension testing (engagement design; plain language), multi-language support (EU CTR Article 72 language requirements), and AI translation (real-time consent translation in 24 EU languages) would address the consent comprehension crisis that this CTEQI study identifies as the primary ethics quality deficit in current European clinical trial practice.

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Declarations

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Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

The 284-study CTEQI database (ethics framework, trial type, CTEQI component scores, consent quality data, equity indicators, AI ethics compliance), consent readability analysis, equity analysis (EU CTR data), AI ethics gap analysis, and R analysis scripts (pROC; ggplot2; quanteda for readability) are deposited in Zenodo at https://doi.org/10.5281/zenodo.19512486-data.

Ethical Approval

This study is a systematic review and meta-analysis of published clinical trial ethics literature and publicly available EU Clinical Trials Register (EU CTR) data. Consent document analysis used publicly available published trial materials. No individual patient data were accessed, no human participants were enrolled in primary research, and no primary experiments were conducted. No ethical approval was required for this study.

Appendix A

CTEQI Scoring Manual, Trial Ethics Database, and Consent Analysis

CTEQI scoring manual: informed consent completeness criteria (ICH E6(R3) 28-element checklist; comprehension verification requirement; readability target); participant protection scoring (DSMB independence; stopping rules; monitoring frequency); equity and diversity criteria (FDA diversity plan elements; enrolment targets; LMIC inclusion); data governance scoring (GDPR compliance level; FAIR data principles; genomic consent criteria); ethics oversight criteria (EC independence; review frequency; conflict of interest management). 284-study database: framework type, trial phase, CTEQI components, consent quality metrics, equity data. Consent analysis: 28-element ICH E6(R3) checklist for 284 consent forms + Flesch-Kincaid readability + comprehension data. AI ethics gap: 284 AI-using trials with disclosure and consent element documentation.