Innovations in Consent: Modifications & Alternative Models in Clinical Trials

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September 2025

Disclosures

- No funding from industry
- Research grants from CIHR, NFRF, HSFC, BHI, U Ottawa & Department of Medicine
- Results included are the product of teamwork

A lot of ACTION

- AcT Trial (*Lancet* 2022): Alteplase compared to Tenecteplase
- ACT-GLOBAL (launched ’24): A multi-faCtorial, mulTi-arm, multi-staGe, randomised, gLOBal Adaptive pLatform trial for stroke
- ACTION (CIHR): feasibility of Advance Consent for participation in acute stroke research
- COMPACT (HSFC): Consent Modernization for Platform Adaptive Clinical Trials
- iCATCHER (launched Sept ’25): international cluster randomized trial of guideline-based care for ICH

Modifications of *What*?

- “Prospective”: after a clinical event, before trial participation
- “Informed”: having reviewed a volume of information consistent with current standards
  - Consent forms often 16-20 pages long
- “Consent”: review of written document, signed in person by potential participant or Substitute Decision-Maker (SDM)

Why Modifications?

- Consent processes can bias or impede research conduct
  - NEJM 2004 Tu et al. experience with Canadian Stroke Registry
- Informed Consent Forms (ICFs) are too long
  - Length does not enhance comprehension or satisfaction, reduces participation
- Comprehension of consent processes is generally mediocre
  - In our studies, participants understand about 50% immediately after
- Under-representation of women & BIPOC communities
  - Through issues of language, trust, lack of substitute decision-makers
- We lack evidence-based best practices
  - Innovation allows for an opportunity to study novel vs standard practices

When modifications?

- Emergency Conditions
  - Time pressure + incapacity of participants
- Platform Adaptive Trials
  - Added complexity, and change over time
- Standard of care trials
  - If a patient were likely to encounter either of 2 interventions in routine care without consent, to what extent is consent required if this is structured within a RCT?
- Cluster Randomization
  - When is cluster appropriate, and how should this impact consent?

How modifications?

- Abbreviated Consent
- Consent using technology
- Deferred Consent
- Advance Consent
- Waiver of Consent

Abbreviated Consent (1)

- Lacking data re: ideal ICF length
- TCPS2 list is neither evidence-based nor determined by law
- CCCTG Template (*CMAJ* 2025): satisfies all regulatory requirements
  - But are these elements all necessary? Important?
  - How much space should be devoted to each element?

Elements outlined in TCPS2

a. information that the individual is being invited to participate in a research project;
b. a statement of the research purpose in plain language, the identity of the researcher, the identity of the funder or sponsor, the expected duration and nature of participation, a description of research procedures, and an explanation of the responsibilities of the participant;
c. a plain language description of all reasonably foreseeable risks and potential benefits, both to the participants and in general, that may arise from research participation;
d. an assurance that prospective participants:
   - are under no obligation to participate and are free to withdraw at any time without prejudice to pre-existing entitlements;
   - will be given, in a timely manner throughout the course of the research project, information that is relevant to their decision to continue or withdraw from participation; and
   - will be given information on their right to request the withdrawal of data or human biological materials, including any limitations on the feasibility of that withdrawal;
e. information concerning the possibility of commercialization of research findings, and the presence of any real, potential or perceived conflicts of interest on the part of the researchers, their institutions or the research sponsors;
f. the measures to be undertaken for dissemination of research results and whether participants will be identified directly or indirectly;
g. the identity and contact information of a qualified designated representative who can explain scientific or scholarly aspects of the research to participants;
h. the identity and contact information of the appropriate individual(s) outside the research team whom participants may contact regarding possible ethical issues in the research;
i. an indication of what information will be collected about participants and for what purposes; an indication of who will have access to information collected about the identity of participants; a description of how confidentiality will be protected (Article 5.2); a description of the anticipated uses of data; and information indicating who may have a duty to disclose information collected, and to whom such disclosures could be made;
j. information about any payments, including incentives for participants, reimbursement for participation-related expenses and compensation for injury;
k. a statement to the effect that, by consenting, participants have not waived any rights to legal recourse in the event of research-related harm; and
l. in clinical trials, information on stopping rules and when researchers may remove participants from trial.

Abbreviated Content (2)

- ESCAPE (2015): Proposal for 2-page consent was rejected
- TICH-2 trial (2022): brief 2-stage consent led to faster randomization & was acceptable to >99% of participants
- Systematic Review (ISC 2025): what ICF content is most important to participants?
  - *Risks, benefits, experimental treatment & standard of care* most important
  - *Costs, contact, voluntariness, ability to withdraw* least important
- ACT-GLOBAL: If participant appears capable or SDM is present, we offer brief info about the trial (1 page, 3 mins) and option to OPT OUT verbally, with full consent to follow enrollment

Use of technology in consent

- Multiple studies suggest that multimedia tech enhances satisfaction & comprehension & reduces time to consent
- ACT-GLOBAL: designed tablet ICF with links to info videos as suggested by REB, then rejected by them
  - https://cumming.ucalgary.ca/departments/dcns/research/act-global
- PLINTH: Salman et al. from Edinburgh assessing feasibility of using 2-3 min video as the consent form
  - With eventual aim of using in trial for intracerebral hemorrhage
- Use of AI to provide real-time translation: appealing but not yet tested
- Use of TEAMS etc. to communicate with distant SDMs

Deferred Consent

- Enrollment occurs with intention to obtain consent as soon as possible from the participant or SDM
  - In time-sensitive setting where potential participant is incapacitated
  - Widely adopted for acute stroke trials in Canada & Europe
- AcT Trial: *universal* deferral of consent using novel protocol
  - Was approved by 21/22 Canadian REBs
  - Facilitated rapid randomization (DTN 30 mins vs 55 mins)
  - Acceptable to participants: >95% gave post-enrollment consent
  - Survey: 86% approved of deferral for AcT, 79% for any stroke trial
- ACT-GLOBAL: universal deferral if patient is incapable & no SDM present
  - But not in Québec

Protocol for Deferral of Consent

SIX-STEP PROTOCOL FOR UTILIZING DEFERRAL OF CONSENT

Identify an ethics lead:
Who is in charge?

Review trial design with a patient focus group:
What do stakeholders think?

Publish the justification of, and protocol for, deferral:
Why is deferral needed?

Support physician-patient communication with scripts:
What do patients need to be told?

Track patient withdrawals and report high rates:
Are patients choosing to remain in the study?

Determine patient attitudes towards deferral of consent:
What did patients think about their experiences?

Stroke 2021; *Neurology* 2023; *Neurology* 2024

Advance Consent

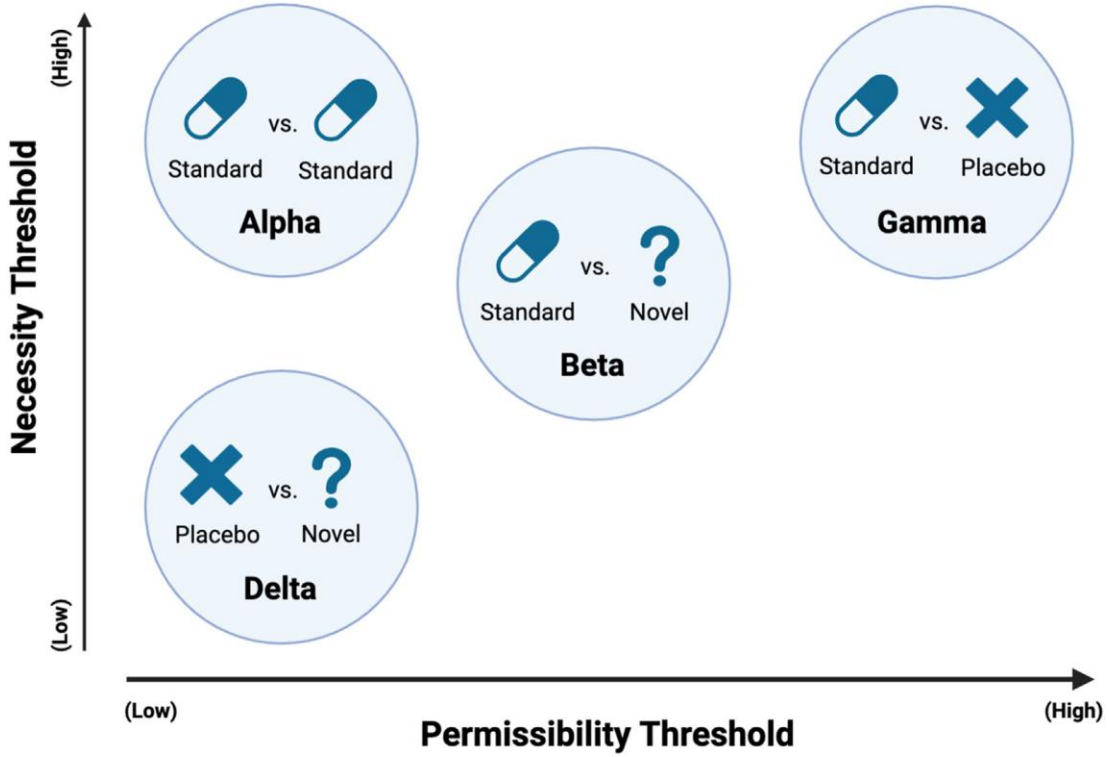
- Identifying patients with a certain condition, who may be eligible for enrollment into a trial in the future
  - Could help in conditions where at risk group can be identified, for emergency event, perioperative care, intra- & post-partum care, etc.
  - Consistent with TCPS2, US FDA regulations
- ACTION: 1547 stroke prevention clinic patients screened
  - 431 eligible, 157 enrolled, 46 gave advance consent, no trial participation
  - Surveys: >95% agree with appropriateness of advance consent
- Legal: REBs uncomfortable, especially with idea of using advance consent when SDM is present
  - Multiple rounds of challenges: advance consent is just consent

Waiver of Consent

- Different from deferral: no intention of gaining consent
  - But some form debriefing often required, as in TCPS2
  - Generally permitted for retrospective, QI
- Siridwarana 2024: systematic review of waiver regulations
  - *Minimal risk, impracticability, protection of welfare, social value*
  - But how to define & operationalize?
- iCATCHER: international stepped-wedge cluster trial of guideline-based care for patients with intracerebral hemorrhage
  - Waiver of consent for in-hospital data collection, but consent for 90 day phone follow up

Four Quadrants of RCTs

vs	**Standard**	**Novel**
Standard	Alpha	Beta
Placebo	Gamma	Delta



- Standard approaches to "equipoise" do not distinguish between RCTs on the basis of the interventions being compared
  - Four Quadrants model defines thresholds to establish *permissibility* & *necessity*
- Extent of consent may vary based on the quadrant
  - For Alpha: waiver
  - For delta: deferral in emergency, etc.
  - For beta & gamma: consent required

J Clin Epi 2020; *J Clin Epi* 2025

Not a new idea…

"The clinician who is convinced that a certain treatment works will almost never find an ethicist in his path, whereas his colleague who wonders and doubts and wants to learn will stumble over piles of them."

Lancet Editorial 1990

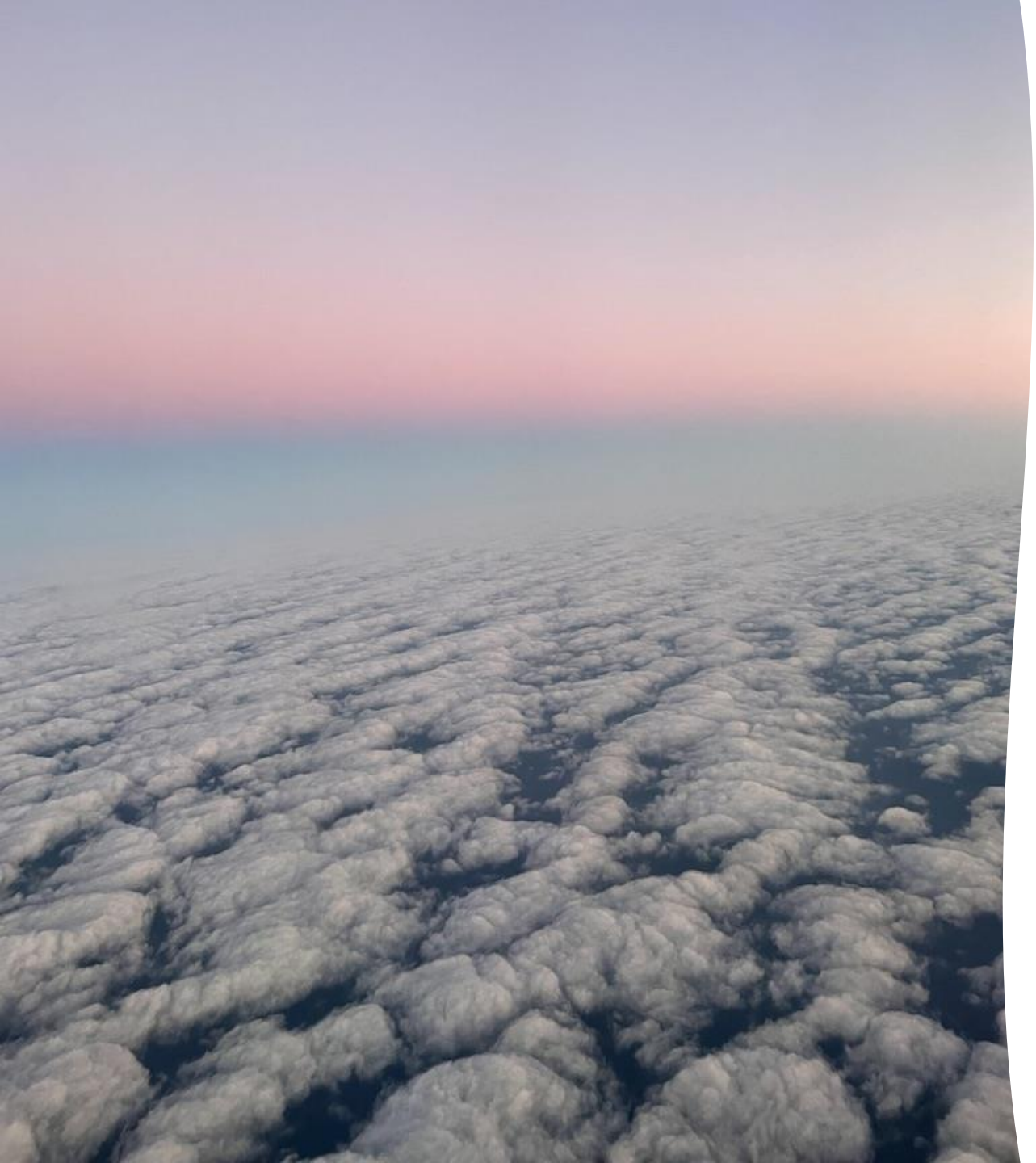
"I need permission to give a drug to half of my patients, but not to give it to them all."

Richard Smithells 1975

- Iain Chalmers (1990): MD, epidemiologist, coordinator, James Lind Initiative
- Smithells (1975): British pediatrician, researcher @ Leeds
- Claude Bernard (1865): "…physicians make therapeutic experimentation daily on their patients…"

Summary & Next Steps

- Modifications to consent practices are common, especially in emergency circumstances
  - With protocols and practices being developed to ensure standardization & transparency
- Experimentation about & around consent is possible & necessary
  - We will be most successful changing practices by obtaining data
- Consent practices for RCTs of standard of care practices remain underdeveloped
  - TCPS2 is a living document that has been, and may be further, amended and updated



Thank you!

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