



NIA IMPACT
COLLABORATORY
TRANSFORMING DEMENTIA CARE

**National Institute on Aging (NIA) IMbedded Pragmatic Alzheimer's Disease (AD) and
AD-Related Dementias (AD/ADRD) Clinical Trials (IMPACT) Collaboratory (NIA U54AG063546)**

MODIFICATIONS AND WAIVERS OF INFORMED CONSENT IN PRAGMATIC CLINICAL TRIALS

IMPACT GRAND ROUNDS: FEBRUARY 20, 2020



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About the Regulation and Ethics Core

Regulation and Ethics Core Members

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Regulation and Ethics Core Aims

- Develop and disseminate guidelines and **best practices for the research community** that address ethical issues and regulatory structures when conducting ePCTs with PLWD and their caregivers.
- Identify and address ethical and regulatory concerns and barriers to conducting ePCTs in PLWD and their caregivers from the **perspectives of health care system stakeholders**.
- Provide **guidance and training to investigators** regarding ethical and regulatory issues.



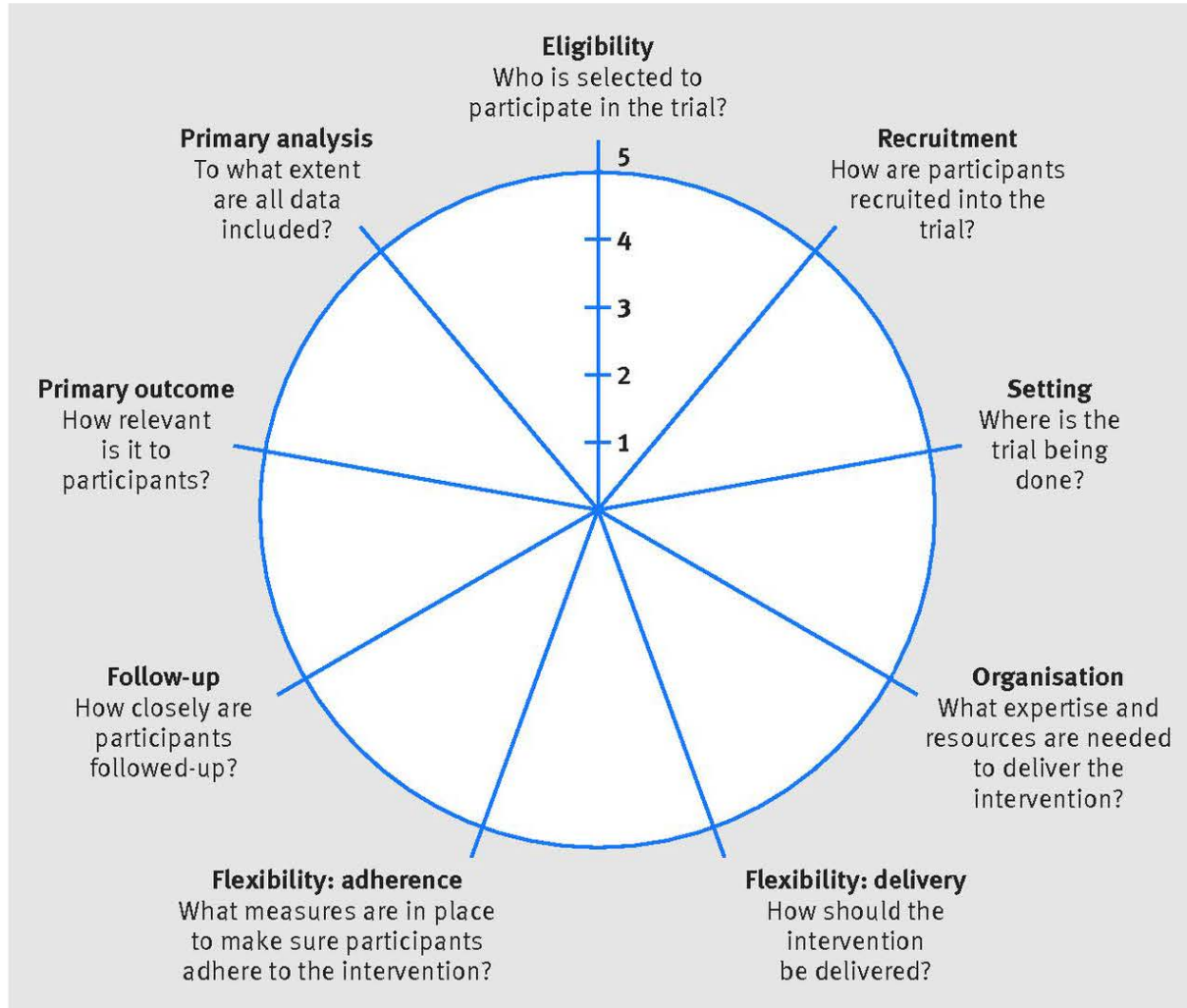
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Waivers and Alterations of Written Informed Consent

Objectives

- Identify how consideration of ethical and regulatory issues in the design phase of an ePCT with PLWD can help make the study more pragmatic.
- Review the regulatory requirements for a waiver or alteration of informed consent and discuss related ethical considerations.
- Apply what we've covered to two case studies.

PRagmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2)

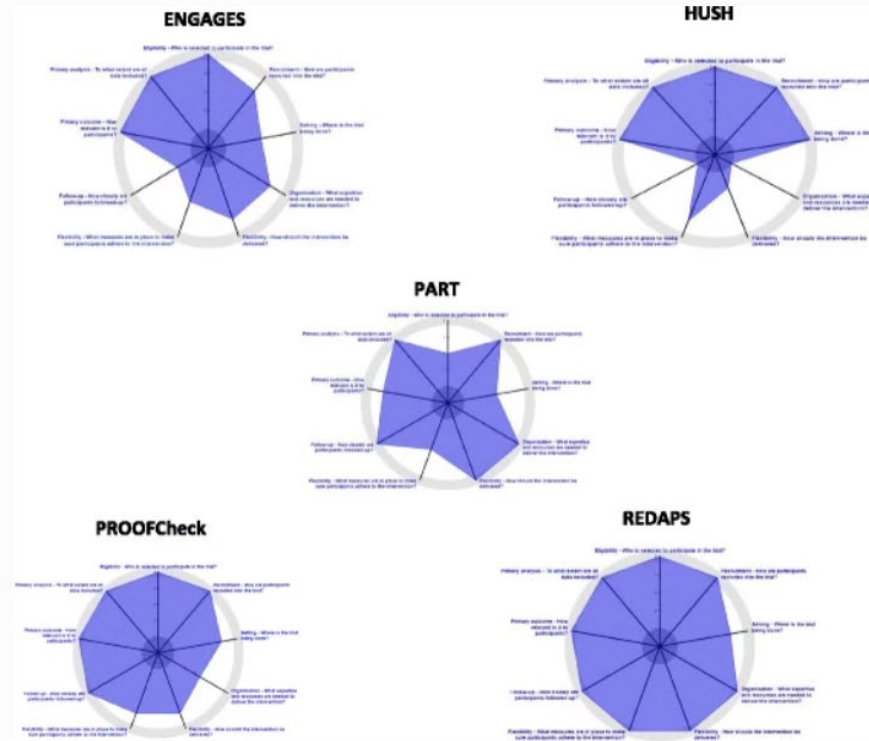


Scoring criteria for each domain

1. Very explanatory
2. Rather explanatory
3. Equally pragmatic and explanatory
4. Rather pragmatic
5. Very pragmatic

The “pragmatic” aspects of a clinical trial are a multi-attribute continuum

From: [Framing the conversation: use of PRECIS-2 ratings to advance understanding of pragmatic trial design domains](#)



PRECIS-2 principal investigator (PI) plots by study trial (trial planning phase – Time 1)

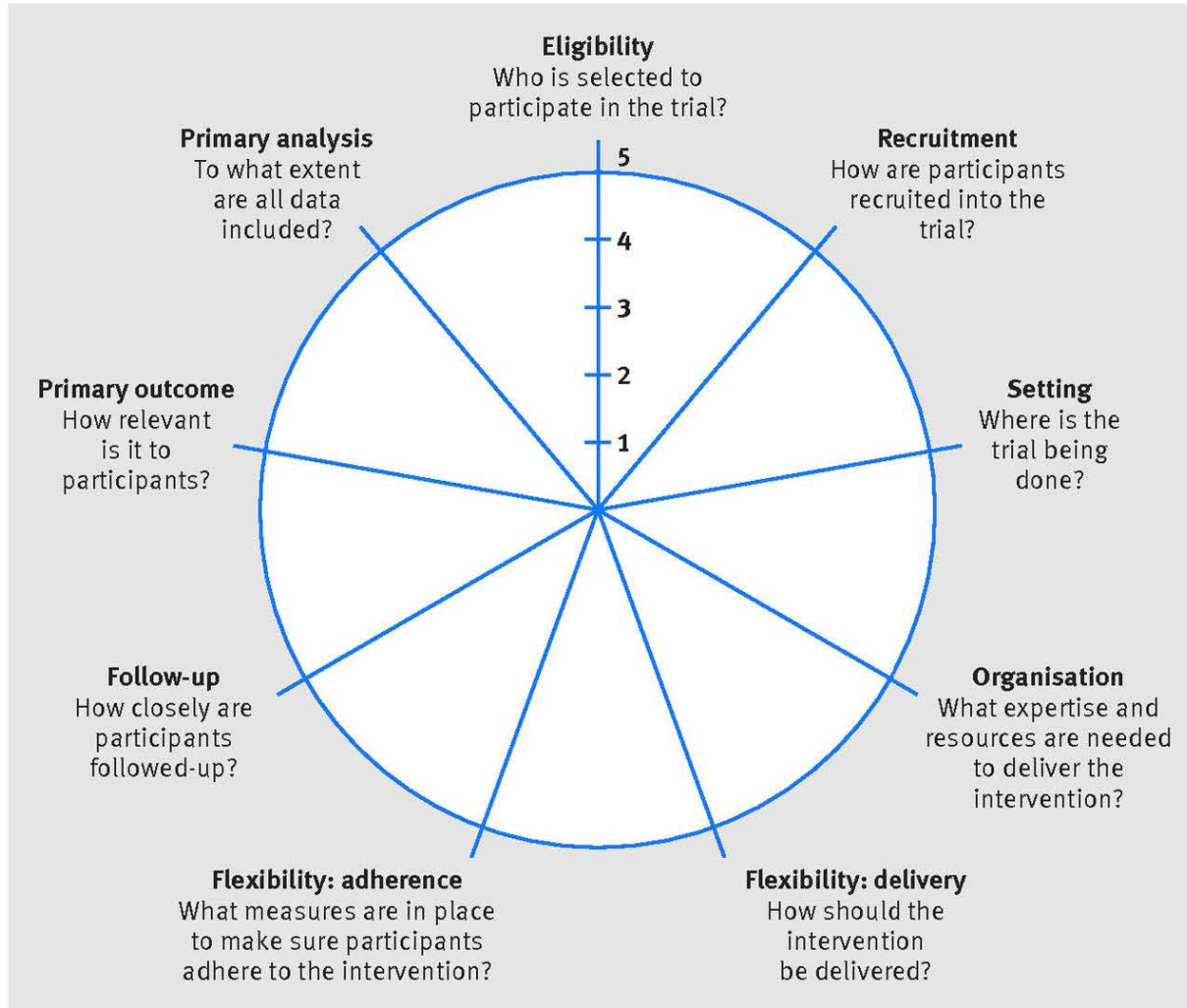
PRECIS-2 Domains

- *Eligibility*—To what extent are the participants in the trial similar to those who would receive this intervention if it was part of usual care?
- *Recruitment*—How much extra effort is made to recruit participants over and above what would be used in the usual care setting to engage with patients?
- *Setting*—How different are the settings of the trial from the usual care setting?
- *Organization*—How different are the resources, provider expertise, and the organization of care delivery in the intervention arm of the trial from those available in usual care?
- *Flexibility (delivery)*—How different is the flexibility in how the intervention is delivered and the flexibility anticipated in usual care?
- *Flexibility (adherence)*—How different is the flexibility in how participants are monitored and encouraged to adhere to the intervention from the flexibility anticipated in usual care?
- *Follow-up*—How different is the intensity of measurement and follow-up of participants in the trial from the typical follow-up in usual care?
- *Primary outcome*—To what extent is the trial's primary outcome directly relevant to participants?
- *Primary analysis*—To what extent are all data included in the analysis of the primary outcome?

PRECIS-2 Domains

- *Recruitment*—How much extra effort is made to recruit participants over and above what would be used in the usual care setting to engage with patients?
 - “Usual clinical encounter = Very Pragmatic”
- *Flexibility (delivery)*—How different is the flexibility in how the intervention is delivered and the flexibility anticipated in usual care?
 - “Identical to clinical care = Very pragmatic”
- *Flexibility (adherence)*—How different is the flexibility in how participants are monitored and encouraged to adhere to the intervention from the flexibility anticipated in usual care?
 - “Identical to clinical care = Very pragmatic”

PRagmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2)



Scoring criteria for each domain

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The first dilemma....

- The subject's written informed consent is typically an ethical and regulatory requirement of research.
- Research informed consent—many pages that conclude with lines for dated and timed signatures from the subject, researcher and, sometimes as well, witnesses—is quite distinct from clinical care.
- But...it seems not possible to both have informed consent and conduct the ePCT.
- A waiver or alteration of research informed consent seems therefore to be an essential part of the design of an ePCT.

The second dilemma...

- PLWD as a group are considered vulnerable because of their impaired decisional capacity, reliance on others and, for some, residence in a “total institution” (e.g. a nursing home).
- A dictum of research ethics is that vulnerable subjects need *additional* research protections.
- A waiver of research informed consent therefore seems, at least on its face, to upend this dictum.

The resolution

- Align the criteria that grade how pragmatic is a trial with the separate ethical and regulatory criteria that permit a modification or a waiver of research informed consent
 - Research design and research ethics are entwined
- Close attention is to regulatory criteria that describe...
 - Acceptable levels of research risk
 - The practicability of conducting the research with informed consent
 - Efforts to respect the rights and welfare of PLWD

Case 1: Detecting cognitive impairment in the ED

- *Research Question:* Does referral to a memory center after ED screening benefit persons with cognitive impairment?
- *Methods:* Test cognition in adults 65+ years who present to the ED. Persons who screen positive referred to the memory center after discharge.
- *Outcomes:* Referral successes.
- *Question to the Core:* Do we need to obtain written informed consent from the older adults?



Case 2. Light therapy for PLWD in a nursing home

- *Research Question:* Can light boxes in residents' rooms and common areas reduce agitation in PLWD in a NH?
- *Methods:* Install smart lights in some residents' bedrooms and in common areas (e.g., corridors, dining rooms and activity rooms)
- *Outcomes:* Pre- / post- light therapy measures of Behavioral and Psychological Symptoms of Dementia (BPSD) from all residents
- *Question to the Core:* Do we need to obtain written informed consent?



The Common Rule (45 CFR § 46.116)

In order for an IRB to waive or alter consent, the IRB must find and document that:

- (i) The research involves no more than minimal risk to the subjects;
- (ii) The research could not practicably be carried out without the waiver or alteration;
- (iii) If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
- (iv) The waiver or alteration will not adversely affect the subjects' rights and welfare;
- (v) Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

Pragmatic Goals and Criteria for Waivers

- Waivers of consent are often associated with ePCTs.
 - But the 5 criteria for consent waivers do not explicitly mention ePCTs; there is no presumption of a waiver of consent for conduct a PCT.
- The researcher has to justify a waiver of consent for their ePCT.
 - Even if consent can be waived for parts of a protocol, an IRB might still require consent for other parts of a study e.g., specific tests required for research purposes

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Step 1: What risks are part of the minimal risk assessment?

45 CFR § 46.111 Criteria for IRB approval of research.

(1) Risks to subjects are minimized:

- (i)** By using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk, and
- (ii)** Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research).

Step 2: What is “minimal risk”?

45 CFR § 46.102 Definitions for Purposes of this Policy

(j) *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Step 2: What is “minimal risk”?

- *Whose* daily life?
 - PLWD face high morbidity and poor quality of care.
- Given this high baseline risk, PLWD could be exposed to significant risks without exceeding “minimal risk.”
- Therefore, assess the risks the subjects face to the daily life of persons with comparable impairment living in a safe, high quality care setting to determine if “minimal risk.”
 - This “real and ideal” standard grounds the minimal risk standard in the lives of PLWD with an expectation that they receive appropriate care.

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- (v) Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

Practicability and PCTs

- The assessment should focus on whether requiring informed consent would make the research impracticable.
 - Focus is **not** that it is impracticable to obtain consent.
 - Practicability therefore should not be determined solely by consideration of cost, convenience, or speed of obtaining informed consent.
- Assessment should address:
 - Whether subjects declining to participate can result in a less representative study population, frustrating the pragmatic goal of a trial.
 - A trial whose required sample size is so large that including only data from subject who consent would prohibit conclusions to be drawn or bias the sample such that conclusions would be skewed.
 - The subjects for whom records would be reviewed are no longer followed and may be lost to follow-up.

Case 1: Detecting cognitive impairment in the ED

- *Research Question:* Does referral to a memory center after ED screening benefit persons with cognitive impairment?
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Case 1. Detecting cognitive impairment in older adults in the ED.

- *Not research risks:*
 - Cognitive testing is routine in the ED & so too is a clinician referral for a visit to a memory center
 - Time and travel to memory center is part of that clinical routine
 - Labels of cognitive impairment are stigmatizing, but the subject will decide whether to go to the center (clinical consent)
 - Tracking referrals is within scope of practice
- *The research risks:* data extraction
 - The data gathered and stored for research purposes is data routinely kept for older hospitalized adults and will be obtained from the EMR. This kind of a “data look and capture” ought to be part of good care of PLWD (would be a different risk assessment if identifiable data were being sent elsewhere).

Case 1. Detecting cognitive impairment in older adults in the ED.

- The practicability of informed consent to extract EMR data:
 - Most older adults come to the ED alone (if no capacity → no LAR).
 - Phone calls to family are not routinely successful.
 - Requiring consent will select for subjects who have an available family member, creating bias.
- The follow-up of outcomes of the memory center is an assessment of clinical care.

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- (iv) The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- (v) Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.**

- Information sheet given to the subjects with the referral paper work respects rights/interests.

Case 2. Light therapy for PLWD in a nursing home

- *Research Question:* Can light boxes in patient rooms and common areas reduce agitation in PLWD in a NH?
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Case 2. Light therapy for PLWD in a NH

- *There are “two kinds of subjects” here.*
 1. Residents whose room will have smart lighting installed
 2. Residents whose room won't smart lighting, but common areas they use will have lighting
- The intervention's risks are not uniformly distributed amongst these subjects.

Subjects whose rooms will be lit up

- *Not research risks:* capturing BPSD data
- *The research risks:*
 - Light therapy for residents on NH, but it is in equipoise with alternative Rx for BPSD
 - The added data collection for research is generally routine items and procedures of observation
- *Practicability:* You can talk to the resident or their family member.

The Common Rule (45 CFR § 46.116)

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- (iv) The waiver or alteration will not adversely affect the rights and welfare of the subjects;**
- (v) Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

- A room is a private space. Putting a light box in it without permission is intrusive.

Subjects whose rooms will be lit up

- *Conclusion:*

- Not all criteria for a waiver or alteration are satisfied.
- Informed consent is needed.

Subjects whose rooms won't be lit up

- *Not research risks:* capturing BPSD data
- *The research risks:*
 - Light therapy for residents on NH, but it is in equipoise with alternative Rx for BPSD
 - The added data collection for research is generally routine items and procedures of observation.
- *Rights and welfare:* A common area is a public space that individuals cannot control.
- *Practicably:* Alterations to public spaces typically don't require individual informed consent.
- *Additional info:* A notice can be sent to all families and posted in the facility.
- **CONCLUSION:** Meets criteria for a waiver of consent.

Informed consent in PLWD

- Never end a sentence with “capacity,” as in “Jason lacks capacity.” Instead, capacity precedes a proposition to do something.
 - e.g. “Does Jason have the capacity *to consent to have a light box in his room and data taken from his medical record?*”
- PLWD may have impaired capacity to consent to research.
 - Among the earliest disabilities are impairments in IADLs such as managing money and medications, using technology, traveling about.
 - Deciding whether to join a research study is a kind of IADL.
- If a PLWD has impaired capacity, you will need to ask a surrogate for consent.

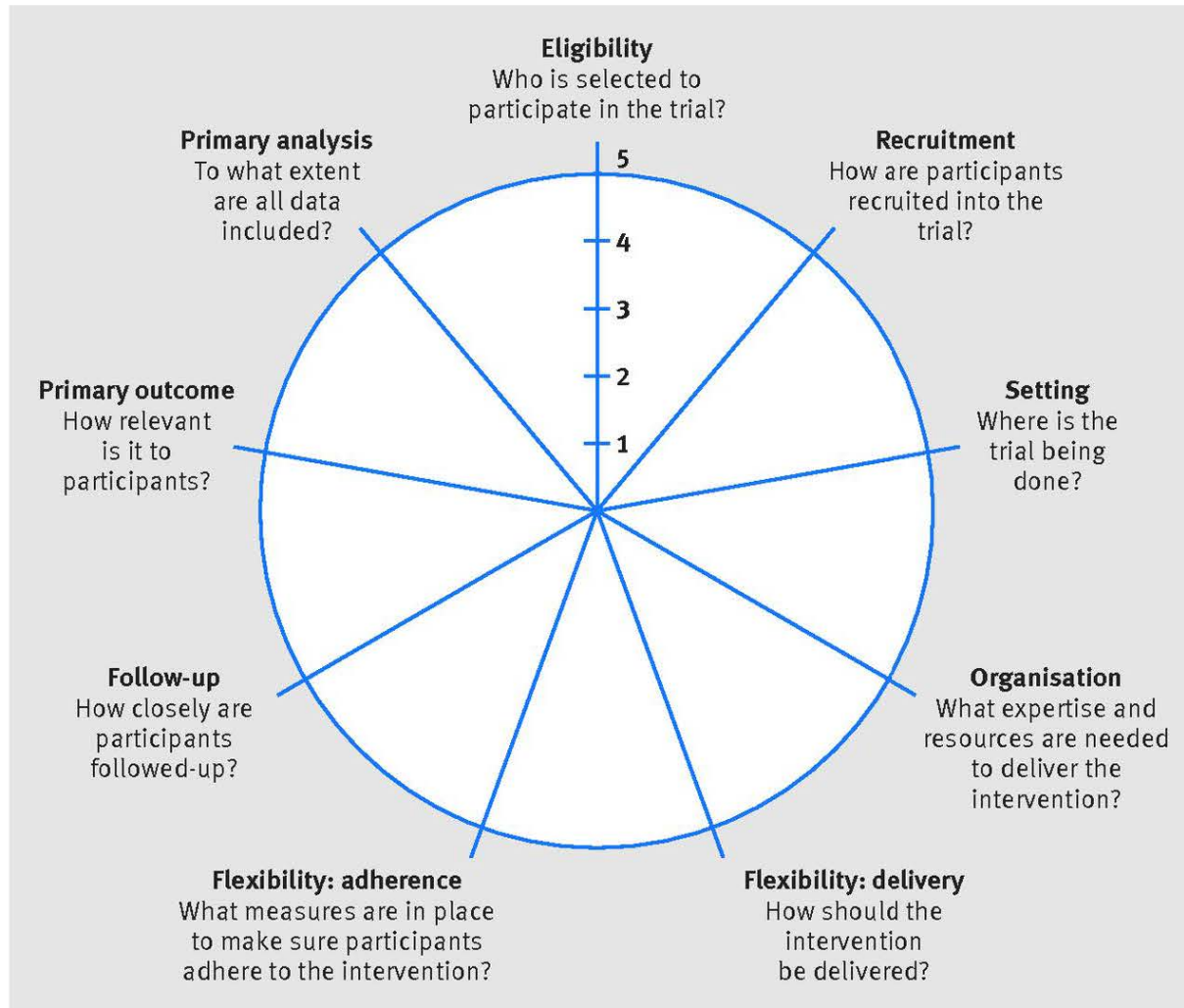
Informed consent in PLWD

- Write out a plan to assess prospective subjects' capacity to consent to the specific research study.
- List the core facts a person needs to know:
 - *This is research not regular medical care.*
 - *We will be looking at your medical record.*
- Use a conversation-based approach to assess understanding.
 - *"Is what we've been talking about research or regular medical care?"*
- Cognitive tests like the Mini Mental Status Exam (MMSE) are useful to predict the likelihood a person will have capacity—but they cannot substitute for an assessment of understanding.
- Seek assent and respect dissent in subjects who cannot give informed consent.

Expert ratings of capacity

		PD Normal Cognition	PD Borderline Cognition	PD Impaired Cognition	p=
Drug MacCAT:					
	Not Capable (Freq, %)	1 (3.3)	10 (33.3)	25 (83.3)	< 0.001
	Capable (Freq, %)	29 (96.7)	20 (66.7)	5 (16.7)	
Surgery MacCAT:					
	Not Capable (Freq, %)	5 (16.7)	13 (43.3)	29 (96.7)	< 0.001
	Capable (Freq, %)	25 (83.3)	17 (56.7)	1 (3.3)	

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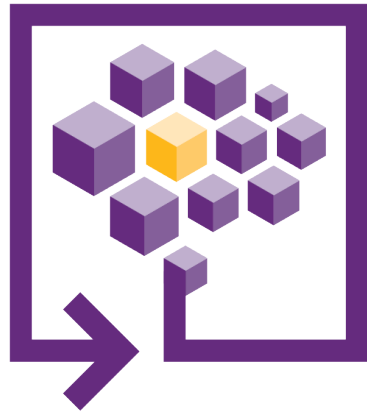


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Citations

- 45 CFR 46 – Protection of Human Subjects
- Scott Kim and Frank Miller. “Waivers and alterations to consent in pragmatic clinical trials: Respecting the principle of respect for persons.” IRB: Ethics and Human Research. January-February 2016, Vol 38, issue 1.
- January 31, 2008 SACHRP letter to HHS Secretary: Recommendations related to waiver of informed consent and interpretation of “minimal risk,” available at <https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2008-january-31-letter/index.html>



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Practicability and PCTs

- One concern: that argument is too general.
- Relevant Issue: can the study be altered to generate comparably valuable information without the need for a waiver?
- “The commonly accepted definitions of the term "practicable" are (a) feasible; (b) capable of being effected, done or put into practice; and (c) that may be practiced or performed; capable of being done or accomplished with available means or resources.”
SACHRP
- The emphasis being that it is impracticable to perform the research, and not just impracticable to obtain consent.
- Scientific validity would be compromised if consent was required
- The sample size required is so large (e.g., population-based studies, epidemiology trials) that including only those samples/records/data for which consent can be obtained would prohibit conclusions to be drawn or bias the sample such that conclusions would be skewed.
- The subjects for whom records would be reviewed are no longer followed and may be lost to follow-up.
- Ethical concerns would be raised if consent were required
- There is a risk of creating additional threats to privacy by having to link otherwise de-identified data with nominal identifiers in order to contact individuals to seek consent.
- There is a scientifically and ethically justifiable rationale why the research could not be conducted with a population from whom consent can be obtained.
- Practicability should not be determined solely by considerations of convenience, cost, or speed.