Ethical complexities in trials of vaccines

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Alliance Coordinating Office Advancing HIV Vaccines

Introduction

- Vaccine trials involve multiple ethical complexities

- Complexities stem from several features
  - International collaborative research (agencies from HIC and LRS)
  - Implemented in LRS with diverse cultural legacies
  - Multiple sites within and across host countries
  - Complex trial designs, stigmatized conditions
  - Vulnerable participants where factors (intra-individual, interpersonal or contextual) elevate research-risks or undermines consent
  - Variable review capacity , variable ethico-legal frameworks

- Ethical responses are being developed
  - Guidelines, frameworks, tools, empirical data

- Promoting rights and welfare while TPs contribute to social good

Issues

1. Ensuring sound informed consent
2. Addressing ancillary-care needs
3. Ensuring access to prevention tools
4. Paying participants
5. Avoiding coercion and undue inducement
6. Engaging stakeholders

- Placebo control – panel discussion

Ethical principles

- Respect for autonomy
  - Respect freedom of thought and action
  - Take special measures to protect vulnerable persons
- Beneficence
  - Minimize potential harms
  - Maximise potential benefits
- Justice
  - Ensure fair spread of burdens/ benefits among collaborators
  - Ensure those assuming burdens access benefits
- Respect for community

- Powerful yet abstract

- Always relevant yet application sensitive to context

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ENSURING SOUND INFORMED CONSENT

Consent

- How to achieve genuine informed consent?
- Addressed in key ethical guidelines (Helsinki 2013; UNAIDS 2012)
- Underpinned by respect for autonomy
- Comprises distinct elements (Levine 1986)
  - Capacity, voluntariness, disclosure, understanding, permission
- Factors complexifying consent (Kilama 2005; Gikonyo 2008; Lindegger 2000)
  - Low literacy
  - Linguistic barriers
  - Diverse cultural beliefs
  - Power imbalances
  - Historical exploitation, low trust
- 'widely valued, yet imperfectly realized' (Grady 2005)

Cont'd

- Consent as a 'pre-emptive legal strike in essentially hostile relationship' *versus* fostering decision-making (Lantos 1993)

- Recommendations (Gikonyo, 2008; Molyneux 2004; Lindegger 2000)
  - Mutual bilateral understanding *vs* unilateral transmission
  - Multi-method approaches *vs* consent form
  - Interpersonal strategies *vs* consent form
  - Prior community engagement *vs* investigator-driven
  - Evaluated implementation *vs* implementation

- Reviews of consent interventions (Flory 2004)
  - Extended discussion better then multi-media or enhanced forms

- Studies exploring assessment of understanding

Comparing ways of 'testing' understanding

Beyond the Checklist

Assessing Understanding for HIV Vaccine Trial Participation in South Africa

Graham Lindegger, PhD, Cecilia Milford, MSocSc,* Catherine Slack, MA,* Michael Quayle, MA,* Xolani Xaba, BSocSc (Honours),* and Eftyhia Vardas, BSc (Honours), MB BCh, DTM&H, DPH, FCPath, MMed†*

Objectives: Informed consent and understanding are essential ethical requirements for clinical trial participation. Traditional binary measures of understanding may be limited and not be the best measures of level of understanding. This study designed and compared 4 measures of understanding for potential participants being prepared for enrollment in South African HIV vaccine trials, using detailed operational scoring criteria.

Methods: Assessment of understanding of 7 key trial components was compared via self-report, checklist, vignettes, and narrative measures. Fifty-nine participants, including members of vaccine preparedness groups and 1 HIV vaccine trial, took part.

Results: There were significant differences across the measures for understanding of 5 components and for overall understanding. Highest scores were obtained on self-report and checklist measures

relevant information, there has been more recent recognition of the need to demonstrate participants' understanding[2] for adequate IC. Although many international ethical guidelines make little explicit reference to the need to test understanding,[3] this has been upheld as a core component of consent.[4,5] The HIV/AIDS Vaccines Ethics Group (HAVEG), part of the South African AIDS Vaccine Initiative (SAAVI), has been concerned with ensuring sound consent procedures (including assessment of understanding) for participants in HIV vaccine trials with particular reference to cultural sensitivity.

Assessment of understanding is potentially complicated. For example, some methods may test short-term recall of disclosed technical information. Although some degree of retention is probably a prerequisite for understanding, it cannot be equated with understanding.[6] In many studies investigators use forced-choice true-false (eg, right/wrong, agree/disagree)

Lindegger et al (2006)

Data on AOU

- Assessment of understanding (Lindegger 2006; Molyneux 2007)
  - Self report
  - Checklist ('quiz')
  - Scored responses to open-ended interviews

- Open-ended measures yield more conservative scores of understanding (Lindegger 2006)
  - Resource intensive
  - Reserve for the 'deal-breakers' e.g. preventive misconception

- What do we need more of…
  - What aspects of consent interactions promote understanding?

Practical recommendations for consent

- Get community inputs to inform consent methods
- Have innovative material to supplement consent forms
- Plan for repeated 'consent discussions' with participants
- Invest in trained consent staff
- Assess understanding in rigorous way
- Evaluate consent strategies
- Declare strategies in protocols submitted to IRB/REC
  - Sensitivity to vulnerability

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ADDRESSING ANCILLARY-CARE NEEDS

Ancillary care

- Responsibilities of sponsor/ investigators to implement responses to address needs in low-resource settings?
  - Where such responses are not required for the science or safety?
  - Where such steps are 'positive helping performances' (Richardson 2012)

- What needs? (MacQueen 2008; Participants 2008)
  - Conditions of interest to the study? (HIV in HVT, malaria in MVT)
  - Conditions of little interest but for which participants need care?

- Who? (Heise 2008)
  - Enrolled participants?
  - Screened but not enrolled?

- How far to go?
  - Slight sacrifice? (Merritt 2011)
  - More than that?

Cont'd

- Why?
  - Reciprocal justice (Macklin 2006); Stobie 2010)
  - Reducing inequities/ promoting social justice (Shapiro 2005)
  - Duty of rescue (cf. Merritt 2011)

- What about consequences of steps for participants but not for non-participants?
  - Introducing local inequalities? (cf. Slack 2005; HPTN 2009)
  - Inappropriate incentive? (Kilama 2005)

Guidance on ancillary care

- Addressed clearly in many ethical guidelines (UNAIDS 2007/12; UNAIDS/AVAC 2011; HPTN 2009)
- Addressed less clearly in others (CIOMS 2002, Helsinki 2008)
- Addressed in leading ethical frameworks (Richardson 2007; Richardson 2012)
- Partial entrustment framework:(Richardson 2007; Richardson 2012)
  - Focus on conditions identified by trial procedures ('entrusted')
    (of varying degrees of scientific import)
  - If certain factors are 'high' (e.g. gratitude for risks, and intensity of interaction) then researchers must take demanding steps
  - Steps should not be excessively costly (scupper budget/results)

The Ancillary-Care Responsibilities of Medical Researchers

An Ethical Framework for Thinking about the Clinical Care that Researchers Owe Their Subjects

by Henry S. Richardson and Leah Belsky

Researchers do not owe their subjects the same level of care that physicians owe patients, but they owe more than merely what the research protocol stipulates. In keeping with the dynamics of the relationship between researcher and subject, they have limited but substantive fiduciary obligations.

Malaria researchers may detect that their juvenile subjects are suffering from schistosomiasis, a serious parasitic disease common in many malarial areas. Do the researchers have a re-

Providing guidance requires confronting some very basic questions about the relationship between researcher and subject. What sort of care, if any, ought medical researchers provide their subjects, be-

Four P's

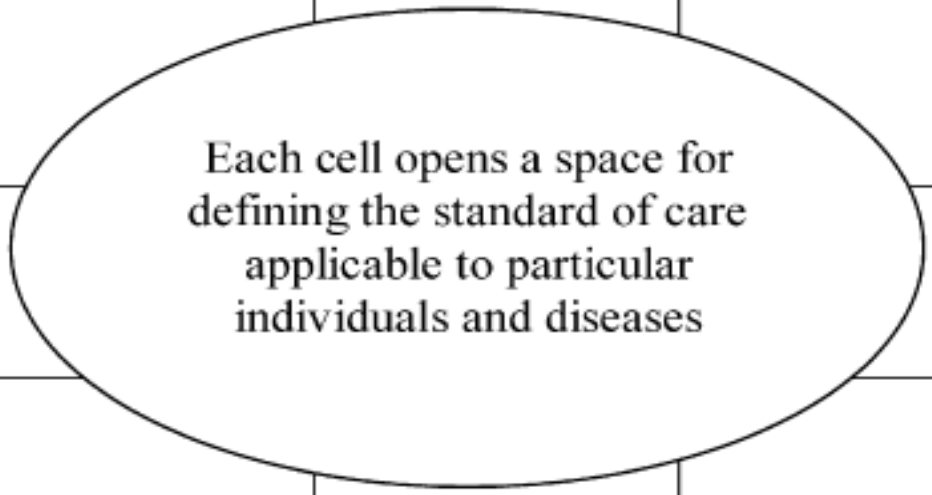
- Addressed in popular accounts (Participants 2008)
  - Recognise positive duty
  - Plan
  - Take pragmatic steps
  - Partner

- Planning is 'chief operational upshot' of ancillary care (Merritt 2011)

- Planning for 'extra-scientific' responses or helping responses (Merritt 2011)

Table 1
Defining standard of care for specific populations and diseases

Populations in the community hosting the trial	**Type of care for consideration**		
	Diseases specifically targeted by the vaccine being studied	Diseases diagnosed as part of the trial design	Diseases unrelated to the purpose of the trial
Trial participants			
Trial participants with severe conditions detected during the trial that are not specifically targeted by the vaccine being tested			
Individuals considered for enrolment but excluded as a result of pre-enrolment screening			
Other persons linked to trial participants, but not considered for enrolment in the trial, (e.g. family members or sexual partners)			
Other members of the community hosting the trial			



Data on ancillary care

- Empirical data is increasingly available for
  - Ancillary care practices
  - Perspectives

- Explorations been conducted for
  - Microbicide trials (Clouse 2010; Heise 2008, MacQueen 2006, 2008)
  - HIV prevention trials (Ngongo 2012)
  - Malaria trials (Pratt 2013)
  - Public health research (Taylor 2011)
  - HIV vaccine trials (Slack 2014)

- Findings
  - Many research staff take 'extra-scientific' steps
  - Research staff hold they have some limited AC responsibilities
  - Research staff view AC as indirectly promoting science
  - Recognized as participant motivator

Practical recommendations for ancillary care

- Consider needs likely to be encountered
- Consider spectrum of possible responses to address needs
  - Onsite provision, referral, 'assisted referral', capacity-building
- Consider resources to offset 'costs' of responses
  - Funding, onsite resources (staff, time), co-located care, care partners
- Where referring, engage referral partners early (MacQueen 2006,2008)
- Consult community representatives about plans
- Describe plans in protocols, get IRB input
  - 'Meeting of the minds' (Tarantola 2007)
- Distinguish between scientific *vs* helping responses in consent
  - Minimize 'therapeutic misconception' (Appelbaum 1987; HPTN 2009)
- Assess ancillary-care approach

Partnering for Care in HIV Prevention Trials: A How-To Manual

3

ENSURING ACCESS TO PREVENTION TOOLS

Access to prevention modalities

- Vaccine trials enroll 'healthy' volunteers but at-risk of acquiring condition (late-phase studies)
- Responsibilities of sponsor-investigators to ensure access to prevention modalities/ services to *prevent* acquisition?
  - Bednets, indoor spraying in MVT
  - Counselling, condoms, VMMC, PEP in HVT
- So-called 'standard of prevention'
- Accentuated when condition is incurable, stigmatized

Issues

- Has modality reached threshold of 'scientifically proven' for specific population? (Heise 2008)

- Has the modality been approved by authorities, where necessary? (Heise 2008)

- What responses will be implemented to ensure access?
  - Inform
  - Refer
  - Provide directly
  - Monitor uptake

- How will uptake affect incidence rates? power of trial to detect effect? (Kilama 2005; UNAIDS 2012)
  - Bigger, longer, expensive, results harder to interpret

- Is higher standard an (in)appropriate inducement? (cf. Macklin 1981)

Recommendations

- Provide high standard of prevention (UNAIDS 2012)
- Consider threshold for 'validation' and relevant authorities (Jay 2013; Dawson 2012)
- Do projections related to adding tools to prevention toolbox
  - Reductions in incidence, increased enrolments, increased time
  - Consider how 'costs' can be borne (Heise 2008).
- Get stakeholder inputs and reach agreement (Heise 2008; UNAIDS 2012)
- Set out efforts to engage stakeholders for IRB to review
- Set out 'prevention package' for IRB to review

4

PAYING PARTICIPANTS

PAYMENT

–City Press: 4 Feb 2007

Medical research trial guinea pigs contract HIV

WONDER HLONGWA

THE Medical Research Council (MRC) this week began a frantic search for more than 600 people, amid fears that the gel they were testing as a preventive measure against contracting HIV, was in fact increasing the risk of infection.

Hundreds of women in South Africa, Benin, Nigeria, Uganda and India, who are being used as human guinea pigs in the US-funded research on HIV prevention, are feared to have contracted the virus during the course of the trials.

City Press spoke to two women who were HIV-negative before using the microbicides and are now positive.

They are bitter, feel used and misled and are now dealing with their HIV-positive status.

This week, Conrad, a US-based reproductive research group funding the study in four African countries and in India, called off its clinical trials on women saying it "could lead to an increased risk of HIV infection".

MRC's HIV Prevention Research Unit (HPRU) has dispatched its staff to call on participants to return samples of the gel.

"There are messages to as many as possible to come and give us back the gel. We have contacted several hundreds of them. Over the next month we plan to see every single one of those patients," said HPRU principal investigator Roshini Govinden.

The study focused on a microbicide gel known as Usherceil that is manufactured by Polydex, a Canadian pharmaceutical company.

hope that it could prevent them from contracting HIV.

City Press understands that in townships around Durban some of the participants have been selling the gel to their peers saying it prevents HIV/Aids, raising fears that more people could be infected.

"It's scary because I know some participants have been selling it as a cure for Aids in townships. They sell it for R5," said one MRC member, who recruited the participants.

When City Press visited one site at Hlabisa, participants claimed that some of the researchers who recruited them said the gel would make them hot in bed.

"When I first applied it, my boyfriend asked me why I was so luscious that night. Then I told him I had applied the gel and he loves it," said one of the women, who cannot be named to protect her identity.

Some of the participants in the remote rural village of Hlabisa in northern KwaZulu-Natal said they were still using the gel and had not heard of the new developments.

Participants are paid R150 a month for transport to and from the research sites and are told that if they contract HIV during the research, the sponsors of the research will look after them.

MaNgidi Sithole, a community leader in Hlabisa, said people allow themselves to be used as guinea pigs because of poverty.

"People are hungry and illiterate. If there is something that promises money they are prepared to participate because it will better their lives, no matter how little the money is," she said.

reproductive healthcare, was testing a gel known as Usher-cell which was to prevent women from being infected.

"My friends used to tell me that it makes you hot in bed. They said my boyfriend will enjoy sex when I apply it. But I was also attracted by the money you get when you are in the study," said Mthethwa.

When trials were called off this week, the gel was in phase three clinical trials – the last phase of drug testing on humans before approval for marketing. The study has become a money-making scheme for some young women in Durban.

Zama Ncwane from Umlazi in Durban said she had registered in three of the MRC sites using three different names.

Each of the participants is paid R150 a month.

An unemployed Ncwane said she was recruited by her friends who told her about this easy way of making money.

"We were told (by recruiters) to visit drinking spots where there are many people and make ourselves available when men approach us.

"We would sleep with these people without a condom and

Medical r

■ From Page 1

are taken to review HIV/Aids research, South Africa could continue to be a playing ground for scientists using people as human guinea pigs in the search for the elusive HIV/Aids cure.

Last year, research on a spermicide known as NonOxynol-9 or N9 had to be called off when a number of women participating in the trial reportedly contracted the HI-virus.

Health Minister Manto Tsha-

-Each participant is paid R150 a month

Debate

- May commercialize an altruistic endeavor (McNeill 1997)
  - Research is commercialized for many stakeholders
- May disproportionately attract the poor (Grady 2005)
  - Reducing payments may deter better-off volunteers
- May influences TPs to be dishonest (Grady 2005)
  - Objective criteria *vs* self-report
- May acts as 'undue inducement' (Grady 2004,5)
  - Offer
  - Excessive (Belmont Report 1979)
  - Distorts decision-making or impairs judgment (IRB Guide-book; CIOMS, 2002)
  - Not merely offer that changes behaviour

Types of payment (Wendler 2002)

- Reimbursement payments – refunds for direct costs
- Compensation payments – offset burdens
  - Time, inconvenience
- Payment may
  - Facilitate recruitment
  - Reduces financial obstacles to participation
  - Acknowledge contribution
- Need for empirical data on acceptability of various types

Guidelines endorse 'reimbursement' and 'compensation' payment

CIOMS (2002)	Guideline 7: Inducement to participate	Participants may be reimbursed for lost earnings, travel costs and other research-related expenses. Participants may be compensated for time and inconvenience.
FDA (1998) Information Sheets: Guidance for Institutional Review Boards and Clinical investigators	Payment to research subjects	Incentive payments and completion bonuses are acceptable
OHRP Guidelines (IRB Handbook) Chapter 3 & 4	Section G: Incentives Section I: Identification and recruitment of subjects	Re-imbursement for travel, babysitting etc may be provided. Volunteers are compensated according to the type and number of procedures, anticipated inconvenience, and the time involved. Payment should reflect the degree of inconvenience associated with participation
UNAIDS (2007) Ethical considerations in biomedical prevention trials	Guidance point 12: Benefits	Participants should receive reimbursement for travel and other expenses related to participation. In recognition of time and inconvenience, the appropriate levels of (and forms) the incentives take will depend on socio-economic context.

Wage Payment model (Grady 2005)

- Reimbursement payments for expenses
  - Travel, parking, meals
  - Often considered a 'due' inducement (Macklin 1981)

- Compensation payments for time
  - Calculate at an hourly rate
  - Commensurate with other essential but unskilled jobs

- Additional payments for inconvenience
  - For procedures that are bothersome

- Advantages
  - Ps can find other opportunities (similar skill, similar amount)
  - Modest amounts
  - Lessens concerns of undue inducement

5

ADDRESSING COERCION OR UNDUE INDUCEMENT

Coercion

- Not a decision made under a set of bad circumstances; under limited options; in the presence of a strong influence
- Is a decision made under threat of negative sanction (Hawkins 2005)
- A wants B to do X. If B does not do X, then A will make B worse off than B was before the interaction
  - Clinic staff member says 'unless you enroll, no care'
- Solution to coercion? Address the threat
- Perceptions that refusal will lead to sanction (Gikonyo 2008; Molyneux 2004/5)
- Offers (medical/ financial) are not coercive, even while ethically complex

Recommendations

- Limit offers in an ethically justifiable manner
  - Carefully consider/ defend care for certain conditions
  - Carefully consider/ defend payment amounts and schedules
- Assess motivations of participants
  - Inquire, consider external influences, impact (Appelbaum, 2009)
- Improve understanding of research risks
  - Strengthen consent strategies so risks not discounted, devalued
- Reduce risks of trial procedures to acceptable level
  - Consult community representatives
  - Seek IRB inputs
  - Seek 'expert determination' that risks are reasonable
- Respect and balance ethical principles
  - Not only respect for autonomy
  - Non-exploitative research transactions *vs* undue inducement

'If you are a hammer, everything looks like nail. If you are a North American bioethicist, everything looks like a problem of informed consent' (Lemmons 2001)

- RECs expected to determine what is undue inducement
- RECs should be expected to determine what is fair

6

ENGAGING STAKEHOLDERS

'Community' Engagement

- How can various 'communities' be authentically involved?

- 'Community'?
  - Geography → shared values/interests/problems
  - Participating community → various 'communities'/'stakeholders' (IRBs, regulator, media, civil society/ advocates, policy-makers)

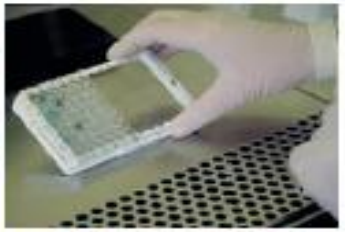
- 'Engagement'? (Marsh 2005; UNAIDS-AVAC 2007, 2011)
  - Implicates a range of actions
  - Providing info → seeking agreement on decisions → sharing power
  - Various structures (CABs, SAMs) (Marsh 2005; UNAIDS-AVAC GPP 2007, 2011)

- Underpinned by principle of 'respect for communities'

Guidance

- Stakeholder engagement improves ethics
  - Increase research quality
  - Increase acceptability
  - Identify risks hidden from researchers (e.g. HVTs & lobola) (Dickert 2005)
  - Identify benefits congruent with community priorities
  - Reduce vulnerabilities
  - Help communicate complex concepts
- Addressed in most major ethical guidelines (CIOMS 2002; UNAIDS 2007/12)
- Also in dedicated guidelines on the topic (UNAIDS/AVAC GPP 2011)

Good participatory practice
guidelines for biomedical HIV prevention trials



UNAIDS

AVAC

What stakeholder engagement is not

- Its not only about recruitment
- Its not only about the participating community
- Its not only about having a Community Advisory Board
- Its not only about one trial
- Its not 'nice to have'

Adapted from M Warren (HTVN Full Group Meeting, 2013)

Data

…it seems curious that we invest millions of dollars in product development, clinical training, design and building of facilities, etc, but often leave vital processes of community engagement largely to trial and error… (Newman 2006)

- More data needed to explore key aspects of engagement and inform a 'science of engagement' (Newman 2006)

- Various approaches being shared (Molyneux 2004/5; MacQueen 2006, Valley 2009; Woodsong, 2005)

Practical recommendations for SE

- Conceptualize key stakeholders
- Consider how ethical goals can be strengthened
- Link ethical goals to strategies and stakeholders
  - Respectful entry? Seek permission from community leaders
  - Ongoing forum for managing concerns? Build dedicated structure
- Get IRB input on engagement plans
- Try get engagement funded
- Assess how engagement is being implemented
- Note investment is 'anesthetic' for negative results (Essack 2010)
- Make use of existing tools (UNAIDS/AVAC GPP 2012)

Stakeholder Engagement Toolkit

for HIV Prevention Trials

by Kathleen M. MacQueen, Sarah V. Harlan,
Katie West Slevin, Stacey Hannah,
Emily Bass and Jill Moffett

Communications Handbook for Clinical Trials

Strategies, tips, and tools to manage controversy, convey your message, and disseminate results

By
Elizabeth T. Robinson

Placebo control permissible when no safe and effective vaccine (UNAIDS 2012) or no established effective intervention (EEI) exists (CIOMS 2002)

- Permissible when effective vaccine/ intervention exists when
  - Needs compelling justification (CIOMS 2002)
  - Efficacy demonstrated against *particular viral strain* and vaccine may not be effective against virus prevalent in study population (UNAIDS 2012)
  - Efficacy demonstrated for *particular population* and biological conditions prevailing in original study can't be applied to study population (UNAIDS 2012)
  - Data collected under circumstances unlike those of the study pop (CIOMS 2002)
  - Results yielded would not be scientifically reliable (CIOMS 2002)
  - Participants exposed to temporary discomfort, no serious or irreversible harm, no serious adverse consequences (CIOMS 2002)
  - Both arms must receive preventive interventions (UNAIDS 2012)
  - Intervention intended for use in a country/ community where an EEI is not available (and unlikely to become so), is responsive/ relevant to the health needs/ problems of the population (CIOMS 2002)

Conclusion

- Vaccine trials raise number of complex ethical concerns
- Ethical direction available in range of resources
  - Principles, guidelines, frameworks/ models/ tools and empirical data
- Ethical concerns and resources cut across disease entities (Mamotte 2010)
- Develop disseminate well-reasoned, data-supported responses
- Disseminate these to improve protections for participants
- Case study

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Case Study – role play

- Read the case (aloud?) in your groups (5-10 mins)
- Choose either (1) researcher/sponsor; (2) IRB or (3) activist

1. Cluster in those groups + plan your position (30 mins)
2. Come together for a debate chaired by REC chair (30 mins)
3. All decide on ethical standards (30 mins)

- Write up brief (2page) record on the decisions (10 mins?)
- Place in BOX at rear of this room as soon as possible
- Record which group you are
- Summary is Monday morning
- *Remember all case studies have missing information. You will have to make assumptions. Make the assumptions explicit*

Key terms

- Ancillary care – steps to address medical needs that are 'extra-scientific' in nature/ form no part of scientific protocol; not required for safety; nor injury

- Coercion – direct threat of negative sanction

- Undue inducement – offered good excessive enough to distort processing of risks/ distort judgment

- Vulnerability – characteristics (intra/interpersonal or contextual that undermine consent or elevate risk of research related harm)