Benefits in research: How should we think about and communicate them?

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These are my views and do not represent the position or policy of the NIH, DHHS, or US government.

Benefits

Objectives for this session:

1. Describe regulatory guidance regarding benefits
2. Distinguish different types of benefits
3. Consider what goes into determining a prospect of benefit
4. Discuss communicating benefits to participants

Research risks and benefits

- Assessing potential benefits and risks of harm is essential to scientific and ethical evaluation of clinical research
  - To determine whether the study has social value and scientific validity
  - To protect participants by minimizing and justifying risks
  - To facilitate informed choice by participants

King N and Churchill L. Assessing and Comparing Potential Benefits and Risks of Harm. Oxford Textbook 2008

Research benefits

Potential benefits are assessed in relation to risks of harm

- Yet, especially when compared to the attention paid to risk
- Little guidance regarding benefits
- Less attention to benefits in IRB discussions, on consent forms
- Limited theoretical or practical work
- Some disagreement and confusion about benefits

Regulatory language-research benefits

Criteria for IRB approval of research. IRB must determine that

1. Risks to subjects are minimized…

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…

3. Selection of subjects is equitable.

45CFR.§46.111(a); 21CFR.§56.111(a)

Regulatory language- research benefits

General requirements for informed consent. (b) Basic elements of informed consent…in seeking informed consent the following information shall be provided to each subject or the legally authorized representative:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental;

(2) A description of any reasonably foreseeable risks or discomforts to the subject;

(3) A **description of any benefits to the subject or to others** that may reasonably be expected from the research

(4) …

45.CFR.§46.116; 21CFR.§50.25

Benefit (noun)

Something that is advantageous or good; an advantage

- a payment or gift, as one made to help someone or given by an employer, an insurance company, or a public agency; a theatrical performance or other public entertainment to raise money for a charitable organization or cause; *Archaic*. an act of kindness; good deed; benefaction. https://www.dictionary.com/browse/benefit

A valued or desired outcome; an advantage.

IRB Guidebook 1993 http://wayback.archive-it.org/org-745/20150930182812/http://www.hhs.gov/ohrp/archive/irb/irb_chapter3.htm

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. The Belmont Report. https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html

Distinctions

- Social value (benefit) vs. individual benefit
- Clinical benefits vs. research benefits
- Direct benefit vs. indirect benefit

Social value (benefit) vs. individual benefit

IRBs consider both when comparing benefits to risks

Risks reasonable in relation to

1) **anticipated benefits, if any, to subjects, and**
2) **the importance of the knowledge that may reasonably be expected to result…** 45CFR.§46.111(a); 21CFR.§56.111(a)

Social value, benefit to future patients or society, important/valuable even if negative findings

Societal Benefits beyond individual benefits

- the importance of the knowledge that may reasonably be expected to result (US Regs)
- necessity of producing "fruitful results for the good of society" (Nuremberg)
- "Medical research … only …if the importance of the objective outweighs the risks and burdens to the research subjects". (Declaration of Helsinki).
- "The ethical justification for [human] health-related research is its scientific and social value: the prospect of generating the knowledge and the means necessary to protect and promote people's health". (CIOMS, guideline 1)
- Social value- "..the evaluation of a treatment, intervention, or theory that could improve human health and well-being or increase knowledge" (Emanuel et al)

Justification

- Difficult to justify exposing humans to risk or inconvenience or expending resources if the knowledge expected to result has no value or is not important (Emanuel et al. 2000; Casarett et al.2002; CIOMS 2016; Shah & Rid 2017; Wendler & Rid 2017, others)

Debated Questions

- Identifying and quantifying. How important? How much social value?
  - Sufficient, significant, comparative, any?
- When prospect of individual benefit is low or non-existent?
- How judged?
- Knowledge important to whom? Who are the beneficiaries?
- Exploitation?

Clinical benefits vs. research benefits

Which benefits to count when determining the reasonableness of risks?

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**)..

45CFR.§46.111(a); 21CFR.§56.111(a)

Clinical benefits vs. research benefits

- Important in decisions about minimizing and justifying risks and assessing risk/benefit
  - Consideration of existing alternatives
  - Comparison to a baseline (potential benefits and risks beyond those in clinical care)
- Important in participant understanding of research,
  - E.g. reducing possible therapeutic misconception, other misunderstandings

Direct benefit vs indirect benefit

- Categories of individual benefit
- Direct vs. Indirect (ancillary, secondary, inclusion, add-on, collateral).
- Why is this distinction important?
  - Standard view- in approving research, judge reasonableness of risks compared to *direct* benefits to individual and social value
  - Prospect of *direct* benefit required to justify greater than minimal risk research for certain groups (US regs, ICH, CIOMS, other)

What kind of benefits count?

- …. *Many kinds of possible harms and benefits need to be taken into account*…for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. (Belmont)

- Why do we count many kinds of risks but not many kinds of benefits? (Wendler)

Direct benefit vs indirect benefit

- **Direct**- arising from the intervention being studied (King 2000); clinical benefits that stem from research interventions themselves (NBAC 1998)

  Benefits that result also from interventions needed for scientific reasons to test the intervention. (Friedman et al. 2012)

- **Indirect, inclusion**- "benefits that result from participating in a study regardless of whether participant receives experimental intervention" (King and Churchill 2008; Rennie et al 2019, Wendler 2020)
  - e.g. increased knowledge, psychological benefit, solidarity with others, relationships, sense of purpose, life skills, self esteem, access to medical care, ancillary care, payment, etc.

Arguments against counting inclusion benefits in ethics review

1. Investigators could justify any level of risk by increasing or layering on inclusion benefits; could also unduly influence participants esp. those with limited access
2. Inclusion benefits could create an unjust division between care being provided within and outside of a study (hold out high quality care as a quid pro quo for participating)
3. Experience of inclusion benefits is subjective and variable, and likely influenced by background conditions

King and Churchill 2008

Other views

- But these matter to participants- perceive many non-direct benefits (and risks) as important and often motivating reasons
- “Some commentators argue that reviewers should factor the potential economic, social, or psychological benefits participants might realize during the study—for example, payment, praise, or feelings of altruism—in the risk-benefit calculus for a study” (Sachs 2010; Wertheimer 2010; Jansen 2009, Rid and Wendler 2011).
- Inclusion benefits should sometimes play a role in ethical evaluation of research studies (Bernabe et al. 2012; Rennie et al. 2019)
- Community and participant engagement

Recent example

Check for updates **comment**

Ethical considerations of COVID-19-related adjustments to clinical research

Unexpected direct and indirect risks of participating in clinical trials have emerged during COVID-19 that investigators and institutional review boards may not be sure how to investigate. How should existing guidance and ethical frameworks for clinical trials be applied in a pandemic setting?

Nina S. Hsu, Saskia Hendriks, Khara M. Ramos and Christine Grady

The COVID-19 pandemic continues to affect clinical research considerably, forcing policymakers and institutions to make difficult decisions about delaying, continuing and starting research while protecting public health. Delaying research can affect its social value and possible benefits for participants. As clinical studies re-start — and for those that never halted — most investigators have to adjust their procedures and protocols to protect participants, staff and public health and to adhere to institutional COVID-19 policies. Both the US National Institutes of Health (NIH) and the US Food and Drug Administration (FDA) have endorsed the need for such adjustments[1,2], which may include tele-visits instead of in-person visits, reducing visit frequency, and restricting how many staff members interact with participants. Some of these changes may affect ethically meaningful trial elements, such as risks and benefits for participants, or the trial's social value[3,4].

We learned from investigators and bioethicists during two meetings organized by the NIH BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative[5,6] that these procedural or protocol changes raise some key ethical challenges investigators face due to COVID-19.

First, the pandemic introduces a new risk: possible contraction of COVID-19 during participation in a study. The pandemic also affects certain benefits and risks that are not always considered, including the value of socialization with research staff, for socially isolated participants. How should investigators navigate these altered benefits and risks?

Second, what should investigators do if they anticipate that COVID-19-related changes may substantially impact their study's ethically salient elements, such as the risk–benefit profile? Although the experiences of neurotechnology researchers provided the basis for this Comment, we anticipate, on the basis of reports from other fields[3,4], that these challenges are more broadly relevant in clinical research.

In this Comment, we consider these ethical questions in the context of existing ethical frameworks and provide points for investigators and institutional review boards (IRBs) to consider in navigating these challenges. Finally, we reflect on how these considerations may facilitate clinical research preparedness for future pandemics.

Changes that affect indirect risks and benefits

Some investigators reported that healthy volunteers are increasingly interested in paid study enrollment, potentially due to pandemic-induced financial hardships. Other investigators reported concerns about their socially isolated participants' mental health, as home visits by the study team were curbed to reduce the risk of SARS-CoV-2 transmission. Some investigators described the challenges of remote care for participants who lack access to certain technologies or are uncomfortable with using them[7]. Finally, some investigators recounted that participants requested early release from extended hospital admissions because of COVID-19 restrictions on visitors. These benefits (payment and social contact) or risks (isolation and infection risk) may matter to participants, but how should investigators navigate them?

Bioethicists describe these types of research benefits and risks as 'indirect' or 'collateral': those that arise from participation in a study but are not linked to the study intervention or procedures[8–10]. Other examples of collateral risks and benefits include payment for parking, complementary medical care, or the gratification of contributing to science.

Although this recommendation is sometimes challenged[11–14], bioethics guidance suggests that indirect benefits not be included in an IRB's risk–benefit evaluation, because indirect benefits might distort the risk–benefit profile, which would allow the conduction of trials with highly unfavorable clinical risk–benefit profiles for participants[10,15]. Similarly, IRBs scrutinize how indirect benefits are described in informed-consent documents, to prevent undue influence on patients to enroll against their best interests[11].

While limited bioethics guidance addresses indirect risks, including indirect risks but not indirect benefits in the risk–benefit analysis may skew this evaluation. In our experience, indirect risks (like indirect benefits) are therefore generally not included in an IRB's risk–benefit evaluation. In these COVID-19 cases, adhering to these general guidance and practices seems reasonable, such that neither IRBs nor investigators need to include indirect benefits or risks in evaluating study acceptability or reflect them in the research study's informed-consent process.

Nonetheless, indirect risks and benefits can influence participants' decision-making about study participation[11]. Investigators may consider minor adaptations to study procedures to optimize indirect benefits or mitigate risks that may be meaningful for participants (e.g., offering resources for psychosocial support)[9]. Even if it is not part of the informed-consent process, investigators might discuss new or changing indirect risks and benefits with their participants.

Most trials at present will entail a new risk for participants: exposure to COVID-19 during engagement in research-related activities (e.g., clinic visits). This risk is 'new' because COVID-19 is new, but is not unique because exposure to infectious diseases (e.g., influenza) has always been a risk of visiting hospitals and public spaces.

We suggest that in general, exposure to COVID-19 is an indirect research risk, as it is not specifically linked to the intervention under study. Therefore, consistent with the consideration of other indirect risks and benefits, IRBs do not need to incorporate this risk in assessing whether a study's

Some of the COVID-related changes in clinical trial procedures or protocols could affect ethically meaningful trial elements. Including:

-Risks and potential benefits for participants

-The trial's social value

Assessing benefits

- The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research.

- For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate. (Belmont)

Assessing Benefit (and risk)

- Likelihood (probabilities) and magnitudes of possible harm and anticipated benefits
- Component analysis- evaluate each intervention to ensure risks are minimized and justified. (Natl Commission)
- Component analysis avoids the “Fallacy of the package deal”; potential benefits of one intervention cannot offset or justify risks of another. (Friedman 2012, Levine 1999)
- Procedures cannot be added on unless risks assessed in relation to possible benefits

A proposed modified approach

- Potential benefits of experimental intervention plus potential benefits of any procedures/interventions needed to test the experimental intervention (administration and evaluation) (Friedman et al 2012)

- Compare sum of benefits of all scientifically necessary interventions to sum of risks of all scientifically necessary interventions

- Precludes adding unnecessary procedures nor additional benefits to offset risks

Framework for risk benefit assessment

Step
Ensure and enhance social value
Identify research interventions
Evaluate and reduce risk to participants
Evaluate and enhance benefits
Evaluate whether the interventions pose net risk
Evaluate whether net risks are justified by potential benefits of other interventions
Evaluate whether remaining net risks are justified by social value

Rid A; Wendler D (2011). A framework for risk-benefit evaluations in biomedical research. Kennedy Institute of Ethics Journal, 21(2):141-179. DOI: https://doi.org/10.1353/ken.2011.0007

Enhancing (maximizing) benefit

- Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms. (Belmont)

- Enhancing value and enhancing individual benefit
- Enhancing value-
  - Careful design and rigor
  - Sharing data
  - Future research

Enhancing individual benefit

- How do we enhance or maximize individual benefits?
  - inclusion and exclusion criteria: target people who need treatment
  - choice of design and control
  - add ons- e.g. counselling, ancillary care, palliative care
  - post trial plans

Determining Prospect of benefit

- Prospect= the possibility or likelihood of some future event occurring

<table>
<tr><th></th><th>Minimal Risk (MR)</th><th>Minor Increase over MR</th><th>More than Minor Increase over MR</th></tr>
<tr><td>Prospect ‘Direct’ Benefit</td><td rowspan="2"><u>46.404</u>
Approvable by IRB for all children</td><td colspan="2"><u>46.405</u>
Approvable by IRB if prospect of ‘direct’ benefit justifies risks</td></tr>
<tr><td>NO Prospect ‘Direct’ Benefit</td><td><u>46.406</u>
Approvable by IRB if research concerns subject’s condition</td><td><u>46.407</u>
Approvable only by Government Panel*</td></tr>
</table>

*Special panel is being convened to decide whether the research is appropriate; if the pane agrees, the research will then be approved by top officials in the federal government.

Bitan et al. Determination of Eligibility in Related Pediatric Hematopoietic Cell Donors. 2016

Prospect of direct benefit

- Direct benefit is a tangible positive outcome that may be experienced by the subject and is a result of the research intervention or procedure.

- In studies of a new therapy, typically the benefit of the investigational agent is the possible amelioration of the disease or its symptoms. However, in a natural history study, research procedures generally do not have therapeutic intent, and therefore may not offer *the prospect of direct benefit* to the subject.

- For example, if the protocol requires a CT scan every 6 months, and the only use of that scan is to collect research endpoint data (e.g., size of a lesion etc.), then the scan does not have prospect of direct benefit for the subject. However, if the results of the CT scan are used in a way that is likely to enhance the health and well-being of the subject, for example, by leading to a meaningful change in therapy, then the IRB may consider that procedure as offering the prospect of direct benefit.

file:///C:/Users/cgrady/Downloads/Guideline%20for%20Enrolling%20Children%20as%20Participants%20in%20Research.pdf

Prospect of direct benefit

- FDA's Pediatric Ethics Subcommittee (PES) specifically addressed the question of what benefits may be considered ''direct'' under the FDA subpart D regulations, *and whether benefits need to accrue to children in both the control and treatment arms of a trial.*

- The general consensus was that *the placebo arm of a trial cannot be considered to confer the prospect of direct benefit* under § 50.52 of the FDA subpart D regulations.

- In general, the PES advised that being included is not a ''direct'' benefit, and that children enrolled in the placebo arm of a trial should be exposed to no more than minimal risk or a minor increase over minimal risk (Ref. 9). FDA agrees with this position

USFDA Additional safeguards for children. https://www.govinfo.gov/content/pkg/FR-2013-02-26/pdf/2013-04387.pdf

TABLE 3 Defining Prospect of Direct Benefit: Differing Viewpoints Among Workshop Attendees

A benefit is possible
• Any chance for direct benefit is enough to qualify as a prospect of direct benefit.
A benefit is likely
• A higher and more defined probability of benefit must exist to qualify as a prospect of direct benefit.
A reasonable parent standard
• A prospect of direct benefit exists if a reasonable parent acting in the best interest of his or her child would allow his or her child to participate in the research after weighing the likelihood of a potential benefit against the potential risks.

Bhatnager M et al. Prospect of Direct Benefit in Pediatric Trials: Practical Challenges and Potential Solutions. *Pediatrics*. 2021;147(5):e2020049602

TABLE 2 Defining Prospect of Direct Benefit: Points of General Agreement Among Workshop Attendees

- Benefit relates to the health of the individual child enrolled in the study (eg, how the child feels, functions, or survives).
- Direct benefit arises directly from the research intervention being studied and accrues directly to the individual child enrolled in the study.
- The level of certainty required for determining that a prospect of benefit exists is not commensurate with the rigorous standards for confirming efficacy.
- The anticipated benefit needs to adequately justify the risks in the context of the child's condition and alternative treatment options.

Bhatnager M et al. Prospect of Direct Benefit in Pediatric Trials: Practical Challenges and Potential Solutions. *Pediatrics*. 2021;147(5):e2020049602

Communicating benefit

- How do we (researchers, research teams, IRBs, etc) communicate about benefit
- Participant expectations of benefit

Do consent forms (inappropriately) promise benefit?

- Phase 1 oncology consent forms almost never promise direct benefit to subjects, rarely mention cure, and usually communicate the seriousness and unpredictability of risk. Horng et al. N Engl J Med 2002;347:2134-40.

- "…consent forms used in gene transfer phase 1 trials often contain language that promotes, or does little to deter, therapeutic misconceptions." Kimmelman and Levenstadt 2005, *Human Gene Therapy* 16(4):502-08.

- Language in consent forms is confusing and inconsistent. King NM et al 2005

Table 5.
Recommendations for Consent Forms in Early-Phase Clinical Trials

Avoid Inconsistent and Confusing Terminology:

- Keep terms clear and simple; define them succinctly when necessary
- Describe potential direct benefits* consistently throughout the consent form, or limit their description to one consent form section only
- Limit variation in use of terms referring to the experimental intervention

Avoid Misleading "Treatment" Implications:

- Present benefit to society as the sole or primary goal of the research
- When direct clinical benefit* is not possible or not likely, say so
- Distinguish the ultimate goals of the line of research from what is possible for subjects in the study
- Describe surrogate endpoints* as measurement goals only
- Consistently use "research" terminology to refer to investigators, subjects, and experimental interventions

Avoid Vagueness about Potential Benefits:

- Avoid "empty" benefit statements* like "you may not benefit if you join this study"
- Discuss each type of benefit (societal, direct, and inclusion) separately and distinctly
- When direct benefits are reasonably possible, describe them precisely, including their nature, magnitude, duration, likelihood, and limits
- Clarify whether and how surrogate endpoints relate to potential direct benefits
- Link any potential direct benefits explicitly to receipt of the experimental intervention (not just to "being in the study")
- If describing inclusion benefits,* do so precisely; link them explicitly to participation independent of receipt of the experimental intervention

*For definitions and examples of terms, see text and Table 1.

King NM et al. "Consent Forms and the Therapeutic Misconception: The Example of Gene Transfer Research," IRB: Ethics & Human Research 27, No. 1 (2005): 1-8

Consent forms: “Are there benefits to taking part in this study?”

- There are no direct medical benefits to you from taking part in this study. We hope the information learned will benefit participants in the future”

- “You should not expect to personally benefit from this research, though we might find something important to your health that could benefit you. The main reason you may want to participate is to help researchers and health professionals to better understand the causes of cancer, and other diseases so that they can find better ways to prevent, detect, treat and cure such illnesses. We hope that you will feel good knowing that you may be helping future cancer patients as well as people with other diseases.”

Consent forms: “Are there benefits to taking part in this study?”

- “You might not benefit from being in this study. The purpose of this study is to find out whether xxx is safe and tolerable in patients and whether patients might benefit from long-term treatment. … In the future, other people living with xx might benefit from this study as well…”

- “You might not benefit from being in this study. However, the potential benefit to you might be that your participation in this study will contribute to new ways to make xx safer and more effective. XX may improve the chance that your disease may be cured, but you should understand that this cannot be guaranteed, and your disease may return.”

Perceptions and Expectations

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Cancer clinical trial participants' assessment of risk and benefit

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Note. Items were measured on a Likert-type scale from 1 (strongly disagree) to 5 (strongly agree). Alpha = .90 for the total scale (number of items = 22). The mean scale score is normally distributed (skewness = −0.19, *SE* = 0.23; Kurtosis = −0.22, *SE* = 0.46). IRT = item response theory.
[a]The p value from IRT graded response model discrimination.
[b]The number is the sequential order of the item in the actual scale.

Ulrich C, et al. Development and Preliminary Testing of the Perceived Benefit and Burden Scales for Cancer Clinical Trial Participation *J Empir Res Hum Res Ethics*. 2018;13(3):230-238

What do participants think?

- Expectations and motivations
- Assessment of risks and benefits
- Perception of other benefits

Summary

- Evaluating benefit and risk is essential to scientifically and ethically rigorous research
- Limited analysis and guidance
- Several important distinctions
- Multiple steps
- More work to be done

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