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Rethinking the concept of 'no direct benefit' in clinical research

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Clinical research consent forms commonly state that participants may receive no direct benefit, which reflects the uncertainty that surrounds investigational interventions. Yet research participation can offer other advantages, including earlier diagnosis, closer monitoring and referral to care — particularly where routine healthcare access is limited. Ethical frameworks should distinguish benefits of the intervention from those that arise from participation itself.

Clinical research is designed to generate generalizable knowledge and determine the extent to which interventions are safe and effective. Informed consent therefore commonly states that participants may receive no direct benefit from taking part, particularly when an intervention is unproven or when participants might receive placebo[1]. This language is ethically important: it communicates uncertainty, reduces therapeutic misconception and distinguishes research from clinical care[2,3].

But it raises the question of what 'no direct benefit' actually means. If it means that participants cannot be assured of therapeutic benefit from the intervention being tested, it is appropriate. If it is understood to mean that participation itself cannot provide any benefit, it fails to acknowledge the broader benefits that participation can provide and is therefore incomplete. Clinical research can generate protocol-enabled benefits through systematic clinical assessments, laboratory investigations, monitoring, health education, counselling and referral that are independent of whether the investigational intervention works, and therefore can provide a higher standard of baseline care regardless of which intervention a patient receives[4].

This distinction matters everywhere, but particularly in low- and middle-income countries (LMICs), where access to healthcare can be constrained by cost, distance and limited diagnostic capacity[5]. The question then is not whether research should become a substitute for healthcare but whether our language and ethical frameworks adequately recognize what participants actually experience.

What is meant by 'no benefit'

The conventional statement that participants may not benefit from participation in a clinical trial is intended to communicate uncertainty. Yet participants might reasonably interpret the concept of 'no benefit' more broadly than researchers intend. A trial participant might receive no benefit from an intervention while nevertheless gaining access to a higher level and greater continuity of healthcare than they would otherwise have received[6].

These activities may lead to earlier diagnosis of previously unrecognized disease and/or improved management of an existing disease or its comorbidities. Their value is not necessarily derived from the therapeutic benefit of the trial intervention but from participation in the trial and the requirements of the research protocol.

This distinction is relevant for participants both in LMICs and in high-income countries, who may undergo repeated specialist assessments, laboratory investigations or imaging that can identify previously unrecognized abnormalities[7]. Although routine health systems may provide alternative routes to these services, trial participation can still increase their frequency, coordination or accessibility. Thus, the relevant ethical distinction is not simply between 'benefit' and 'no benefit', but between intervention-related benefit and participation-related benefit.

> "The same research procedure can have a different practical value depending on the healthcare system in which it occurs"

The LMIC paradox

The distinction becomes particularly important where research participation intersects with substantial gaps in routine healthcare. In LMICs, where access to healthcare can be constrained by financial, geographical and health-system barriers, research participation may be particularly valuable in providing access to services that are otherwise unavailable or difficult to obtain[8].

Consider a participant enrolled in a hypertension, diabetes or kidney disease study in Uganda. The investigational intervention may ultimately prove ineffective. Nevertheless, repeated blood-pressure measurements, renal function and urine testing, counselling, dietary advice and referral for newly identified disease may alter the participant's health trajectory. The benefit arises not because the experimental intervention worked, but because participation created opportunities for detection, knowledge and linkage to care.

Such benefits should neither be exaggerated nor dismissed. Research should not exploit deficiencies in health systems by presenting trial participation as a route to care. Conversely, denying that participation can have meaningful health consequences simply because they do not arise from the investigational intervention fails to reflect the reality of many participants' experiences.

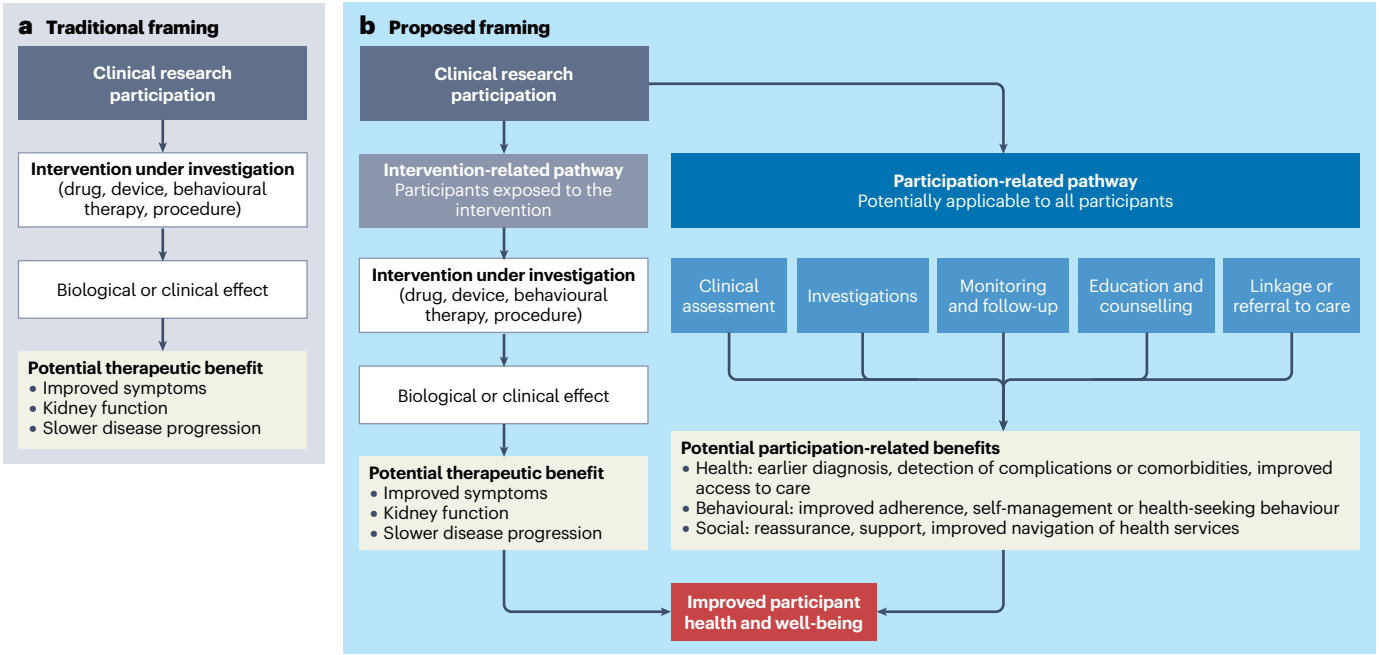

Fig. 1 | Intervention-related and participation-related benefits in clinical research. a, Under the current framework, potential benefits are discussed in relation to the intervention under investigation. **b**, However, participation in clinical research can generate additional benefits through the processes of research participation, distinct from the therapeutic effect of the intervention. The two should therefore be distinguished in informed consent and ethical analysis.

The ethical challenge is therefore contextual: the same research procedure can have a different practical value depending on the healthcare system in which it occurs.

Beyond clinical outcomes

Beyond direct health benefits, trial participation can also produce behavioural and social benefits. Repeated interactions with research teams can improve health literacy, reinforce self-management, encourage health-seeking behaviour and strengthen engagement with healthcare services[5,9] (Fig. 1). These effects may persist beyond the study period, particularly among participants with chronic diseases who require sustained engagement with healthcare services.

Such interactions may also influence trust. Respectful communication, counselling and continuity of contact can help participants to navigate otherwise-fragmented health systems. Such outcomes are seldom primary trial end points, and they should not automatically be classified as benefits of the intervention. Nevertheless, they are potentially important consequences of participation.

This raises a broader question: should ethics review consider only what the intervention might do or also what participation itself enables?

> "...should ethics review consider only what the intervention might do or also what participation itself enables?"

A more precise approach to consent

We do not propose replacing the statement that participants may not benefit with assurances that they will benefit, and nor should participation-related benefits be used to justify recruitment, weaken safeguards against undue inducement, or blur research with clinical care. Instead, informed consent could distinguish explicitly between four categories: potential therapeutic benefits of the intervention; benefits that may arise from research procedures; benefits that may arise from the discovery of incidental findings or from opportunities for referral; and benefits that remain uncertain or are unlikely.

This distinction would make consent more transparent. It would also enable ethics committees to examine an important but underrecognized possibility: that access to protocol-enabled care may itself influence willingness to participate, particularly among people with limited alternatives. Recognizing participation-related benefits therefore need not weaken research ethics. Rather, it may strengthen them by making the participant experience more accurately visible.

Rethinking benefit

Clinical trials are designed to test interventions, and not to deliver healthcare. Yet participants are not merely recipients of an experimental intervention; they are people who undergo a structured set of interactions, assessments and decisions because they participate in research. Some may receive no therapeutic benefit from the intervention. They may nevertheless gain earlier diagnosis, better information, closer monitoring, referral or sustained engagement with care[9,10].

The ethical language of research should capture both realities.

We should therefore move from the blanket statement "you may receive no direct benefit from participating" towards the more precise proposition: "you may receive no guaranteed benefit from the intervention being studied, although you may experience other benefits or advantages from research participation."

That is not a promise of benefit. It is a more honest description of participation and an important distinction for ethical research in unequal health systems.

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Competing interests

The authors declare no competing interests.