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Minimizing Risks Is Not Enough:

the relevance of benefits to protecting research participants

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Abstract

Forty years ago, the *Belmont Report* counseled that a "systematic, nonarbitrary analysis of risks and benefits" is vital to ensuring the ethical appropriateness of research with human subjects. Since then, research ethics has devoted considerable attention to the first half of this advice, emphasizing the ethical importance of assessing and minimizing the risks of research with human subjects. Significantly less attention has been devoted to a systematic assessment of the potential benefits of research participation. To the extent that benefits for individual participants are considered at all, commentators tend to focus on their potential to undermine the goal of minimizing risks. A chance for clinical benefit may obscure the fact that research poses risks not present in clinical care, while an offer of financial compensation or ancillary care may induce individuals to accept risks that conflict with their long-term interests. This article argues that, while undoubtedly important, minimizing risks fails to offer sufficient protection for research participants, especially those who cannot consent, because it neither ensures that the risks of research are justified nor protects participants from exploitation. *Belmont*'s advice to develop systematic and nonarbitrary ways to ensure that research participants receive appropriate benefits needs to be heeded as well.

Martin Luther King, Jr., quoting the 19th-century clergyman Theodore Parker, claimed that the arc of the moral universe "bends toward justice." One hopes he is right, perhaps especially at times when history appears to have taken something of a detour. The 40th anniversary of the *Belmont Report* offers the opportunity to evaluate the arc of research ethics, to assess where it is going and whether it too is bending toward justice.

The *Belmont Report* is the work of the National Commission, which was charged with identifying "the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects." The Commission first considered the possibility of deriving these principles from moral theory more generally. This approach was ultimately rejected out of concern that the Commission's resulting recommendations would be as controversial as the moral theories on which they were based. In hopes of finding wider acceptance, the National Commission bypassed moral theory for three middle level moral principles: respect for persons, beneficence, and justice.

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While these principles gained fame from their appearance in the *Belmont Report*, it is difficult to imagine a context involving the actions and interactions of human beings for which respect for persons, beneficence, and justice are not relevant. The National Commission's reliance on these principles thus helped gain widespread support for its recommendations for human subjects research. At the same time, this approach has left us with many challenges regarding the implications of these three general principles for research with human subjects, especially for those who cannot consent.

While all three principles are important to this context, the greatest concern involves the possibility that individuals who cannot consent may be exposed to excessive risks, thereby violating the principle of beneficence. The Nuremberg Code had previously tried to address this concern by prohibiting research with human subjects who cannot consent. But, as the National Commission appreciated, excluding individuals who cannot consent undermines efforts to identify safe and effective treatments for the conditions that affect them. It thus permitted investigators to enroll individuals who cannot consent when sufficient protections are in place.

The *Belmont Report* maintains that sufficient protection for those who cannot consent requires adherence to two rules: first, do not harm, and second, maximize the possible benefits and minimize the possible harms. In the wake of public disclosure of the scandal that was the Tuskegee syphilis study, and with a background of the long history of problematic research on prisoners and the more recent history of thalidomide and its devastating impact on fetuses, it is not surprising that the *Belmont Report*—as well as subsequent US research regulations—tended to emphasize doing no harm and minimizing risks, rather than maximizing potential benefits. Research involves subjecting individuals, who are thus labeled "subjects," to risks, in order to collect data that might benefit others.

This widely endorsed approach frames the demands of the principle of beneficence primarily as a matter of protecting research participants from excessive risks. This explains why the *Belmont Report*'s discussion on how to apply the principle of beneficence, titled "Assessment of Risks and Benefits," concentrates on risks and has little to say about potential benefits to participants. Research ethics has made substantial progress in this regard—perhaps too much progress, some might say. To consider just one example, significant attention has been focused on assessing and minimizing the risks of research with stored biological samples. This level of attention is striking, given that no significant harms have been documented in literally billions of research uses of human biological samples.

In contrast to all the attention paid to assessing and minimizing research risks, there has been relatively little work, both practically and theoretically, on the potential benefits individuals might derive from their research participation. To the extent commentators consider individual benefits, it has typically been with a skeptical eye, especially when the participants are unable to consent. Research ethics is one of the rare contexts in which arguments against paying individuals tend to be made mostly by those who take themselves to be protecting them. And the potential benefits of research participation more generally tend to be seen not as things that might promote participants' interests, but as potential screens that can obscure risks, and potential lures that might prompt participants to accept

excessive risks. This attitude is exemplified by a prominent 2001 US court case involving research with individuals who cannot consent, *Grimes v Kennedy Krieger Institute* (366 Md 29; 782 A2d 807; Md LEXIS 496). In its decision, the Maryland Court of Appeals expressed alarm over the practice of offering benefits to research participants who cannot consent: "The record reflects that in addition to the $5.00 and $15.00 sums mentioned in the consent form as periodic payments for participation in stages of the study, there was a stream of compensation flowing to the research subjects and the parents. Gifts, trinkets, coupons for food, etc., would be given to the subjects or their parents periodically." This passage nicely illustrates the common thought that the extent to which subjects who cannot consent might benefit from research participation is largely irrelevant to, and potentially conflicts with, the goal of protecting them. That goal, and the more general principle of beneficence, is best realized by doing no harm and minimizing the risks participants face.

This approach to protecting participants who cannot consent is insufficient, for two reasons. First, whether the risks of research are excessive is not a function of the absolute level of risks, but of the level of *net* risks, which is determined by the extent to which the risks exceed the potential benefits to participants. It follows that appropriate protection cannot be assured simply by minimizing the risks faced by individuals who cannot consent. Protection also depends on the extent to which the risks they face are justified by a potential for subject benefit. To make this assessment, stakeholders need to consider systematically and nonarbitrarily, which benefits can justify the risks to which research participants are exposed.

Second, appropriate protection requires that participants be protected from more than just the risks of research. They also need to be protected from exploitation, which is a function of both the risks to which participants are exposed and the extent to which others benefit from their participation. Reduce the research risks even to zero, and the potential for exploitation remains. To address it, stakeholders need to ensure that participants themselves receive sufficient benefits, given the extent to which others benefit from their involvement in the research.

Meeting the National Commission's challenge of ensuring an appropriate risk-benefit profile for research with individuals who cannot consent, and bending the arc of research ethics towards justice, thus requires more than minimizing the risks to which they are exposed: it also requires that participants receive appropriate benefits. The challenge of ensuring appropriate benefits arises in all human subjects research. However, this concern is especially pressing for research with individuals who cannot consent. For research with capacitated adults, we can rely to a certain extent on their judgments of whether a given risk-benefit profile is reasonable for them. When it comes to research with individuals who cannot consent, these determinations must be made by others—by surrogates, investigators, and IRBs—raising concern over whether these determinations are being made correctly.

To address this concern, we need to develop systematic and nonarbitrary ways to assess the benefits of research. In this article, I will not endorse a particular method. I will not, for example, take a stance on the controversy over whether monetary payments can justify the risks to which research participants who cannot consent are exposed. Instead, I will try to

make the case that living up to the standards set by the *Belmont Report* requires systematic and nonarbitrary ways to ensure research participants receive appropriate benefits without undermining the clear progress that has been made on protecting them from risks.

Which Benefits to Participants Can Justify the Risks They Face?

While the National Commission entertained many controversial issues, it considered the most difficult to be research that poses more than minimal risk while not offering a compensating potential for benefit to individuals who cannot consent. Focusing on pediatric research, the Commission observed that: "Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices." Most of the attention devoted to these difficult choices has focused on minimizing the risks of research with those who cannot consent, and capping the permissible level of any remaining risks. The National Commission argued that pediatric research without the prospect of direct benefit should be limited to a minor increase over minimal risk, and this standard has since been incorporated into the US regulations. (Explicit risk limits for research with adults who cannot consent were also endorsed by the Commission, but never codified in US regulations.) While risk limits are important for protecting human subjects who cannot consent, they apply only when the research fails to offer a compensating potential for subject benefit.

Consider an early-phase study of an experimental chemotherapy for medulloblastoma, the most common cancerous brain tumor in children. The study involves administration of the experimental chemotherapy in five cycles over four months, along with two research lumbar punctures to look for the presence of cancer cells in the participants' cerebrospinal fluid (CSF). The risks posed by the experimental chemotherapy are likely to be significant, including a risk of death. However, the experimental chemotherapy also offers some chance for clinical benefit. The challenge, then, for protecting research participants who cannot consent is not whether the absolute risks are high. It is whether the risks exceed the potential benefits and, if so, by how much.

Imagine that the potential benefits of receiving the experimental chemotherapy justify its risks. In that case, the net risks of the study—the extent to which the risks exceed the potential individual benefits—are limited to the risks of the two research lumbar punctures. In all cases, but especially in research with individuals who cannot consent, it is these risks that raise the most ethical concern, and that need to be justified.

The National Commission was concerned that investigators might try to justify exposing individuals who cannot consent to research risks by citing distant potential benefits. Perhaps the two lumbar punctures have the potential to yield information that might be of clinical significance in the distant future. In the view of the Commission, that possibility is too speculative to justify risks to subjects who cannot consent. To try to block such overly speculative justifications, the Commission introduced the term "direct" to refer to the

potential benefits that can justify risks faced by individuals who cannot consent, and it characterized direct benefits as “fairly immediate.”

Reference to direct benefits has been incorporated into numerous regulations. For example, US regulations permit IRBs to approve research with pregnant women that poses greater than minimal risk to the fetus when it offers the potential for “direct benefit to the pregnant woman” (45 CFR 46.402 d). The International Conference on Harmonization (ICH) guidelines stipulate that research with “no anticipated direct clinical benefit” may enroll individuals who cannot consent only when the risks are low (ICH 2017). None of the many regulations that refer to “direct benefits” defines them, nor do they adopt the Commission’s characterization of direct benefits as “fairly immediate” benefits. The result has been significant uncertainty over which benefits can justify research risks faced by individuals who cannot consent.

Belmont argues that these assessments should take into account “many kinds” of possible benefits, including psychological, physical, legal, social, and economic ones. Similarly, in his seminal book Ethics and Regulations of Clinical Research (1988), which was significantly influenced by the National Commission, Robert Levine considers the extent to which economic, psychosocial and kinship benefits can justify the risks to which participants are exposed. More recent emphasis on minimizing the risks of research, and concern that offers of benefit might be used to justify excessive risks, have led commentators to dramatically reduce the range of benefits which qualify as “direct.” The US National Bioethics Advisory Commission claims that direct benefits are limited to the clinical benefits that “stem from the research interventions themselves” (NBAC 1998, 1:45). Perhaps the most influential account defines direct benefits even more narrowly, as benefits that trace to receiving the intervention being studied (King 2000).

These more recent accounts limit which benefits can count as “direct” in two ways. First, they place limits on the *type* of benefits that count as direct: benefits need to be health-related. They also place limits on the *source* of the benefits. Research studies typically include a range of research procedures that offer some potential for clinical benefit. For example, a research imaging scan might identify a treatable tumor. On the current view, those potential benefits cannot justify the risks of research with individuals who cannot consent, even the risks of the scans themselves. Only the potential benefits of receiving the intervention being tested qualify as “direct” and can justify the risks of research.

To see the practical implications of these differing accounts, consider a study designed to assess the safety in adults who cannot consent of a potential new treatment for Alzheimer’s disease. The first phase of the research involves giving a small number of participants a single dose to assess how well they tolerate the drug. Because the condition is chronic, and the participants in the initial study receive only a single dose, enrollment does not offer them the potential for clinical benefit. Hence, if a single dose of the drug poses more than minimal (or more than a minor increase over minimal) risk, a likely possibility, existing guidelines maintain that it should not be approved. Offering participants full-time daycare for a year would not justify the risks of participation; neither would offering access to another treatment. In contrast, extending the study and offering participants several months

of the experimental treatment would introduce potential direct benefits that might justify the (increased) risks of receiving the experimental treatment. This example illustrates that, on current approaches, offering participants services they would otherwise not be able to afford, or providing them with a proven safe and effective medication that is not being tested in the study, cannot justify the risks they face. But offering them additional doses of an experimental treatment that has not been proven effective can justify the risks of research.

One might defend this narrower understanding of direct benefits on several grounds. First, offers of ancillary care are largely under the control of the investigators. Hence, if these benefits qualify as direct, investigators could, in principle, increase the benefits to justify essentially any level of research risks. That seems right, and it seems a significant concern to the extent that one regards subject protection as a matter of minimizing research risks. But to the extent participants do benefit from these offers, and the associated risks are tied to socially valuable interventions, they do not increase the net risks to which participants are exposed. Hence, it is unclear on what grounds they might be objectionable.

Second, one might argue that, as part of their mandate, review committees are required to assess and weigh the potential benefits of research interventions. As a result, they are more likely to get these assessments right compared to assessments of whether, say, some economic or ancillary benefits justify the risks of research participation. The fact that review committees are required to assess the risks and potential benefits of research interventions does not mean that they are good at these evaluations, nor that assessing these potential benefits is easier for them than assessing other types of benefits that might be offered to research participants. In some cases, assessing the potential benefits of research interventions may be relatively straightforward. However, the intervention being tested is being tested precisely because it is not known whether it is safe and effective. Given that little is known about the efficacy of experimental interventions, assessing their potential benefits is often more difficult than assessing the potential benefits of ancillary care that might be offered to participants.

Third, one might assume that, if the potential benefits of receiving the intervention do not justify its risks, investigators should not be studying it in the first place. This suggests that limiting direct benefits to the benefits of receiving the treatment being tested might provide a means to ensure that participants who cannot consent are enrolled in research only when it has sufficient social value. The problem with this view is that the risk-benefit profile of receiving a treatment during a research study, especially an early-phase study, may be very different from the risk-benefit profile of receiving the treatment in standard care. During development, when little is known about an intervention—which dose to use, whether it leads to allergic reactions—the risk-benefit profile might be unfavorable, even though the treatment turns out to be safe and effective.

Ensuring appropriate protection for research participants who cannot consent requires that we return to the *Belmont Report* and take seriously its advice to develop systematic and nonarbitrary methods to ensure that research participants receive appropriate benefits. The need for such methods is highlighted by current thinking on what is widely known as the “fallacy of the package deal” (Levine 1999). Many commentators and guidelines maintain

that the potential benefits from one component of a research study cannot "offset or justify" the risks presented by other components in the same study (Field and Behrman 2004). This approach is intended to prevent investigators from adding "biopsies, blood tests, or scans that are unlikely to yield any information of benefit to society by justifying them on the basis of including an intervention that holds the prospect of direct benefit" (NBAC 2001, 78). While it protects participants who cannot consent from undergoing unnecessary procedures, this approach also has the potential to block necessary procedures.

Taken literally, the fallacy of the package deal maintains that the potential benefits of experimental treatments cannot justify the risks of procedures that are necessary to administer them. For example, some experimental medications are delivered through central lines or Ommaya reservoirs placed under the scalp. The claim that the potential benefits of one intervention cannot justify the risks of other interventions suggests that the risks of these interventions cannot be justified by the experimental treatments they make possible. That seems clearly mistaken. Just about everyone, including proponents of the fallacy of the package deal, think that the potential benefits of experimental interventions can justify the risks of interventions that are clinically necessary to administer them. Without the central line or Ommaya reservoir, investigators cannot give participants the experimental treatment. Hence, the potential benefits of the experimental treatment can justify the risks of those procedures. But that acceptance implies that the potential benefits of receiving the experimental treatment can justify the risks of at least some other procedures in the same study (Wendler, Nelson, and Lantos 2018).

If the potential benefits of receiving experimental treatments can justify the risks of procedures necessary to administer them, can they also justify the risks of procedures that are necessary to evaluate them? For example, can the potential benefits of receiving experimental treatments justify the risks of biopsies that are needed to evaluate them? Investigators could give participants the experimental treatment without having them undergo the biopsies, but that approach would undermine the point of administering the experimental treatment. Perhaps, then, the scientific necessity of doing the biopsies implies that the potential benefits of receiving the experimental treatment can justify their risks. If that is right, it raises the question of whether the potential benefits of receiving experimental treatments can justify risks that research participants face in the control arm. Can the potential benefits of receiving experimental treatments justify other risks only when individuals actually receive the experimental treatment? Or can the fact that, prior to randomization, participants had a chance of receiving the experimental treatment justify risks they subsequently face in the control arm? The importance of these questions, and the fact that their answers are anything but obvious, highlights the need to heed *Belmont*'s advice to develop systematic and nonarbitrary ways to assess the risks and also the potential benefits of research with individuals who cannot consent.

When Do Participants Have a Claim to Benefit?

Research with human subjects raises the potential for exploitation at several levels. The risks and burdens of research tend to fall on certain groups, with many individuals not participating in clinical research at all. Some research participants—for example, individuals

in the US who lack health insurance—do not share equally in the benefits of interventions developed through research (Dal-Re, Rid, and Wendler 2016). This raises concern that research as an institution may be exploiting some research participants. With respect to individual trials, the potential for exploitation arises with the possibility that investigators may enroll participants in studies that pose excessive risks in order to benefit others. While all human subjects, whether they can consent or not, face this risk, this possibility is especially acute with respect to individuals whose inability to consent increases the chances that they will be exposed to excessive risks, or enrolled in research that offers them insufficient benefits.

According to an influential account laid out by Alan Wertheimer (1999), exploitation in individual transactions, such as individual clinical trials, occurs when the benefits and burdens of the transaction are distributed unfairly. Specifically, in a transaction between A and B, A exploits B when (1) A benefits from B's involvement in the transaction; and (2) B receives an unfair level of benefits. Whether the benefits that B receives are fair depends on the risks and burdens that the transaction places on B and the extent to which A and others benefit from B's involvement in the transaction.

This account suggests there are three possible ways to protect research participants who cannot consent from being exploited. The first approach would be to reduce or eliminate the extent to which others benefit from the participants' involvement in the research. If no one else benefits, the first condition is not satisfied and participants cannot be exploited. While this approach eliminates the potential for subject exploitation, it conflicts with another widely endorsed ethical requirement for clinical research—namely, the social value requirement. This requirement maintains that research studies should collect data that has the potential, often in conjunction with the results from other studies, to benefit future patients (Wendler and Rid 2017). Essentially all clinical trials should satisfy this condition; when they do, they have the potential to benefit others and, hence, the potential to exploit participants who cannot consent.

The second way to address the potential for exploitation is to reduce the risks to which participants are exposed. Minimizing risks is of course also important for protecting participants from harm. It makes sense, then, that there has been significant attention to minimizing risks as a means to protecting research participants, and there have been very few documented cases over the past 40 years of research participants who cannot consent being subjected to clearly excessive research risks. This is important, and it represents a significant victory for research ethics. However, minimizing risks is not sufficient for protecting research participants from exploitation. As long as clinical trials offer potential benefits to others, a possibility that is assured by satisfaction of the social value requirement, eliminating even all the risks is not sufficient to eliminate the potential for exploitation.

This brings us to the third possibility: working harder to ensure that participants receive a fair level of benefits, given the extent to which others benefit from their research involvement. To the extent that the value of a study lies in its potential to gather data that can be used to improve health and well-being for future patients, one might argue, plausibly I think, that satisfying two requirements will be sufficient. First, the burdens of research

participation should be shared fairly and not fall disproportionately on certain individuals or groups. Second, the individuals who participate and face the risks should have access to the interventions identified through research. This is not to say that the benefits to participants must derive from the same study that poses the risks; instead, the potential benefits and the risks of clinical research as a whole need to be distributed fairly across individuals.

When these two conditions are satisfied, and the benefits others realize from clinical research are limited to improvements in health and well-being, participants seem protected from exploitation. Yet many studies do not satisfy these two conditions. As noted previously, some research participants do not share equally in its benefits, and many beneficiaries of research never shoulder any of its risks. Moreover, the extent to which clinical trials are funded by private entities, which profit from them, has increased dramatically since the publication of the *Belmont Report*. In these cases, one cannot address the potential for exploitation without assessing whether participants receive sufficient benefits, given the extent to which others profit from their research involvement.

To consider one example, a recent class of direct-acting antivirals for hepatitis has been developed through clinical trials (Lawitz et al. 2013). These drugs are very effective and very expensive, and companies and individuals are making significant profits from them. One of the first, sofosbuvir, was developed under the leadership of Raymond Schinazi, a professor at Emory University, who received over $400 million for his efforts (Goozner 2014). In December 2013, the FDA approved Sovaldi (the brand name for sofosbuvir) for the treatment of chronic hepatitis C, and the company set a list price of $84,000 for a treatment course of approximately 12 weeks (Charlton et al. 2017). The next year, a second set of drugs, Harvoni and Viekira Pak, were approved by the FDA for the treatment of hepatitis C (Gritsenko and Hughes 2015). The 2014 sales for Gilead, one of the leading companies, were $10.3 billion (Pollack 2015b).

That is a lot of money. Of course, the development of these medicines was not cheap either (DiMasi, Grabowski, and Hansen 2016). One estimate suggests that the total funding from Gilead and other private sources for Sovaldi was between $300 and $500 million (Sachs 2015). Private companies recover the costs of developing new interventions through the prices they charge for marketed treatments. Moreover, many tested medicines turn out to be ineffective or overly toxic. Because these medicines are not marketed, private companies must recover the costs of their testing through the prices they charge for the medicines they do market. Here too, one might argue that participants do not need to receive fair benefits, given the profits others realize from their contributions to specific trials. Instead, participants need to benefit fairly from the enterprise of clinical research as a whole. Their overall access to treatments and interventions that are developed through clinical trials should constitute a fair deal in the context of the risks of the trials in which they are enrolled and the extent to which others profit from those trials.

This response makes sense, but there are compelling reasons to doubt, even at this general level, whether the risks and benefits of clinical trials are being distributed fairly. First, many patients have access to effective medications, but only a small percentage participate in clinical trials. Second, no method exists for estimating the extent to which research

participants have a claim to benefit when others profit from the trials to which they contribute. Rather than emphasize the need for such an analysis, commentators in research ethics tend to be skeptical of the appropriateness of paying research participants at all. Absent such an analysis, it seems extremely unlikely that the prevailing approach of using some profits to test new treatments, and providing the rest to employees and shareholders, yields a fair distribution of the benefits realized from clinical trials.

Furthermore, the price of new medicines has doubled in recent years, and prices for older medicines regularly increase, sometimes by 1,000% or more in a short period of time (Pollack 2015a). Given an absence of corresponding costs, if dramatic price increases lead to increased profits, these would need to be offset by increased benefits to the participants of the relevant trials. Additionally, price increases make it more difficult for patients to afford the treatments they need, and they also place pressure on insurers to restrict access to more expensive medicines and pass the cost increases on as higher insurance premiums that further reduce access to affordable insurance. The result of higher prices at the systems level, then, may be to decrease rather than increase the benefits for the individuals who contributed to the original trials.

Taken together, these considerations raise concern that clinical research, as it is currently structured, satisfies the two conditions for exploitation: others profit, while research participants fail to receive sufficient benefits. As we have seen, eliminating the social value of clinical trials is no way to address this concern, and minimizing the risks participants face is important but insufficient. This suggests that, in order to protect from exploitation research participants who cannot consent, we need to ensure that they receive appropriate benefits. And this, in turn, provides further reason to think that research ethics needs to develop systematic and nonarbitrary ways to assess the appropriateness of the benefits of clinical trials. In order to protect research participants, especially those who cannot consent, from exploitation, research ethics needs to determine the extent to which participants should benefit in relation to the benefits others realize from their research contributions, together with ways to ensure these benefits are realized in practice (Johnson and Wendler 2015).

Conclusion

The *Belmont Report* maintains that it can be acceptable to enroll individuals who cannot consent in research when it offers them an appropriate risk-benefit profile. For the past 40 years, commentators and guidelines have responded to this challenge by emphasizing the need to minimize risks. While this approach is important, it is insufficient. Whether a given risk-benefit profile is appropriate depends not on the level of absolute risks, but on the level of net risks, which is a function of the extent to which the risks exceed the individual potential benefits. Research participants also need to be protected from more than research risks. They need to be protected from exploitation, which requires an assessment of the extent to which participants benefit in relation to the benefits others realize from their research participation. To satisfy the *Belmont Report*'s challenge of a systematic and nonarbitrary analysis of risks and benefits and thereby ensure the ethical appropriateness of research with individuals who cannot consent, there remains, 40 years on, a significant amount of work to do.

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