ABSTRACT

How much risk can we expose our research subjects to? There is a special challenge answering this question when the evidence on which we base our assessments of risk is fragmentary, conflicting or sparse. Such evidence does not support precise assignments of risk (eg, there is a 24.8% chance that this patient will develop AIDS in the next year if she participates in my study). At best it supports imprecise assignments of risk (eg, there is between a 5% and 35% chance that this patient will develop AIDS in the next year if she participates in my study). Here I discuss three approaches to evaluating risk when probability assignments are imprecise—an optimistic approach, a moderate approach and a pessimistic approach. I offer a practical reason to favour the pessimistic approach.

A central question in HIV research ethics is this: “Antiretroviral therapy for HIV works pretty well. HIV positive patients who interrupt it for the sake of participating in our research studies are often taking a risk. How much of a risk should we, the researchers, allow them to take?”

One reply: “We should allow them to take whatever risks they infomrmedly consent to. They are autonomous adults. So long as we have told them all that we know about the possible costs and benefits associated with participating in the study, we should respect their decisions to participate”.

Another reply: “Fully informing research subjects will sometimes involve presenting to them a complex picture that they are unqualified to assess. In these situations, particularly when the possibility of a ‘cure’ is salient to them, some subjects may want to take risks that we, the researchers, judge to be desperate. It is not okay to be complicit in desperate risk taking. It is doubly not okay to do that when we stand to benefit from the desperate risk taking. There is an upper bound to how much risk we should allow our subjects to take”.

If we take the second reply seriously, then we have the job of specifying just what the upper bound is, and explaining how we tell whether it is being exceeded. Roughly speaking, this will be a matter of comparing the patients’ chances if they participate in the study with their chances if they do not. Less roughly speaking, it will be a matter of comparing the prospect for the patient associated with participating in the study with the prospect for the patient associated with continuing with antiretroviral therapy. (Generally, the prospect for you associated with an option is the set of all things that might happen to you if you take it, weighted by the chances they will happen if you take it. So the prospect for the patient associated with continuing with
confidence can be represented by a rough bounded interval—from around 25% to around 45%.

The problem is how to assess whether or not participation is too risky when our levels of confidence in the prospects associated with participation are imprecise. Three basic approaches spring to mind.

**The optimistic approach**

Take the most optimistic precisification of your imprecise levels of confidence in the prospects associated with participation. If participation is too risky, under that precisification, then do not allow it.

**The moderate approach**

Take the precisification at the mid-point of your imprecise levels of confidence in the prospects associated with participation. If participation is too risky, under that precisification, then do not allow it.

**The pessimistic approach**

Take the most pessimistic precisification of your imprecise levels of confidence in the prospects associated with participation. If participation is too risky, under that precisification, then do not allow it.

Suppose my confidence that a patient will develop AIDS within a year if she participates in my research study is best represented by a rough bounded interval from around 5% to around 30%. The optimistic approach would have me imagine my being given a large volume of statistical evidence that licenses precise 5% confidence in her developing AIDS within a year. If and only if it would be okay for me then, with precise 5% confidence, to allow participation, then it is okay for me now, with imprecise 5–30% confidence, to allow participation. The pessimistic approach would have me imagine my being given a large volume of statistical evidence that licenses precise 30% confidence in her developing AIDS within a year. If and only if it would be okay for me then, with precise 30% confidence, to allow participation, then it is okay for me now, with imprecise 5–30% confidence, to allow participation. The moderate approach would split the difference.

Which approach is right? Philosophers who write about rationality tend to adopt a more optimistic approach to the rational permissibility of action. Their idea is that with imprecision in levels of confidence comes an expansion in the range of things that it is rationally permissible to do.1–4 If you have 40% confidence in a proposition and I offer you an even bet on it (if it is true I pay you a dollar, if it is false you pay me a dollar) then it is rationally permissible for you to refuse the bet, rationally impermissible for you to take it. But if you have imprecise 20–60% confidence in the same proposition, then it becomes both rationally permissible for you to refuse it (because it would be rationally permissible for you to refuse it if you were precisely 20% confident) and rationally permissible for you to take it (because it would be rationally permissible for you to take it if you were precisely 60% confident).

The philosophers have reasons for going this way. They see just three alternatives.

**The lax theory of rational permissibility**

It is rationally permissible for you to take an option if and only if it would be rationally permissible for you to take it under some precisification of your imprecise levels of confidence.

**The moderate theory of rational permissibility**

It is rationally permissible for you to take an option if and only if it would be rationally permissible for you to take it under the precisification at the mid-point of your imprecise levels of confidence.

**The strict theory of rational permissibility**

It is rationally permissible for you to take an option if and only if it would be rationally permissible for you to take it under every precisification of your imprecise levels of confidence.

They find the strict theory unsatisfactory because it says that very often there is nothing that it is rationally permissible to do. So, for example, when you have 20–60% confidence in a proposition, the strict theory says it is neither rationally permissible to accept my even bet on it nor rationally permissible to refuse my even bet on it. They find the moderate theory unsatisfactory because it says there is no practical difference between having imprecise 20–60% confidence in a proposition and having precise 40% confidence in a proposition. Surely there is a difference. So they are left with the lax theory.

These general considerations about rational permissibility might seem to tell in favour of the optimistic approach to enrolling research subjects. After all, enrolling research subjects is just a special case of rational action. And there are obvious further policy reasons to favour the optimistic approach. The bar for participation will be much lower. We will get more research subjects.

But here I want to suggest one less obvious policy reason to favour the pessimistic approach to enrolling research subjects. A peculiar feature of research studies is that, typically, they generate good statistical data on the prospects of their own subjects. Because of this, we can often reasonably expect that our attitudes, once the study is concluded, will be different and more precise than our attitudes now. The intervals representing our imprecise levels of confidence will in some way shift and contract. Just how will they shift and contract? Where our present levels of confidence that patients will develop AIDS are imprecise—say 5–30%, will it later be 2–4%? 4–10%? 20–25%? 25–40%? 80–90%? Typically, we do not know. Indeed, typically, we do not have precise levels of confidence about our future levels of confidence. But there is something we can say. Here are three propositions about our future levels of confidence in bad outcomes for our research subjects.

**Rising lower bound**

The lower bound of our future levels of confidence will exceed the lower bound of our present levels of confidence.

**Rising mid-point**

The mid-point of our future levels of confidence will exceed the mid-point of our present levels of confidence.

**Rising upper bound**

The upper bound of our future level of confidence will exceed the upper bound of our present levels of confidence.

Because we expect the intervals representing our imprecise levels of confidence to contract, we should be more confident in rising lower bound than in rising mid-point, and we should be more confident in rising mid-point than in rising upper bound. (Why? Note that, if the interval contracts, any shift that raises the mid-point also raises the lower bound, but some shifts that raise the lower bound do not raise the mid-point, and any shift that raises the upper bound raises the mid-point, but some shifts that raise the mid-point do not raise the upper bound.)
own standards, to enrol them. What should we do, as this evidence begins to accumulate? Our options are effectively to ignore the accumulating evidence until the study is complete or to refuse to allow the now too risky subjects to participate further in the study. Neither of these options is good. Just as it is not okay to allow subjects to take risks that we consider desperate, so it is not okay to allow subjects to take risks that we know we would consider desperate, if we were not now wilfully ignoring evidence. And releasing research subjects mid-study is a waste of time and resources—better never to have enrolled them at all.

So we have a reason to be pessimistic in our assessment of risks to our research subjects. That will allow us to expect to keep them in our studies without exposing them to risks that are by our own lights unacceptable.

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