

When money talks: Judging risk and coercion in high-paying clinical trials

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## Abstract

Millions of volunteers take part in clinical trials every year. This is unsurprising, given that clinical trials are often much more lucrative than other types of unskilled work. However, offering very high pay is sometimes considered ethically inappropriate. To investigate why, we asked 1,372 respondents to evaluate a hypothetical medical trial for a new Ebola vaccine offering three different payment amounts. Some individuals used very high pay as a cue to infer the potential risks a clinical trial poses. At the same time, despite the risk they may pose, some clinical trials may be too lucrative to be turned down. Both perceived risk and coercion shape how people evaluate clinical trials; they also help explain why there is a distaste for markets in which parties are remunerated for the risk they take—that is, why markets in which health and wellbeing are turned into commodities are considered repugnant.

*Keywords:* clinical trials, payment, risk, coercion, repugnant transactions

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### Introduction

All of us, with the exception of the independently wealthy and the unemployed, take money for the use of our body. (Nussbaum, 1998, p. 693)

Would you volunteer to take part in a drug study that offered €1,900, travel expenses, and a two-week stay at a pharmaceutical research institute in return for swallowing a drug on 10 consecutive days, undergoing extensive medical tests, and providing at least 40 blood samples? In 2015, 128 people volunteered to do just that at a Biotrial research institute in France. For one volunteer, who died, and six others, who were hospitalized, the money was not worth it. Later, experts underlined “the astonishing and unprecedented nature” of these incidents, which were the result of a reaction in the brain “unlike anything seen before” (AFP, 2016). No such effects were observed in pretests with animals, despite doses 400 times stronger than those the human volunteers received (Randerson, 2016). If the researchers could not have anticipated the risks, how could the volunteers have suspected what they were signing up for? And even if volunteers had somehow intuited the risks, could the study have been too lucrative to be turned down?

These are important questions to ask given the role clinical trials play in the development of new pharmaceutical treatments. The transition from animal testing to phase 1 trials, which assess the safety and effectiveness of a particular substance in humans, is critical. Millions of volunteers, both healthy and with existing health conditions, are sought for clinical trials every year. While volunteers with existing conditions may take part in medical research studies in the hopes of improving their health, healthy volunteers find their motivation elsewhere: More than 90% say money is their main incentive for participating (Bigorra & Baños, 1990; van Gelderen et al., 1993). Clinical trial volunteers sign an informed consent that outlines the details of the study including potential risks, and the research institute and the person offering their body

engage in a voluntary market transaction. This transaction is, to some, no different from any other market transaction (Wilkinson & Moore, 1997).

To others, however, such a market transaction is hardly comparable to getting a haircut. In fact, clinical trial markets are sometimes placed in the same category as paid kidney donations and prostitution—*repugnant* transactions that people deem morally repulsive and therefore want to prevent (Roth, 2007). The repugnance of clinical trial markets has been attributed to coercive remuneration for volunteers, since payment in clinical trials is usually much higher than unskilled work, which often pay minimum wages. In 2015, minimum wage workers in France would have earned €729 in two weeks, less than 40% of what the volunteers earned (Fric, 2016).

In support of this, Ambuehl et al. (2015) found that some people, who we call “Doubters,” rated a clinical trial offering \$10,000 as *more* coercive than the same trial offering \$1,000.<sup>1</sup> Consistent with this evaluation, Doubters also thought participants would regret enrolling in the higher paying study and be better off not participating. Finally, the Doubters stated they would be less likely to approve such a study if they were on an institutional review board (IRB) panel. A second group of respondents, who we call “Trusters”, rated the trial offering \$10,000 as *less* coercive. They also thought that individuals would be better off if they took part and would not regret participating. Trusters on an imagined IRB panel were more likely to approve the study offering \$10,000 than the one offering \$1,000.

The sense of possible coercion may not be the only factor that discerns between these two groups. The key difference between clinical trial participation and other types of jobs is that clinical trials expose participants to unknown risks (McNeill, 1997). Volunteers may be compensated *after* side effects are experienced, but policies vary.<sup>2</sup> In other cases, the

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<sup>1</sup> We call the “ethicists” of the original survey Doubters and refer to “economists” as Trusters to reflect the fact that Doubters are consistently more critical than Trusters of high-paying clinical trials.

<sup>2</sup> Member states of the European Union must offer systematic compensation for research-related injuries; no such regulation exists in the United States (Pike, 2012). Approximately 59% of institutions conducting clinical research in the United States explicitly offer conditional or unconditional compensation for

compensation volunteers receive for participating in the clinical trial may be considered to directly offset the risks to which they are exposed: Around one third of surveyed research institutes reported that one rule of thumb for determining pay is the anticipated risk participants incur (Dickert et al., 2002). This may explain why payment is sometimes treated as a cue indicating the risk of negative consequences from participating in a clinical trial (Cryder et al., 2010, though results are inconsistent, see Mantzari et al., 2014).

Consequently, people who judge the ethicality—and by extension, the repugnance—of a high-paying clinical trial may not only heed the coercion caused by the high payoffs, but also the risks that the payoffs signals. Very high payoffs offered in clinical trials could stress the potential harm to participants and thereby decrease people’s approval of the study. If so, the difference between the two groups of respondents in Ambuehl et al. (2015) may at least be partly due to different inferences about the implied risks. This is not an uncontested hypothesis. Ambuehl et al. (2015) maintained that the risks of the \$1,000 and \$10,000 payment schemes were seen as equal because respondents got the same description of the trial and saw all the possible payoff schemes (see their Footnote 7). Moreover, others have argued that high payment amounts may conceal the risk involved in taking part in a study (Bentley & Thacker, 2004; McNeill, 1997), or even impair prospective participants’ ability to think carefully about the risks and benefits involved (Casarett et al., 2002).

To investigate whether the ethicality of high-paying clinical trials is influenced by the risks inferred from the payoff magnitude, we presented online survey respondents with a hypothetical medical trial that compensated volunteers with £50, £1,000, or £10,000 (materials adapted from Ambuehl et al., 2015). Respondents estimated how many prospective participants would experience side effects, and evaluated the clinical trial on several other dimensions pertaining to coercion and ethicality. We asked four research questions: (1) Do the results from Ambuehl et al. (2015) replicate? (2) Do people perceive

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research-related injuries (Resnik et al., 2014). Yet, even where laws exist, volunteers are often not fully aware of their financial vulnerability when they enroll in clinical trials (Manning, 2017).

higher payment to be associated with higher risk? (3) Why do people consider high pay in clinical trials to be ethically inappropriate? and (4) How do payment-dependent inferences shape judgments on the repugnance of clinical trials?

## Method

### Participants

In total,  $N = 1,565$  respondents completed our survey posted on Prolific Academic for a flat payment of £2.10. Inclusion criteria were fluency in English (self-assessed), and a minimum approval rate of 80% in earlier studies completed on the platform. The data were collected in two waves ( $N = 354$  in wave 1,  $N = 1,211$  in wave 2). The first sample size was determined based on the availability, and a reasonable allocation, of funds ([osf.io/yftvh](https://osf.io/yftvh)), since our survey added several sets of questions, which lengthened the original 12-minute survey to an estimated 25 minutes. Wave 1 was smaller than the sample size in the original study ( $N = 1,445$ , Ambuehl et al., 2015). After examining the results, we sought additional evidence to test our predictions regarding the estimated side effects *between* respondents. We aimed to recruit an additional  $N = 1,200$  respondents in wave 2 ([osf.io/kumge](https://osf.io/kumge)). We improved our survey in wave 2 by asking respondents to assess how repugnant they find clinical trials in general. The total sample size of waves 1 and 2 roughly matched that of the original study. Inclusion criteria, predictions, survey questions and the reasoning behind collecting additional responses were preregistered. The surveys were approved by the IRB of the Max Planck Institute for Human Development. We collapsed our data in the main manuscript and report effects of wave 1 vs. wave 2 in the analyses of interest in the Supplementary Materials (in short: They were largely independent of wave). We analyzed data from  $N = 1,428$  ( $N = 316$  in wave 1,  $N = 1,112$  in wave 2) respondents who passed three simple attention checks (questions pertaining to the instructions and the clinical trial description that could be found on the same page). The final sample consisted of 885 females, 535 males, and eight who identified as ‘other.’

and was on average 36.1 years old (range 18–78 years,  $SD = 11.8$ ).

## Survey

**Vignette.** We used a vignette from a study about a hypothetical clinical trial testing an Ebola vaccination (Ambuehl et al., 2015). Respondents were put in the position of an IRB panelist evaluating the trial, which was described as a phase 1 trial which sought to test the vaccination for the first time on 100 female volunteers, after pretests in rats and chimps. The vaccine was described as having “low, but nonzero risks” (see Supplementary Materials for full vignette). The clinical trial remunerated prospective participants with one of three payment amounts [ $\pounds 50/\pounds 1,000/\pounds 10,000$ ]. Each respondent saw the vignette with all three payment amounts, but the primary analyses in the manuscript are based on the first payment amount respondents saw (i.e., between-respondents). Within-respondent analyses were consistent with the between-respondent analyses and are reported in the Supplementary Materials. The original survey included U.S. residents recruited via Amazon Mechanical Turk and hence used U.S. currency (\$). As our sample was British, we used British currency ( $\pounds$ ) and did not transform the values according to exchange rates.

**Side effects.** After reading the scenario, respondents were asked to assess how many of the 100 participants they expected to experience [any/mild/severe] side effects.

**Clinical trial evaluations.** As in the original survey, each respondent evaluated the clinical trial answering the following questions in order. (1) *IRB approval*. Suppose you are a member of the ethics committee that has to approve the institute’s study with [payment]. How would you decide? (2) *Personal approval*. How much do you personally approve of the institute’s proposal to enlist and compensate study participants from both rich and poor neighborhoods in this way? (3) *P (better off without)*. [Description of A.S., a woman earning \$1,500/month] Suppose that 10 women similar to A.S. see the institute’s study participation invitation. How many of the 10 would be better off if the institute had

never posted the study participation invitation?<sup>3</sup> (4) *P (enroll)*. How many of the 10 do you think will eventually participate in the study in exchange for [payment]? (5) *Voluntariness*. If A.S. decides to participate in the study for [payment], how would you describe her decision? (Likert scale with extremes labelled “She was coerced” and “Her decision was entirely voluntary”). (6) *P (regret accepting)*. If A.S. decides to participate in the study, how likely is it that she will later regret her decision? (7) *P (regret rejecting)*. If A.S. decides NOT to participate in the study, how likely is it that she will later regret her decision?

Since *IRB approval* and *personal approval* were highly correlated, we focus on *IRB approval* in the main manuscript. Similarly, since *P (regret accept)* and *P (regret reject)* were highly correlated, we focus on *P (regret accept)* in the main manuscript (corresponding models for the other variables can be found in the Supplementary Materials).

**Different types of respondents.** At the end of the survey, participants rated the appropriateness of different payments side by side, on a 7-point Likert scale (“For each of the following ways of compensating study participants, please indicate how ethically appropriate you think it is. Recall that the study tests for effects of a vaccine, and although nobody expects such side effects to occur, if this were known, there would be no need to run a study. There is no special compensation if side effects occur.”). This question, as in Ambuehl et al. (2015), was later used to categorize respondents into three types (Doubters, Trusters, and Others): Doubters’ strictly preferred offering £1,000 over £10,000; Trusters’ strictly preferred offering £10,000 to £1,000, and Others were indifferent to these two payment amounts. These names reflect that Doubters are more critical of clinical trials (in particular those that offer high pay) throughout, whereas the responses of Trusters are consistent with payoff-independent clinical trial *risk inferences*.

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<sup>3</sup> In the original survey, respondents rated the ethicality of the trial for two women: one earning £1,500/month and one with a minimum-wage job. In our survey, participants only evaluated the trial for a woman earning £1,500/month. Since the minimum wage in the United Kingdom is around £1,250/month (“National Minimum Wage”, 2018), we did not expect results to differ substantially in these two conditions.



**Repugnance.** In our second wave of data collection, we also asked respondents to rate the “repugnance” of clinical trials in general, based on four items: “Clinical trial markets... (1) are deplorable, (2) morally permissible (R), (3) should be banned (R), (4) should be monitored (R)”. Participants responded to these questions on a Likert scale from strongly agree (1) to strongly disagree (7). We recoded the answers to questions 2–4 (R) such that (1) denoted ‘less repugnant’ and (7) denoted ‘more repugnant’. Based on these items, we computed a repugnance measure for each respondent (their average rating across the four items). Individual responses to questions 1–3 were highly correlated. Responses to question 4 (“should be monitored”) were uncorrelated to the other responses. Since including and excluding question 4 from our repugnance measure led to qualitatively identical results, and we had not predicted it to be uncorrelated to the other measures a priori, we included it in the reported regressions. All “repugnance” analyses are based on wave 2 data—the repugnance questions had not been included in wave 1 (also see OSF).

**Numeracy, risk-taking and demographics.** Lastly, respondents completed the Berlin Adaptive Numeracy Test (Cokely et al., 2012), an ‘insurance task’ (not reported, but see OSF for wording) and items on their self-rated willingness to take risks. Six domain-specific risk-taking items were included (driving, financial, recreational, occupational, health, and social). The wording was as follows: “People can behave differently in different situations. How would you rate your willingness to take risks in (e.g.) *the financial domain?*”. A general risk-propensity item was included in wave 2 (“How willing are you to take risks in general?”, Dohmen et al., 2011). Respondents also indicated whether they had ever thought about participating in medical research themselves. The survey concluded with demographic questions (gender, age, education). The final sample, on average, took 22.5 minutes (range 8.7 – 74.5 minutes,  $SD = 10.38$ ) to complete the survey.

## Statistical analyses

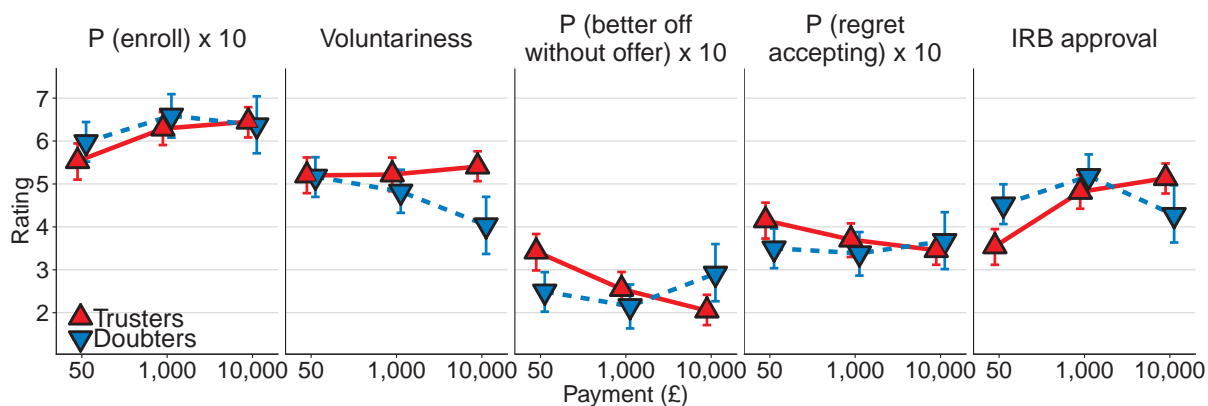
We relied on Bayesian estimation techniques (Kruschke, 2014) and applied Bayesian Generalized Linear Models using Stan in R for regression analyses with the `rstanarm` package (*RStanArm Version 2.9.0-4*, 2016). We ran three chains using Markov Chain Monte Carlo sampler to draw from posterior distributions of parameters, with 10,000–30,000 samples per chain (to ensure an effective sample size of >10,000 for each regressor), and a burn-in of 500 samples. We investigated the convergence of our posteriors through visual inspection and the Gelman-Rubin statistic (Gelman & Rubin, 1992). In general, we report the mean of the posterior distribution of the parameter or statistic of interest and two-sided 95% equal tail credible intervals (CI) around each value. In the replication section, our data analysis corresponds to the analysis in the original study.

## Results

The results section is organized as follows: First, we present a qualitative replication of Ambuehl et al. (2015), again showing that Doubters and Trusters disagree about offering £10,000 when evaluating various clinical trial dimensions. Second, we show how payment can leak information about the riskiness of clinical trials. Third, we investigate the extent to which risks and coercion were linked to clinical trial evaluations (i.e., linking sections 1 and 2). Lastly, we explore risk and coercion as determinants of repugnance for clinical trials more generally.

### Clinical trial evaluations (replication of Ambuehl et al., 2015)

Following the original survey, we categorized respondents into three types, based on how they rated the ethicality of different payment amounts ( $\delta_{rating} = rating_{£10,000} - rating_{£1,000}$ ). Trusters rated a payment of £10,000 as strictly more ethically appropriate than a payment of £1,000 ( $N = 712$ , 50%,  $\delta_{rating} = 1.84$ ,  $CI = [1.77, 1.91]$ ). Doubters rated a payment of £1,000 as strictly more ethical than a payment of £10,000

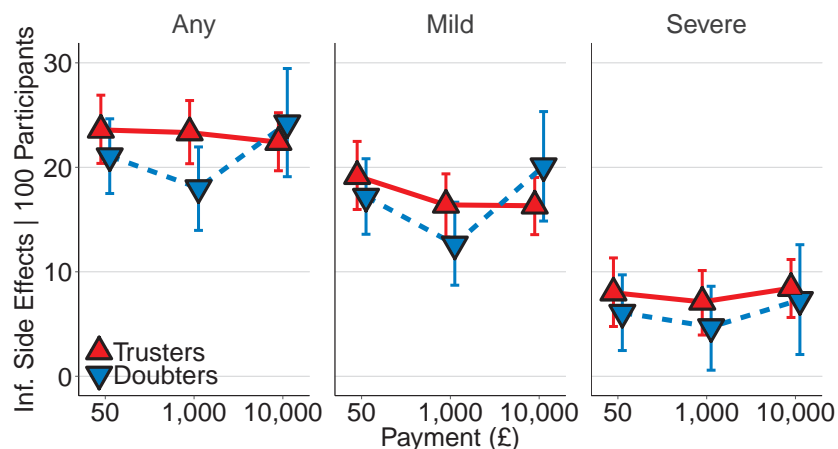


**Fig. 1.** Responses of Doubters and Trusters for various payment amounts (between-respondents). Black triangles represent sample means. Colored triangles and error bars represent the means and the 95% highest density intervals of the posterior predictive distributions.

( $N = 378$ , 27%,  $\delta_{rating} = -2.24$ ,  $CI = [-2.33, -2.14]$ ). A subset of respondents rated both payment amounts equally (Others,  $N = 338$ , 23%,  $\delta_{rating} = 0.00$ ). The proportions of each type were highly similar to the proportions reported in Ambuehl et al. (2015). In the main results section we report analyses using responses to the first payment amount a respondent saw; each respondent therefore appears only once in the analyses (results for Others and within-respondent analyses shown in Supplementary Materials).

As in the original survey (Ambuehl et al., 2015), both groups (Trusters, and Doubters) evaluated clinical trials similarly as pay increased from £50 to £1,000 (Figure 1): For instance, both Doubters and Trusters were more likely to give IRB approval for a trial offering £1,000 compared one offering £50, likely because the trial was described as requiring 40 hours of commitment, for which £1,000 seems fairer than £50. Figure 1 also shows that Trusters and Doubters expected approximately the same number of people to enroll in a trial that offered £10,000 compared to one that offered £1,000 (all CIs across payment amounts and interactions between groups included 0). This is different from the original survey, where both groups expected more people to enroll for £10,000.

However, as in the original survey, offering £10,000 rather than £1,000 to clinical trial volunteers was evaluated differently by Doubters and Trusters with regard to



**Fig. 2.** Estimated side effects for various payment amounts by Doubters and Trusters (between-respondents). Black triangles represent sample means. Colored triangles and error bars represent the means and the 95% highest density intervals of the posterior predictive distributions.

‘voluntariness,’ ‘being better off without the offer,’ ‘regret accepting’ and—as a possible combination of the aforementioned concerns—‘IRB approval.’ Specifically, as Figure 1 shows, Doubters considered the enrolment of a woman earning £1,500/month in the clinical trial as less voluntary when she was offered £10,000 ( $b = -0.97$ ,  $CI = [-1.49, -0.44]$ ). In addition, Doubters said a woman earning £1,500/month would be better off had she not even seen the high offer ( $b = 1.26$ ,  $CI = [0.26, 2.26]$ ). Consistent with this, Doubters also considered a woman earning £1,500/month to be more likely to regret accepting the offer ( $b = 0.53$ ,  $CI = [0.05, 1.02]$ ). Lastly, Doubters on an IRB panel approved the study offering £1,000 more than they approved the same study offering £10,000 ( $b = -1.22$ ,  $CI = [-1.69, -0.77]$ ).<sup>4</sup>

<sup>4</sup> All models tested the effect of offering £10,000 over £1,000, using “Truster” as a baseline. As in the original study (Ambuehl et al., 2015), the “IRB approval” variable is different from the variable used to define the types that appears later in the survey, in which all payment amounts were presented side by side, and participants were asked to judge the ethicality of each amount. However, the two variables are correlated: “IRB approval” (Figure 1) asked respondents to evaluate the trial *given* a particular payment. Later, respondents were asked to evaluate the trial and *determine* appropriate payment. As we show later, clinical trial evaluations can be explained using *inferred risks* and *voluntariness*—and without relying on the Truster/Doubter dichotomy.

### Inferred side effects

While Doubters found offering £10,000 to be less ethically appropriate than offering £1,000, Trusters found both amounts to be approximately equally appropriate. To investigate whether Doubters, unlike Trusters, employed high payment amounts as a cue to higher risks, we once again analyzed estimates for the first payment a respondent saw. We ran separate analyses for each type of side effect (any/mild/severe). There were no main effects of compensation amount on the estimated number of side effects (£50 versus £1,000, as well as £1,000 versus £10,000; all CIs included 0). Moreover, as Figure 2 shows, increasing compensation from a very low amount (£50) to a moderate amount (£1,000) did not result in differential estimates of side effects for the two groups.

However, as in earlier analyses, individual differences emerged as a trial offered a very large compensation—£10,000, compared to £1,000. Specifically, Doubters expected more side effects for trials that offered a very large compensation ( $b_{any} = 6.19$ ,  $CI = [1.15, 11.33]$ ,  $b_{mild} = 7.47$ ,  $CI = [3.30, 11.46]$ ,  $b_{severe} = 3.00$ ,  $CI = [-0.15, 6.17]$ , note the CI includes 0 for severe side effects), whereas Trusters' inferred side effects were independent of payoff magnitudes (all CIs included 0).<sup>5</sup> When analyzing the estimated number of side effects within-respondents, Trusters also judged trials offering very high payments to be riskier, but they were less sensitive than Doubters to the payoff information in the vignette (Supplementary Material S3.2).

In sum, consistent with our hypothesis, we found a positive relationship between the amount a clinical trial offers and its inferred riskiness for Doubters but not Trusters. One qualification of this result is that extremely small payoffs (£50) did not reduce inferred risks compared to moderate amounts (£1,000)—only extremely large payoffs (£10,000) increased inferred risks compared to moderate amounts (£1,000).

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<sup>5</sup> All models tested the effect of offering £10,000 over £1,000 (or £1,000 over £50, using “Truster” as a baseline. Results of all analyses are listed in Supplementary Material 3.1.

### Inferred side effects and clinical trial evaluations

Next, we examined whether respondents' ethical approval of the clinical trial was linked to their estimated number of side effects. Again, we focused on the first payment amount respondents saw. The judged number of participants to enroll in the study was unrelated to the estimated number of side effects (all CIs included 0): While the estimated number of side effects increased with increasing payment amounts from £1,000 to £10,000 (Figure 2),  $p$  (*enroll*) did not (Figure 1). It is plausible that inferred risks and high financial gain offset each other as respondents consider whether or not volunteers would enrol. However, a participant was considered to be better off without the offer if side effects were expected to be higher ( $b_{any} = 0.034$ ,  $CI = [0.025, 0.043]$ ). Consistent with this, respondents who estimated a higher number of side effects also thought that participants would be more likely to regret accepting an offer to take part in the study ( $b_{any} = 0.022$ ,  $CI = [0.017, 0.026]$ ). Lastly, higher risk assessments lowered respondents' IRB approval of the clinical trial ( $b_{any} = -0.013$ ,  $CI = [-0.017, -0.009]$ , all modeled as main effects; coefficients are smaller for the side effects regressor due to its scale [0–100] as compared to the voluntariness scale [0–7]).

The role of estimated side effects in evaluating the trial did not depend on whether a respondent was a Doubter or a Truster (clinical trial evaluations modeled in three-way interaction using type [Doubter vs. Truster]  $\times$  payment  $\times$  estimated number of side effects as predictors; all CIs included 0). This is unsurprising since comparable interaction effects between these groups were present in clinical trial evaluations (Figure 1) and the estimated number of side effects (Figure 2).<sup>6</sup> These findings suggest that subjective risk estimates influence how ethical they find a given trial.

Earlier research suggested that these evaluations were also related to how coercive respondents found the clinical trial (Ambuehl et al., 2015). To study whether both inferred

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<sup>6</sup> The results also held in other specifications of the model, for instance after controlling for the [Doubter vs. Truster]  $\times$  payment [£50/£1,000/£10,000] interaction or the other side effect types as predictors [mild/severe]; see Supplementary Material 4.1.

risks and coercion (i.e., lower voluntariness) have separable influences on clinical trial evaluations, we simultaneously entered voluntariness and side effects as predictors in a linear regression; we found that both variables do explain unique variation in how respondents evaluated clinical trials. Participants were considered to be better off without seeing the offer when voluntariness was judged to be lower and inferred side effects were higher ( $b_{volun.} = 0.3709$ ,  $CI = [-0.4819, -0.2594]$ ,  $b_{risk} = 0.0229$ ,  $CI = [0.0209, 0.0390]$ ). Participants were thought to have less regret about accepting a trial if voluntariness was judged to be lower and inferred side effects were higher ( $b_{volun.} = -0.2612$ ,  $CI = [-0.3118, -0.2107]$ ,  $b_{risk} = 0.0188$ ,  $CI = [0.0146, 0.0229]$ ). Moreover, IRB approval increased when voluntariness was judged to be higher and inferred side effects were lower ( $b_{volun.} = 0.2800$ ,  $CI = [0.2291, 0.3311]$ ,  $b_{risk} = -0.0098$ ,  $CI = [-0.0139, -0.0057]$ ; regression tables reported in Supplementary Material 4.1).

We also explored the ‘net effects’ payoffs had on IRB approval for Doubters and Trusters using a mediation approach: As expected, there was a smaller net effect of payoff on IRB approval for Doubters and not Trusters after controlling for estimated side effects and coercion (Supplementary Material 4.2). A similar pattern emerged in within-respondent analyses: Doubters relied on payoff information when assessing risks and voluntariness, and ultimately when determining IRB approval (Supplementary Material 4.3). Trusters were more insensitive to changes in payoff magnitude.

## Repugnance

In a final set of analyses, we also examined whether respondents who estimated a higher number of side effects also considered clinical trials as generally less ethically permissible. That is, can the perceived risk of a clinical trial at least partially explain whether or not individuals find clinical trials repugnant? We hypothesized that respondents who considered clinical trials to be riskier may also find them more repugnant, or less ethically permissible in general (independent of payoff magnitude). Indeed, higher

repugnance was linked to a higher number of estimated side effects ( $b_{\pounds 10,000} = 0.0082$ ,  $CI = [0.0058, 0.0106]$ , estimates for ‘any’ side effects, given a payoff of  $\pounds 10,000$ ). This link was stable across side effect estimates for different payment amounts and in other specifications of the model (Supplementary Material 4.2). The link between side effects and repugnance was present for Doubters ( $b_{\pounds 10,000} = 0.0082$ ,  $CI = [0.0039, 0.0125]$ ) and Trusters ( $b_{\pounds 10,000} = 0.0048$ ,  $CI = [0.0013, 0.0082]$ ; main effects; comparable results for  $\pounds 1,000$  and  $\pounds 50$ )—again, the link was more pronounced for Doubters (comparison of  $\beta$  regressors).

Since coercion is another explanation for repugnance (Ambuehl et al., 2015), we also tested whether voluntariness affected repugnance ratings in a regression using both side effects estimates and voluntariness as predictors. Indeed, clinical trials were considered less repugnant when they were judged to be less coercive (or more voluntary). This held in addition to the variance explained by the estimated number of side effects ( $b_{risk} = 0.0065$ ,  $CI = [0.0042, 0.0088]$ ,  $b_{volun.} = -0.1489$ ,  $CI = [-0.1803, -0.1172]$ , in a model relating repugnance to both side effects and voluntariness; see Supplementary Material 4.2) as well as to several demographic characteristics that can help explain who finds clinical trials repugnant, such as whether or not respondents had thought about participating in a clinical trial themselves (but not being a Doubter/Truster; see Supplementary Material 4.4 for full model).

## General Discussion

More than 90% of healthy clinical trial volunteers say money is their main motivation for taking part (Bigorra & Baños, 1990; van Gelderen et al., 1993). However, the high pay—often significantly higher than other types of “unskilled” labor—these studies offer can make this transaction repugnant (Ambuehl et al., 2015; Roth, 2007; Wilkinson & Moore, 1997). There are at least two reasons that this is the case. First, high payments can be seen as manipulative and even coercive. Second, as we hypothesized, high pay can be used as a cue to the risk involved. Both reasons can cause clinical trials offering high



payments to be less ethically permissible.

Do people perceive higher payment to be associated with higher risk? We found this to be the case for one group of respondents. Doubters expected more people to experience side effects than people in the same trial with a smaller payoff. Trusters, in contrast, inferred similar risks across payoff magnitudes. Consistent with earlier results (Cryder et al., 2010), these findings do not support the conjecture that high pay *impairs* peoples' ability to think carefully about the risks and benefits of a clinical trial (Casarett et al., 2002); or, alternatively, that high pay conceals the risk involved in a clinical study (Bentley & Thacker, 2004; McNeill, 1997). To the extent that payments are actually correlated with risk (Grady, 2005), our results resonate with adaptive cognition theories (Anderson, 1991; Gibson, 1979; Gigerenzer et al., 1999; Marr, 1982; Simon, 1956; Perkovic & Orquin, 2017; Hertwig et al., 2013; Stewart, 2009). These theories state that the mind is often well-attuned to statistical structures in the environment: For instance, people are aware that the high rewards they desire are unlikely to occur due to fair-bet assumptions between seller and buyer (Pleskac & Hertwig, 2014). By the same token, people may also assume there are no "free lunches" in clinical trial markets and infer that high payments compensate for high risk.

Our analyses revealed individual differences in the extent to which inferred risks were payoff-dependent. There may be several reasons for this. First, some people may not consider payments and potential risks to be linked, either because the relationship is imperfect (in fact, only a third of surveyed research institutes claimed to factor in risk when determining payment; Grady, 2005), or because they have only been exposed to very few instances of the relationship (e.g., clinical trial advertisements). Second, since descriptions of clinical trials have to disclose known risks to potential participants, payoff information may not be the only cue people rely on to infer the riskiness of a clinical trial. For instance, in our vignette people were told that, "*Since no side effects occurred in animal studies, the institute's experts consider it unlikely that they will occur in humans.*",

and “*If side effects occur, they may range from [...] nausea to [...] migraines*”. The fewer additional cues they have, the more people may focus on payoff information (Leuker et al., 2018). More generally, people may have prior beliefs about the phase of the clinical trial and the medication in question. Thus, payment may be just one of several cues that could characterize a study’s underlying risk. This may help explain variability in earlier results (Cryder et al., 2010; Mantzari et al., 2014).

From a purely economic perspective, high pay in clinical trials is not unethical. Why should someone be worse off if they are offered £10,000 instead of £1,000 for the same work? One concern—also voiced by our respondents—is that socioeconomically disadvantaged people in particular may feel coerced to take part (Ambuehl et al., 2015; Roth, 2007; Wilkinson & Moore, 1997). But another reason is that high payments are suspected to be associated with high risks. In contrast to a proposition by Ambuehl et al. (2015), Doubters made this inference for £1,000 versus £10,000 payment schemes despite the trials being otherwise identical. Ultimately such payoff-dependent expectations of more side effects from a very lucrative clinical trial can lead to lower IRB approvals, stemming from the expectation that more people would regret participating and the judgment that people would be better off without the offer. Higher pay does not monotonically increase IRB approval solely because it may be coercive, but also because it can change people’s perception of risk.

In a final analysis, we showed that subjectively riskier trials were considered to be more repugnant. Objective risk has been established as playing a role in some repugnant markets (Table 1, p. 39, Roth, 2007), but to our knowledge the role of subjective, inferred risk has been overlooked when studying feelings of repugnance. This link between risk and repugnance may generalize to markets in which parties may be partially remunerated for the risk they take, such as surrogate motherhood.

Our findings may have practical implications for both research institutes and governments. Currently, extremely high payoffs are, by some, perceived to compensate for

higher risks. However, severe incidents such as the 2015 French drug trial (AFP, 2016; Randerson, 2016) show that not even institutes themselves can accurately determine the risk a trial entails in advance. We suggest that research institutes should not compensate in advance for suspected higher risk. Instead, volunteers should be explicitly informed that they will be paid a fair wage for their time—and, as is already the case, all measures will be taken to minimize potential harm. If unanticipated side effects do occur, the research sponsors will compensate for research-related harm or injuries. This approach is consistent with Manning’s (2017) statement that “the beneficiaries of research (researchers, sponsors, society) have a moral responsibility to compensate for research-related injury” (p. 426). This can be achieved, for instance, by implementing no-fault compensation (e.g., through a public fund). These policies may ultimately help reduce the repugnance of clinical trials.

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**Open Practices Statement:** Preregistrations of this work (wave 1: [osf.io/yftvh/](https://osf.io/yftvh/), wave 2: [osf.io/kumge/](https://osf.io/kumge/)), data and analysis code ([osf.io/5kewt/](https://osf.io/5kewt/)) can be found at the Open Science Framework.

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