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Acceptability of donor-funding for clinical trials in the UK: a qualitative empirical ethics study of the views of PPI groups members, REC chairs and clinical researchers.

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ABSTRACT

Objectives To explore, for the first time, the acceptability of donor-funded research where the donor funds the entire trial and in so doing secures a place on it (the 'Plutocratic Proposal')

Design Qualitative empirical ethics using focus groups held online between September and December 2020

Participants 3 separate focus groups were convened for Patient Public Involvement group members, research ethics committee chairs and clinical researchers. Of the total of 22 participants, 8 were female. All were based in the UK.

Results Maintaining the scientific integrity of clinical research was the primary concern in all groups. Participants considered whether it was unfair for people to use their wealth to secure a place on a trial but recognised that, because the donor funds the whole trial, others would also potentially benefit. Concerns that donors may be exploited were also expressed, primarily related to potential therapeutic misconception. Views about whether the donor should be identified as the funder in the trial's information for participants were mixed. Also considered were the addition of further donors to supplement funding and potential ways to mitigate ethical concerns. All but one participant thought it would be generally acceptable to introduce this form of clinical research funding.

Conclusions Using donor-funding of the kind described in the Plutocratic Proposal to meet the shortfall in funding for clinical research is likely to be acceptable to key stakeholders. Caution and careful guidance, however, particularly in relation to donors securing a place on the trial, is necessary to help researchers and reviewers navigate ethical concerns. Work is now needed to generate this guidance and introduce it to research ethics committee members.

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ARTICLE SUMMARY: STRENGTHS AND LIMITATIONS OF THIS STUDY

- The ethics of donor-funding has been discussed in the literature, but this is the first study to explore whether donor-funding is acceptable to potential stakeholders (those designing, reviewing and potentially participating in clinical trials).
- Empirical ethics is a recognised methodology for understanding and evaluating ethical issues that affect policy in healthcare services and research.
- Focus groups are a qualitative tool for exploring potentially controversial topics, as they permit participants to engage with each other's views.
- Given the complexity of the ethical issues discussed, participants may have arrived at more considered and nuanced views if more substantial engagement process, such as citizen juries, had been possible.

INTRODUCTION

Many promising clinical interventions do not progress to early clinical trials due to a lack of research funding, and those that do may fail for commercial reasons. One solution proposed by two patient-advocates, Masters and Nutt,[1] is that very wealthy individuals fund an entire phase I or phase IIa clinical trial in exchange for the guarantee of a place on the trial (subject to the inclusion and exclusion criteria being met at the point of recruitment). They call this the Plutocratic Proposal (PP) and envisage a 'matching agency' that would 'pair' donors and researchers without exploiting the donor or interfering with normal and accepted research review and governance procedures. Their proposal grew out of their experience of crowd sourcing a clinical trial to help a friend with metastatic pancreatic neuroendocrine cancer. They argue that there is a moral imperative to explore new, acceptable avenues for research funding.

The PP presents ethical challenges. These were evaluated by King and Ballantyne[2], against current research practices and also other forms of donor-funding – pay-to-play[3] where individuals pay for their own participation in a trial, and pay-to-try[4] where individuals pay for access to a promising intervention but not obviously as part of any trial. They concluded that there is "nothing inherently unethical" about PP (p.39). Donor-funding should, they argue, be assessed against "real-world ethical standards" and "standard health research legislation/guidelines and undergo IRB/REC and scientific peer-review" (p.39) rather than being measured against aspirational standards that current research practice fails to live up to. Compared with other forms of donor-funding, they regarded the PP as most likely to reduce the potential ethical risks.

METHOD

Our aim was to explore potential barriers to securing favourable research ethics committee (REC) review for PP donor-funded clinical trials. Overcoming any such barriers would remove a potential obstacle to this novel funding stream. Finding that these barriers are insurmountable was an alternative potential outcome of the project.

An empirical ethics approach[5] was chosen to meet this aim. This enabled us to combine a purely ethical analysis with the stakeholders' views about acceptability. Identifying and exploring issues philosophically enabled a systematic evaluation of ethical issues based on key features of the PP, the role and remit of RECs and broader principles of research ethics. Including stakeholders' views helped to ensure that key issues were not inadvertently missed, and provided some understanding of what matters most to those stakeholders, which acts as a check to the researchers' analysis.[6]

There were, therefore, three key components to the project:

1. To undertake an initial analysis of the ethical issues raised by PP in the light of Health Research Authority (HRA) policies and guidance to RECs, and to use this analysis to create a topic guide to explore the stakeholders' views;

2. To explore, using focus groups, the views and ethical concerns about the PP for REC members, clinical researchers and potential research participants as key stakeholders in the research ethics review process;
3. To determine, based on components 1 & 2 what guidance around PP might be needed.

A topic guide was designed by HD in consultation with the whole project team. There is only a small literature on the potential ethical objections to donor-funding, which is located in the larger literature on research ethics. We considered this alongside published HRA policies and guidance for RECs and researchers making REC applications, to determine considerations a REC should have in mind when reviewing research protocols and other supporting application documents.

We also considered how potential concerns might be met, mitigated or pre-empted, and what additional concerns might be raised by such measures. For example, should the donor be named in the information sheet of the trial they funded? If so, how would they be protected from exploitation or intrusive publicity? Another potential objection to PP is that the donor has effectively 'bought' a place on the trial that would otherwise have gone to another person. One solution might be for the donor entirely to fund a trial plus an additional place for themselves. But while this might allay concerns about fairness, it would compromise harm minimisation (more participants than necessary) and the donor-participant's data could not be collected for General Data Protection Regulations reasons (if strictly supernumerary). Anticipating potential responses meant these could be included as potential prompts for further discussion.

The draft topic guide was piloted in February 2020 first with a group of researchers and REC members, and then with two research patient public involvement (PPI) group members, who also helped to shape the participant information for the study. The topic guide was revised and then finalised (supplemental1) based on the comments from each pilot group sequentially.

Three focus groups were convened, one for each of the stakeholder groups (REC chairs, clinical researchers and research PPI members, who were our proxy for potential study participants).

REC chairs were recruited by email, using information in the public domain. Everyone approached and who was available on the date selected agreed to participate. Our intention was to recruit clinical researchers via published lists of REC-reviewed research for the period Jan-March 2020. The response rate using this method was, however, extremely low and only two participants were recruited this way. UK Spine then circulated information about the project to researchers in its network and two researchers were recruited by this method. A further two were recruited by circulating information through known contacts in clinical trial units. One heard about the project through our recruitment drive for PPI participants and offered to be included. Our PPI participants were recruited via PPI networks associated with clinical trials units and selected on the basis of availability and achieving gender balance and representation across the three groups approached.

Recruitment commenced in July 2020 and finished in Dec 2020. Recruitment was at first delayed and then prolonged because of the effects of the coronavirus (COVID-19) pandemic. Focus groups were convened in September, October and December 2020, using Microsoft Teams. Participants provided audio-recorded consent individually using Microsoft Teams prior to the focus groups taking place. The consent process also provided an opportunity for the participants to familiarise themselves with Microsoft Teams, guided where needed by the researchers gaining consent (KS, HD). One PPI participant was unable to participate due to microphone issues that we were unable to resolve during their consent meeting.

Each of the focus groups started with a short presentation, reminding the participants about the features of PP. It mirrored a recorded presentation that was produced to supplement the written participant information sheet on the recommendation of the pilot PPI members. Participants tended to respond to the first question from the topic guide at length, and, in doing so, provide answers to questions that appeared later in the guide. When this occurred, these broader responses were explored in detail at that initial point.

The focus groups were recorded and transcribed verbatim. Participants were invited to send any further reflections or comments by email to HD. Two participants sent comments that were added to the end of the transcriptions for their respective groups (PPI and researchers). Each transcription was reviewed by HD: identifying information was removed and participant identifiers allocated. The transcripts were independently coded (HD, KS), using a thematic analysis informed by the range of ethical issues raised by the participants in each group. The resulting codes were then reviewed and discussed by the research team

and organised into categories and themes that reflected the aims of the project. Preliminary analysis was presented to, and discussed for validation purposes with, a 'user panel' drawn from each focus group.

When discussing our findings, we have adopted the "conservative argument from consistency" (p.39) in line with King and Ballantyne's evaluation of donor funding.

There was PPI involvement throughout (supplemental2)

A favourable ethics opinion was received from the Biomedical & Scientific Research Ethics Committee of the University of Warwick [reference: BSREC 126/19-20].

RESULTS

Twenty-two participants attended three focus groups (table 1).

Table 1. Focus groups and participants.

Focus Group	Participant Type	Gender
1 (112 minutes)	REC Chairs (n = 7)	4 male; 3 female
2 (88 minutes)	Members of PPI groups (n = 8)	4 male; 4 female
3 (75 minutes)	Researchers (n = 7)	6 male; 1 female

Seven themes were identified from the coded data (table 2). Three fell outside the scope of this paper (and are reported for completeness in supplemental3)

Table 2 Seven themes identify specifying those to be reported in the main paper

Outside scope	Reported and discussed
'Dirty' money/donors of bad character Disruption to research agenda/infrastructure Matching agency governance and processes	Good science Concerns raised by donor gaining a place on the trial Further funding from additional donors General acceptability

Three themes met the objective of this study, which was to identify and address the potential obstacles for PP at the REC review stage: good science; concerns raised by donor gaining a place on the trial; further funding from additional donors. The fourth theme, 'general acceptability', represents participants' overarching view of PP.

Illustrative quotations are provided in table 3, grouped into themes and numbered.

Table 3 Illustrative quotations

Participants (P) were allocated an identifier according to focus group (REC, PPI and Res=researcher) and then order in which they spoke (P1, P2, P3 etc.).

Good science

1. 'We know that good science is good research, and that's good ethics.' (RECP5)
2. 'I think, you know, we've mentioned the word crackpot schemes a few times over the course of the past 20 minutes and it's clear that, that, that that is where the danger really lies and, and the concept, the idea really that this is gonna be funding areas of research which just shouldn't be funded.' (ResP5)
3. 'I would have grave concerns about creating a system which allowed donor-funded research to fund poor quality research…once you put a system in which doesn't have the safeguards of UKRI type panel, then it is gonna be vulnerable, I think, to having crackpot ideas funded.' (ResP3)

4. 'I have concern around scientific validity. I'd want to be convinced that the donor had no role or influence in the design, the conduct or the reporting of, of the research.' (ResP6
5. 'The potential for the donor to influence the science, which raises concerns and it's the same concern as if there's a pharmaceutical company that's funding. And, there's a conflict of interest there, and I can imagine there being all sorts of pressures.' (ResP1)
6. 'But I would be worried about the conduct and bias, perhaps, in analysis of the results, and do we bend rules for people who want to get into the trial?' (PPIP5)
7. 'It's certainly true in doing research with independent healthcare companies, I've done several studies that if they don't like the results they really come after you in a way. They want you to… there's pressure to, "Well, couldn't you just, sort of soften it down here?" or whatever. Instead of, you know, perhaps always facing what you've actually found out.' (RECP3)

8. '… there's a particular need for anyone involved in this expert review and RECs to be certain about the science and the background literature as it relates to a piece of research through this route.' (RECP4)
9. 'If they're clinical trials, they have to go through the MHRA, erm, in which case that is one independent review.' (RECP7)
10. 'I would have concerns about how you could have the same level of critical independent review in this parallel universe.' (ResP4)
11. '… and there must be PPI everywhere to ensure the views of the public are expressed and acted on at all levels.' (PPIP5)

12. 'if the researchers do know who it is has provided the cash for this then there is going to be, however well intentioned, a tendency to treat that individual differently.' (PPIP1)

Concerns raised by the donor gaining a place on the trial

Disclosing the identity of the donor

13. 'I think if somebody is, is prepared to put the money up for this then it should be known by everybody who's involved in the process.' (PPIP1)
14. 'Clearly this is of some concern to some people, of high concern to others, and of no concern to others, so I think you have to put the information in just morally.' (PPIP7)
15. 'In the documents that I've read, that perhaps CRUK fund this, I don't know how they're gonna write down, you know, "a donor," cos that will immediately raise suspicions in somebody's mind.' (PPIP6)

16. 'I was thinking just now of the ways in which having a named donor might actually influence recruitment. You know, just thinking about, for example, Britney Spears and Kanye West, two people with long term severe mental health problems, and one of whom repeatedly is presented as mad and the other who's presented very sympathetically as, "Oh, poor dear, she's struggling." … Do those sort of images have a knock on effect if you see them on the participant information? You know, 'I'm not going to sign up for something, you know, funded by him, but I might, you know, if it comes from her." … There is an argument for that, that anonymity.' (RECP3)
17. 'That was one of the reasons why the ethics committee was so cross about it [piece of research proposed by a celebrity], because we thought there was someone who is using his celebrity to try and push through a piece of research and, indeed, get a head start on recruitment prior to even getting a review by the ethics committee.' (RECP1)

18. 'I mean, the alternative is you just say it's the matching agency, but I don't think that's being transparent - sufficiently transparent.' (PPIP7)
19. 'To say that…a piece of research is funded by an anonymous donor, from…the very little I know of the Helsinki Agreement, is probably okay.' (PPIP4)
20. 'We don't go into lots of details about where money's come from through…organisations that we generally tend to think are reputable, like Cancer Research. We wouldn't ask who's donated to that, you know, and what proportion of that donation has gone through to this project, but we'd just put "Cancer Research" at the top.' (RECP6)
21. 'There are good reasons not to tell participants who's funding trials in some circumstances, and I have seen the ethics committee swayed by arguments that you shouldn't tell participants who's funding specific trials.' (RECP1)

22. 'I suspect that many potential participants would be more concerned about that [the science] than…they would be about who's funding it.' (RECP6)
23. 'The evidence is that people aren't interested in funding.' (RECP7)
24. 'I mean, my experience of working with participants is that very few of them are concerned about who's funding it, and, you know, as… comparing funding from drug companies, is it vastly different?' (PPIP3)

The therapeutic misconception

25. 'People think that if you throw enough money at something then in 18 months you might have a cure for any disease when in actuality that almost certainly is never likely to be true again.' (ResP5)
26. 'People [researchers] are convinced about their treatment, they will take money from many sources for it, and if somebody is charismatic and persuasive about their treatment, I'm not convinced that the donor is gonna be in a position to make an informed decision that that's the treatment that they want to put their money into.' (ResP1)
27. 'These people, one assumes, are very desperate, you know, they are really going to just want it for their own end initially.' (PPIP6)
28. 'There's quite a difficulty, I think, isn't there, in how donor money is going to be used properly to fund good research without it becoming a 'looking around for something that might help me. And those would have to be very clear to the people who are intending to give the money, the people who're in the matching agency, and the people doing the research.' (RECP4)

29. 'If at the end of the, of that consent process the patient says, "thanks, I'm delighted to go in as long as it's going to help me," at that point, that patient's consent is not valid and therefore in a sense there is something implicit about this whole transactional relationship which is problematic.' (ResP4)
30. 'If I have an illness and I agree to participate in a trial, then I generally believe that that trial is happening because there's been good review that it's an appropriate thing to do, that the intervention is going to be likely to be successful, that, you know, it has been fully peer reviewed…they're not gonna do it unless it's likely to be successful, whether it's got a good chance, or whether it's by charity or government funding.' (ResP1)

Donor benefit

31. 'I have concerns around the fairness of participant selection. It should really be based on scientifically valid criteria not ability to pay and, and research risk and benefits should be fairly distributed, I think, in society.' (ResP6)
32. 'Are other participants going to know that it's being funded for one particular person, with that person in mind, or that problem in mind? So, you know, other participants might feel aggrieved, if you like, that it's funded for this particular one person.' (PPIP3)

33. 'I haven't heard anything that says they need to be included in the analysis.' (PPIP2)
34. 'This is my lay suggestion, why do they have to actually be part of the analysis? Be part of the, the research…there's a donor who's… For which they get the treatment and that's fine, that's done, and nobody actually knows who they are. But when it comes to the analysis there's some flag put into some system somewhere that says, "Don't include this person." And as I say, I'm not very sure about the ethics of what I've just said but it seems to me pragmatic.' (PPIP3)
35. 'Well, my first reaction is that that [excluding donor from analysis] sounds a very good idea, as you say it means nobody's losing their place. I haven't thought, at the moment, of any disadvantage of that.' (PPIP4)

36. 'I would agree with RECP1's point, you know, you know, my dear father, when I sat on his knee, said to me, "Life's not fair," and I haven't forgotten that one.' (RECP7)
37. 'It's the same thing as why can that person buy a Rolls Royce yet I can't? It's those sort of things, why can people have first class train fare or flight, when I can't?' (PPIP7)

38. 'If you try to argue that it's not fair that that happens and, therefore, this shouldn't be a way of funding research you're then depriving all the other ten of being involved in a piece of research that may well be of benefit. So, you know, I think somebody using a lot of money, erm, to benefit others, and it also benefits them, seems entirely reasonable.' (RECP4)

Further funding from additional donors

39. 'Again, er, the fact that 100 people fund and it's 100 participants who are the funders, I've no issue… its benefit that's what's, are what's important here, for the common good.' (PPIP7)
40. 'It seems to be that there should be a limit, but I can't… choosing a number it would be entirely arbitrary, in the way I'm thinking about it.' (RECP6)
41. 'I don't think this is a problem that is specific to this particular type of trial, I think it's something that would, would apply right across the board for any sorts of trials, and it's just part of good trial management that you make sure that the thing doesn't run out… that sort of stuff shouldn't happen no matter what type of trial it is.' (RECP1)

General acceptability
42. 'I can't see any fundamental issue that would make me want to say, "No. Can't even consider it." I think there are lots of things to thrash out, but I think it's something that needs to be on the table.' (RECP6)

43. ‘So I have no major objections to this model because it's already happening that the rich are accessing novel and experimental treatments. If we allow it to have donor-funded research, it may lead to some breakthroughs that will eventually be available to the public. And at the moment many things are being crowd funded, video games, et cetera, films, so I have no serious objections.’ (PPIP8)
44. ‘It would be something I’d be quite happy to sign up to so long as we are able to maintain that scientific integrity and we do have these balances and checks in place.’ (ResP5)

45. ‘I think it's an interesting subject, and it can be a novel way of funding research as well, because researchers who are applying for grant applications, what you mentioned, it's, kind of, becoming more and more difficult to get studies funded.’ (RECP5)

46. ‘I think having a separate committee to review these, these sort of studies, unless we actually demonstrate a need for it it surely just reinforces that this is a special case when, actually, erm, if it's going, if it's going to work at all it's got to be come normalised. I can see the argument for special committees that deal with defence or, er, defence projects, or, erm, certain other factors, but why should this be a separate category? If it's going to work it's just another funding stream.’ (RECP3)
47. ‘You know, an area that’s not normally funded cos there’s nothing in it for the pharma companies and I don't see anything different in principle, really, between a pharma company funding research to a private individual, what's the difference?’ (PPIP7)
48. ‘So many of these things are so study dependent, and it just depends upon the context of the study as to exactly what, what you come down to.’ (RECP1)
49. ‘There are specific considerations that come up, and what’s needed, and might come from this sort of work is a, a framework of questions and considerations where… Of the particular issues in this type of trial.’ (RECP7)

50. ‘I've listened with interest and I think people have made some excellent points but I'm afraid they haven't really moved me from my initial position, that this is a bad thing, erm, and it may or may not have good results but, erm, in the lap of the gods. I suspect it’s going to happen regardless of, er, of my personal feelings, as many other things happen. I don't like it.’ (PPIP1)

Good science

Participants in all three focus groups highlighted the ethical importance of robust science and trial design for donor-funded research (quotations 1-3).

The greatest concern raised in relation to the science was that donors might influence the study design. Many participants felt that a funder participating in a trial may be allowed to influence not only the conduct, but also the results of the research (quotations 4-7).

For some participants ‘good science’ encompassed the need for independent expert review, with some participants acknowledging that all clinical trials would be subject to Medicines and Health Products Regulatory Agency (MHRA) review, and PPI input (quotations 8-11).

Some participants were concerned that a donor-funder also being a participant could introduce bias or result in preferential treatment (quotation 12).

Concerns raised by donor gaining a place on the trial

Three concerns relating to the donor gaining a place on the trial were identified. These were disclosing the identity of the donor, the therapeutic misconception, and donor benefit.

Disclosing the identity of the donor

The REC and PPI groups discussed whether the identity of the donor ought to be disclosed to the other trial participants. The PPI participants tended to think that their identity should be disclosed in the interests of transparency (quotations 13-15).

Two REC participants were concerned that if donors' identities were known, and they publicised their participation on social media, this might influence the public to take part in the trials (quotations 16-17).

In the PPI group, views were mixed as to whether disclosing the name and details of the matching agency instead would be sufficient. Some felt that this would not be transparent enough, while the REC group were more receptive to this idea (quotations 18-21).

Participants from both groups pointed to their own experience with participants, or other existing evidence, suggesting that potential participants would not be very interested in funders of studies they are considering (quotations 22-24).

The therapeutic misconception

Ensuring that the donor was sufficiently informed about the process was mainly discussed by the researcher group, but also by some participants in the other groups. Two situations were discussed. First, that donors should be fully aware at the funding stage that no medical benefit was guaranteed, nor even a place on the trial itself (quotations 25-28). Second, that as a participant giving consent to the trial, it should be clear to the donor that no medical benefit was guaranteed (quotations 29-30).

Donor benefit

Core to PP is that the donor secures a place on a trial they have funded, subject to meeting the inclusion criteria for the study at the time of recruitment. Some participants in our PPI and researcher groups were concerned about fair participant selection, and ensuring that the risks and benefits of trial participation are distributed fairly rather than allowing the rich to 'buy' a place on a trial (quotation 31-32).

Some PPI participants felt that the potential unfairness of the recruitment process could be remedied by allowing the donor to be supernumerary to the sample size required for the trial. They were unperturbed that the donor's data might need to be excluded from the trial as a consequence (quotations 33-35).

Others were less concerned about the potential unfairness, particularly in the REC group, and thought that wealthy individuals having an advantage was just a fact of life (quotation 36-37).

A further consideration for some participants was that allowing a donor to fund a trial, even where they gained one place on that trial, created opportunities for patients that would not exist but for the donor funding the trial (quotation 38).

Further funding from additional donors

The REC and PPI groups discussed the possibility of further funding being sought from additional donor/s during a trial and their views here reflected their views about PP with one donor. There was no general agreement on how to reconcile increasing the number of donor-guaranteed places with potential objections that this may magnify any unfairness. Participants highlighted the importance of ensuring studies were adequately costed beforehand, including funds for unforeseen difficulties and to avoid pauses in trial activity (quotations 39-41).

General acceptability

There was a general feeling across the three groups that the PP was acceptable (quotations 42-44). There was a recognition that donor-funding would generate more funding, and in turn facilitate more research, which was perceived positively (quotation 45).

Some participants thought that research applications using donor-funding could be treated like any other applications, and should not, for instance, require a specialist committee to be established by the HRA (quotation 46-47). It was generally felt that each application could be considered on a case-by-case basis as opposed to, for example, the HRA issuing a formal broad-brush 'yes or no' approach, but that a framework outlining the relevant issues would be useful (quotations 48-49).

One participant felt very strongly that the PP was not acceptable but acknowledged that it was likely to happen regardless (quotation 50).

DISCUSSION

In order to address our third research component, we organised our findings into two broad groups (see table 4). In the first group are issues squarely within the REC remit. Findings here are broken down into two categories: (i) issues that would be accounted for in a standard REC review and (ii) issues that are specific to the PP, which therefore require further discussion and guidance. The second group contained ethical issues that were important considerations but fell outside the usual scope of REC review. These we have put to one side for the purposes of this paper (for the reasons explained in Supplemental3). Categories (i) and (ii) will be discussed through the lens of King and Ballantyne's conservative consistency approach and mindful that our participants thought that PP was generally acceptable.

Table 4 Categorisation of ethical considerations highlighted.

Issues that fall within the remit of RECs		**Issues outside the scope of REC review**
Category (i): Issues covered in standard REC review	*Category (ii): Issues specific to the PP*	*Outlined and explained in Supplemental3*
Ensuring scientific validity and rigour	Concerns raised by donor obtaining a place on the trial: ▪ Identifying the funder	'Dirty' money/ donor's character
Further funding from additional donors		Disruption to the research agenda

	▪ Fairness ▪ Pre-empting any therapeutic misconception	Matching agency governance

(i) Issues covered in standard REC review

Ensuring scientific validity and rigour

This was perceived as one of the most important ethical considerations. When outlining the PP, Masters and Nutt concentrated on studies funded by donors that could be based on existing protocols for trialling promising drugs that had not received funding from other sources. But the possibility of new protocols, designed with inclusion criteria that the donor would meet at least at the time of funding was left open. Our participants were uncomfortable with a donor having any influence over trial design. This was perceived as undermining scientific rigour. It is arguable whether or not this is the case. It is possible to envisage a study that has been designed to maximise the chances that a donor will be eligible, without its scientific validity being compromised. Given the strength of our participants' concerns, however, we suggest that, at least in the short term, the matching agency should maintain a distance between researchers and donors rather than allowing specific characteristics of the donor to influence the design of putative studies. Although this will go some way to making PP more acceptable to the stakeholders in our study, it must be recognised that this may make PP less attractive to researchers, who will have to invest time in designing a protocol for consideration for funding that may not be acceptable to the donor because they would not be eligible to participate. Accordingly, in the medium to longer term, once PP is established, more informed engagement with stakeholders should be encouraged. Provided such trials will result in meaningfully generalisable results, are not unfairly excluding groups who could potentially benefit from promising therapies and would not pose undue risk to those included, we do not think that designing trials to include donors would be unethical bearing in mind that otherwise no research in this area may be conducted. Other research ethics norms would also need to be respected, such as the norm that wherever possible vulnerable individuals are not exposed to research risks ahead of those who are not vulnerable.

For some participants, particularly in the researcher group, there was a perception that the PP would encourage 'wacky' or 'crackpot' studies, with many reiterating the need for independent expert review to provide reassurance about the scientific basis of the study and trial design. The HRA makes clear, however, that RECs are not expected to undertake their own scientific review of research; they are not to reconsider the quality of the science presented to them, as this is the responsibility of the study sponsor. Governance Arrangements for RECs (GAfREC)[7] S5.4.2.a states that a REC will be 'satisfied with credible assurances that the research has an identified sponsor and that it takes account of appropriate scientific peer review'. The appropriate REC role is therefore to *check* that sufficient scientific review has been obtained, not to conduct such a review themselves. As clinical trials, the studies funded using PP would require MHRA approval in addition to REC approval. Some of our participants noted that MHRA review entails an expert review of the science and safety of clinical trials. GAfREC (S5.4.2c) says that RECs should not duplicate the work of another public body's regulatory duties. Concerns about the science and design of PP donor-funded research should therefore be resolved by the study sponsor ensuring that a robust, independent scientific review is provided to the REC, along with confirmation that the study has been submitted to the MHRA.

The inclusion of PPI was also recommended by our participants. REC application forms already collect information on PPI so this is something RECs should already take into account. Moreover, the HRA issued a joint briefing with INVOLVE endorsing the merits of PPI, particularly its beneficial impact on the ethical aspects of research.[8] Researchers ought, therefore, already to be routinely engaging in PPI. Any matching agency should also consider PPI in the design and implementation of its processes, recognising that whilst the wealthy are users of health services and potential donors are themselves a source of PPI, they are not representative of all service users in all respects. It should also be noted that the PP is itself a user-led creation, as we have explained in our introduction.

Further funding from additional donors

All studies should be adequately costed and financed from the outset: the sudden halting of medicinal products may be harmful, and incomplete data collection is wasteful of resources, results in unreliable evidence and undermines participant's consent. Our participants tended to think that donor-funded research costings must account for all overheads and unforeseen emergencies, whilst recognising that it is relatively common for research proposals to be underfunded. Where, however, a trial did require more funding, no substantial objections

were raised to allowing one or more other donors to add funding through the matching agency on the same terms as the original funder. We found this surprising given that one of the primary objections to the PP (see below) is that donors are guaranteed a place on the trial. Arguably, adding donors compounds the any unfairness. Despite probing, our participants did not engage with this counterargument, but it was acknowledged by Masters and Nutt's paper.

Ensuring sufficient funding is an important ethical consideration for all research, and not just donor-funding. REC applications for donor-funded research should address funding considerations in the same way as any other REC application. The role of a REC in assessing funding is again one of checking that proof of funding is provided. Researchers are expected to provide this with clinical trial applications. Moreover, adequacy of funding in relation to trial design is something subject-expert reviewers are standardly asked to consider.

(ii) Issues specific to PP

Identifying the funder

Participants in the REC and PPI focus groups discussed whether the identity of the donor ought to be disclosed. Some participants felt that the source of funding would not be of interest to many participants, and that they would be more interested in other aspects, such as scientific validity. This view reflects findings from other studies. Innes et al, for example, found that information about funding was ranked amongst the least important pieces information that could be included in an information sheet (29th out of 32 items ordered in terms of importance). The top-ranked items were potential side-effects, disadvantages/risks, what participation requires and potential advantages. Confirmed scientific quality was ranked 11th.[9] Similarly, Kirkby et al found that most participants viewed some information (less than that in a REC reviewed information sheet) on the purpose of the study, risks and benefits, but information about funding was only viewed by a minority of participants.[10]

Our PPI participants tended to think it important to disclose the identity of the donor in the interests of transparency, or in fulfilment of the Declaration of Helsinki (para 26).[11] In PP, however, the funder is not an organisation but an individual, who may also be a participant, whose privacy must be considered. In being tasked with protecting participants' interests, RECs must consider the protection of the donor's privacy as a trial participant. Donors are

likely to be very rich individuals, and given the types of trials amendable to PP (phase I or IIa), they (or a loved one) may also be very unwell. To disclose their names in information sheets would be render them more vulnerable by highlighting their financial and health status to other participants, and anyone else who can access the information sheets. Indeed, interest in, and the potential influence of, the funder as a rich person in a celebrity culture was raised by REC participants as something that may unduly influence others to participate in the same trial. They feared 'celebrity endorsement' of, or publicity stunts around, the donor's participation. These kinds of concerns led them to consider that, on balance, the matching agency rather than the donor should be identified as the funder.

To include the donor's name would, moreover, disclose their identity to the research team. This conflicts with our participants' strong views that maintaining scientific rigour was the main concern with funding of this kind. Some participants were concerned that the donor should not be treated differently by researchers by, for example, receiving preferential treatment or attempting to influence the results. This is much less likely if their identity is not included on the information sheet.

A balance therefore needs to be struck between the participants' views about the need to maintain a distance between the donor and the researchers, and their views about transparency in relation to the donor as the source of funding. In attempting to achieve this balance, the question as to how much information participants should have, or are entitled to have, about how studies are funded is pertinent. Arguably, participants' right to know who has funded the study is not unfettered. As one participant pointed out, when funding is provided through a charity, participants are not provided with the names of the donors whose money has been directed to that particular study. The matching agency is analogous to other organisations that sit between donors and the participants. It would control and administer the research funds. It seems, therefore, more appropriate to name the matching agency rather than the donor, as suggested by some of the REC participants. This suggestion is in line with the approach taken by King and Ballantyne, that donor-funding should be measured against the norms of current practice. It provides parity with information participants typically receive about funding sources and ensures the privacy of donors is adequately protected.

Fairness

It is well established in research ethics that the potential risks and benefits of research must be distributed fairly.[12] In PP, the donor obtains a place on the trial by virtue of their wealth. Some participants thought that it unfair that a donor can 'buy' potential benefits that others cannot afford whilst others regarded differences of buying power as a fact of life. In considering these opposing views, we offer two thoughts:

i). Rather than focussing on wider wealth disparities, we should concentrate on what is normal in research. King and Ballantyne provided three examples of ways in which the distribution of the benefits and risks of research are inequitable. They argued that donor-funding models are not *more* commodifying than other research practices that are currently regarded as acceptable. It would therefore be inconsistent, they argued, to prohibit donor-funded work whilst tolerating these other examples. One participant, however, suggested that acknowledging existing inequalities does not justify multiplying them. King and Ballantyne offer two responses to this point: either donor-funded research and other unethical research practices should be prohibited (a "radical conclusion" (p.38)) or the consistency approach must be rejected. The decision to reject the consistency approach should, however, be justified.

From the perspective of our project, this philosophical problem is not something to be resolved at local REC level. Rather it needs to be tackled by the HRA. If the HRA considers that donor-funding is unacceptable, then applications for REC review will be rejected before they are passed to a local committee. If the HRA has no stated position on donor-funding but passes on the application and a local REC rejects it on the grounds that donor-funding is unethical, the applicant should feel encouraged to appeal. A more satisfactory situation would be for the HRA to have a position on donor-funding and make this position clear in its guidance to RECs and researchers. Of relevance here is that, by and large, our participants felt that PP was acceptable. Despite the concerns conveyed, only one participant expressed outright opposition. Some felt, however, that deliberation was required on a study-by-study basis, with guidance provided, rather than the HRA embracing or rejecting the funding model.

ii). As some participants noted, blocking donor-funded research on the grounds of unfairness deprives both the donor and other eligible patients of the potential benefits of participation.

Some participants suggested the donor ought to be supernumerary to mitigate the potential unfairness. This would mean the donor would receive the trial drug or innovation, but their data would not be included in the study, thereby maximising the number of places available to others. This solution has its own ethical difficulties. Whilst the trialled innovations may be promising, there are still risks involved in trial participation. For this reason, to reduce risk it is generally considered unethical to recruit more participants than are statistically needed to meet the study aims. Moreover, PP was devised for phase I and IIa trials. In these small trials, data from each participant is likely to be statistically significant and of critical value in determining whether to suspend or close a trial due to adverse reactions. These are both reasons against making the donor supernumerary.

Furthermore, PP was developed in response to the paucity of research funding for rare or orphan diseases. As King and Ballantyne point out, these are diseases that do not attract funding from private or public sponsors because they are comparatively rare and are perceived as having low social utility and marketing potential. Opportunities for patients with these conditions to take part in research are limited or non-existent. Donor-funded research might therefore be the *only* funding model creating such opportunities for these patients. These inequalities also need to be factored into any reactions to PP on equity grounds.

Pre-empting any therapeutic misconception

The 'therapeutic misconception' (TM) occurs when a research participant misunderstands the difference between clinical treatment and research and expects participation to result in medical benefit.[13] There are two points at which a donor might be affected by the TM.

First, at the funding stage. Some participants felt that by agreeing to provide a significant amount of money for a trial, the donor might expect a medical benefit. However, it is highly likely that the contracting process between donors and the matching agency would protect them from the TM. As with any research funding, the terms and conditions and responsibilities of the donor and the matching agency would be set out in a legally binding agreement. Here it should and would be made explicit that agreeing to fund a trial may not result in a benefit.

Second, as a participant the donor, might be particularly vulnerable to the TM at the consent stage. King and Ballantyne suggest that donor-participants who are paying for a trial may be more likely to believe that the intervention will be medically beneficial, despite efforts to explain otherwise. However, as they point out, the TM is unfortunately prevalent in other clinical trials, and health research more widely. Much existing work demonstrates that research participants expect a benefit and cite this as a key factor in their decision to participate.[14-16] King and Ballantyne support Miller and Joffe's contention[17] that the TM should not prevent research where it is more likely to arise, but instead requires enhanced informed consent processes.

Limitations

Two of the authors (AM, DN) devised PP. They have been actively involved in promoting this type of donor-funding. This project represents a continuation of this effort and as such is a potential source of bias. They were not, however, involved in the data-collection nor the initial coding. The other three researchers (HD, SB, KS) were open-minded about whether PP is an acceptable funding model.

It is arguable that having a topic guide shaped the data collected. However, the first open question in each group elicited a range of responses which either covered most areas in the remainder of the topic guide (REC and PPI groups) or lead the discussion in a direction we had not anticipated (researcher group). Participants did not receive the questions in advance, and each focus group met only once for a relatively short amount of time (between 75 – 122 mins) given the complexity of some of the issues discussed. Only two participants submitted follow-up comments. The user panel agreed that the analysis represented the discussions that took place. We also explained our categorisation of the issues and they agreed that this was a reasonable approach. Nonetheless, we acknowledge that participants may have reached more nuanced, or even different, positions if lengthier process (such as a citizen's jury approach) had been adopted.

Some participants in the research group felt that the data collected would have been enriched if a further focus group had been held with participants from each of the stakeholder groups present. Our user panel was, however, drawn participants from all groups and this feeling was not borne out in our meeting with them.

A total of twenty-two participants took part, from three quite different stakeholder groups, which is a respectable size for an exploratory qualitative study. Nonetheless, given that the

groups tended to focus on different concerns, with only some overlap between the groups, we cannot be confident that we achieved data saturation even though we have offered some valuable insights into the responses of these groups.

Our project was confined to exploring the ethical concerns about PP from the perspective of REC review.

CONCLUSIONS

There is a need to increase medical research funding, particularly in areas where commercial viability rather than safety or efficacy concerns is stalling progress. This project explored one model of donor-funding, the PP, where a donor funds an entire phase I or IIa clinical trial in exchange for a place on that trial (subject to meeting inclusion and exclusion criteria at the time of recruitment). We convened three focus groups to explore the views of REC chairs, clinical researchers and PPI group members about potential ethical concerns for RECs reviewing proposals clinical trials that are funded in this way.

Our participants generally responded favourably to the proposal, primarily as a means of increasing research funding to maximise potential future benefits for patients. On the basis of their responses, and following King and Ballantyne's consistency approach, we have identified areas where guidance on the careful completion of IRAS forms for donor-funded trials would be welcome, namely around identifying the funder, fairness and addressing potential TM. These issues arise from the donor being guaranteed a place on the trial. Other issues raised were either outside the scope of REC review or involved areas already covered by the IRAS application and review process (such as proof of MHRA submission, independent scientific review, PPI involvement, sufficient funding).

We agree that some of the concerns (outlined and discussed in Supplemental3) that are not addressed in this paper do merit further consideration – just not at the level of RECs. We suggest that they, along with the wider philosophical question of whether donor-funding should or should not be judged using a consistency approach, needs to be considered at the level of the HRA.

Our results suggest that the PP should be modified to ensure that donors do not influence the design of trials. More work is needed, however, on how scientific integrity is understood and whether robust scientific design is compatible with greater donor involvement, if other

conditions are met, namely the resulting trials will result in meaningfully generalisable results, are not unfairly excluding groups who could potentially benefit from promising therapies and would not pose undue risk to those included.

Next steps: we aim to use the data from this qualitative study to develop empirically informed policy and good practice guidance for donor-funded clinical trials that could reassure stakeholders and remove potential barriers to developing ethically acceptable research protocols for donor-funded clinical trials.

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Author contributions

KS & HD were responsible for the first draft of this paper. AM, DN & SB provided comments on this and subsequent drafts. All authors approved the final version.
HD, AM, DN & SB designed the study.
HD designed the topic guide, and with KS collected and coded the data.
HD, KS, SB, AM & DN decided how the data should be categorised and presented.

Conflicts

There are no conflicts of interest

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Supplementary Material

1 Topic guide questions (prompts and probes not included)

Thinking as a researcher/potential participant/REC member, what are your thoughts about this funding model?

How could any concerns, questions or worries be addressed in the protocol, standard operating procedures or by other means?

One of the distinctive features of this funding model is that the donor (or their nominee) is guaranteed a place on the trial PROVIDED that they meet the inclusion/exclusion criteria at the time of recruitment. What concerns might this raise from your point of view?

As a general rule, no one should be excluded from research participation on economic grounds. To what extent does guaranteeing the donor (or their nominee) a place on a trial disadvantage other potential participants?

On occasions, researchers have to go back to funders for additional funding. This can happen, for example, if it takes them longer than expected to recruit sufficient participants or if there are other unanticipated and unavoidable delays. Funders do not always agree to additional funding. In the case of this model of funding, if for whatever reason, the original donor is unable or unwilling to fund an extension, what concerns, if any, might there be about an additional donor being sought on the same terms (i.e. being guaranteed a place on the trial PROVIDED they meet the inclusion/exclusion criteria at the time of recruitment)?

The Declaration of Helsinki states that potential participants should be told about the 'sources of funding' for clinical trials. Normally, this means including the name of the funding agency (e.g. Medical Research Council) in the participant information. In the case of the model we are exploring, this could be the actual name of the donor (e.g. Josephine Blogs). Or it could be the name of the matching agency, since they are responsible for the administration of the funding – like Cancer Research UK, which raises funds in a variety of ways and from a variety of sources. What are your thoughts about the information that should be provided to potential participants?

Taking all of our discussions into account, to what extent do you think that potential concerns RECs may have about this funding model can be satisfactorily addressed?

That's all of our questions, what else should we be considering from your point of view?

2. Statement of PPI involvement

Masters and Nutt are neither clinicians nor academics. They are lay people and in one case also a patient affected by the lack of funding for neglected drugs. They devised the Plutocratic proposal for donor-funding that lies at the heart of this study. They were full co-applicants on the funding application and have been active co-investigators on the project. They have been remunerated for their contribution on an hourly basis in line with INVOLVE recommendations.

Masters and Nutt helped to design the project and their agenda forged the research questions and limited the scope of the study to REC review. They were involved in the categorisation of the findings and the drafting of this paper, on which they are co-authors.

In addition, PPI group members from a local clinical trials unit assisted with the evaluation of the topic guide and advised on the timing for the PPI focus group (to take account of the burdens of participation in terms of length and the need for regular breaks). They were instrumental in the design of the participant information sheet and we followed their advice about creating a video presentation to explain the Plutocratic Proposal in the context of research funding. One of our focus groups was comprised solely of PPI members. Members from this group were also members of our user panel and reviewed the summary of findings that will be distributed to all those who participated and post on our website, once our findings have been peer reviewed. They were renumerated for this work in line with INVOLVE recommendations.

Masters and Nutt are taking our findings forward in that they are working on ways to realise their aim of establishing a matching agency and using this (and other models of donor-funding) to fund clinical trials.

3. Elaboration and discussion of the themes which fell outside the remit of REC review, and therefore outside scope of project

Three themes, whilst raising interesting ethical issues, are not clearly within the remit of REC review. We identify and discuss these themes here for completeness and to justify their exclusion from the main results paper.

First, a concern that allowing donor-funded research would disrupt the general research agenda and infrastructure. This only arose in the researcher group, but was a serious concern for many researcher-participants, who were worried that resources such as trained researchers would be directed to donor-funded studies rather than others:

> *You know, clinical research is an ecosystem, right? And it's, in some ways it's a closed ecosystem. Funding or taking part in some research means that resources and people and academics are deployed in something and it cannot be deployed somewhere else.* (RECP7)

Second, the idea of money being 'dirty' if given by someone of dubious character. This idea was only identified by the PPI group (though it was actually raised during the first pilot group, too). Some participants were concerned about money donated by people who they perceived not to be 'good' being used to fund research:

> *I don't have a problem with many people, but if they're offshoring money… Pharmacy and insurers have to make a profit, everybody has to make a profit to be able to live, if those are excessive then, perhaps, they're immoral, if they're offshored they're definitely immoral, if they don't pay their taxes they're immoral because the rest of us ordinary people suffer because of that, and some people are suffering more. And, I'm sorry, I really do think we should stick to basic principles because once they start eroding they go very quickly.* (PPIP5)

Third, participants in all three groups indicated that they might want to consider details of the operations and governance of the matching agency when reviewing a PP donor-funded research application:

> *I just wanted to perhaps think about…a little bit about how this matching agency is actually going to work…. how does the matching agency function with regard to tapping wealthy people for money? What sort of advertising is it going to have to do? How is it going to engage with people who are fantastically wealthy to promote itself? I think there are possibly issues around that, about how it actually… How the money actually comes to the agency, how the agency engages with donors, what it's putting forward as, 'this is what's in it for you,' and how it does that.* (RECP3)

These concerns raise interesting ethical issues, but do not fall within the official remit of RECs (though we accept that RECs often feel that they are free to comment widely on protocols and feel that no constraints should be placed on their considerations). Regarding the disruption to the research agenda, some participants noted that public and charity funding calls are generated to reflect priority areas and greatest need. They thought that this was the right way to allocate research funding, and noted that donor-funding is allocated according to the needs of just one person – the donor. But not all research funding is allocated on the basis of greatest need. Commercial research, for example, could be said to direct researchers and research facilities towards work that is likely to prove profitable, rather than that which meets the greatest need. Yet this is not usually a consideration that RECs take into account when reviewing commercial research, which is subject to, and often successful in obtaining, favourable REC review. The idea that RECs or research

participants might, or should be, interested in the perceived moral goodness of the donor is a curious concern. If it is important to assess the morality of donor-funders, it should follow that it is also important to assess the virtues of donors, including anonymous donor, to charities and sources of other funding. This is not information RECs are privy to with any other applications, so it is not clear why this should be a particular concern for PP donor-funding applications (although the user panel noted that this measure protects against reputational damage: which perhaps more of a concern for researchers and their employers than RECs). Details around the governance and operations of the matching agency, or any research funding body – is also not information that is currently made available to RECs or participants. It could be argued that these are issues that *ought* to be taken into account. If they are, this may render much current research funding unacceptable. In determining that these issues are outside of the scope of this paper, we are not contending that they are unimportant. Rather we do not believe that these are issues that RECs should or do routinely debate as part of their review at present.

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Acceptability of donor-funding for clinical trials in the UK: a qualitative empirical ethics study using focus groups to elicit the views of research patient public involvement group members, research ethics committee chairs and clinical researchers.

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ABSTRACT

Objectives The Plutocratic Proposal is a novel method of funding early phase, clinical trials where a single donor funds the entire trial and in so doing secures a place on it. The aim of this study was to identify and explore concerns that may be raised by UK RECs when reviewing clinical trials funded in this way.

Design Empirical ethics combining ethical analysis and qualitative data from three focus groups held online using Frith's symbiotic approach. Data were analysed using inductive thematic approach informed by the study aims and ethical analysis.

Participants 22 participants were recruited: eight research patient public involvement group members, seven research ethics committee chairs and seven clinical researchers. All were based in the UK.

Results With one exception, participants thought the Plutocratic Proposal may be 'all things considered' acceptable, providing their concerns were met, primary of which was upholding scientific integrity. Other concerns discussed related to the acceptability of the donor securing a place on the trail including: whether this was unfair distribution of benefits, disclosing the identity of the donor as the funder, protecting the donor from exploitation, and funding a single study with multiple donors on the same terms. Some misgivings fell outside the usual REC purview: detrimental impact of donors of bad character, establishing the trustworthiness of matching agency and its processes, and optimising research funding and resources. Despite their concerns, participants recognised that because the donor funds the whole trial, others would also potentially benefit from participating.

Conclusions We identified concerns about the Plutocratic Proposal. UK RECs may be open to approving studies if these can be addressed. Existing governance processes will do some of this work, but additional REC guidance, particularly in relation to donors securing a place on the trial, may be necessary to help RECs navigate ethical concerns consistently.

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ARTICLE SUMMARY: STRENGTHS AND LIMITATIONS OF THIS STUDY

- The Plutocratic Proposal has received a cautiously favourable reception in the literature, but this is the first study to explore whether studies funded using this model may be deemed acceptable by UK RECs.
- Empirical ethics, which combines philosophical analysis and empirically obtained insights, is a recognised methodology for understanding and evaluating ethical issues that affect policy in healthcare services and research.
- Focus groups are a useful qualitative tool for exploring potentially controversial topics, as they permit participants to engage with each other's views but we cannot be confident that we reached data saturation in this study.
- Qualitative findings are not generalisable beyond the study sample.

INTRODUCTION

Many promising clinical interventions do not progress to early clinical trials due to a lack of funding, and some that do may fail for commercial reasons.[1, 2] The 'valley of death' in which promising therapies may flounder, is a persisting, multi-faceted and international problem.[3, 4] One solution to this funding shortfall in the initial stages of development proposed by two patient-advocates, Masters and Nutt,[5] is that a single, very wealthy individual commits to funding an entire single-arm phase I or phase IIa clinical trial in exchange for the guarantee of a place on the trial. Importantly, this guarantee is subject to the inclusion and exclusion criteria being met at the point of recruitment. Their 'Plutocratic Proposal' (PP) envisages a 'matching agency' that 'pairs' donors and researchers without exploiting the donor or interfering with normal and accepted research review and governance procedures. This they describe as 'committed philanthropy' because one donor commits to funding the trial fully aware that they may not meet the inclusion criteria. Masters' and Nutt's proposal grew out of their experience of crowd-funding a clinical trial for a friend with metastatic pancreatic neuroendocrine cancer. They argue there is a moral imperative to explore new, acceptable avenues for research funding, especially for potential therapeutic responses to rarer diseases that would otherwise be shelved.

The idea of patients funding novel treatments is not new, particularly in relation to small-scale, single-arm trials and off-label use. It has been seen, for instance, in regenerative cell treatment[6-8] and oncology,[9, 10] where it has been noted that large scale randomised control trials, especially against placebo, might not be the most ethical or economical way of gathering data on clinical effectiveness.[10] More recently, crowd-funding has been considered as a potential source of finance for clinical trials on rare diseases.[9]

PP presents ethical challenges. These were evaluated by King and Ballantyne[11] against current research practices and also other forms of funding by participants – pay-to-play,[12] where individuals pay to participate in a trial, and pay-to-try,[13] where individuals pay for access to a promising intervention but not obviously as part of any trial. They concluded that there is "nothing inherently unethical" about PP. Donor-funding should, they argue, be assessed against "real-world ethical standards" and "standard health research legislation/guidelines and undergo [institutional review board/research ethics committee] and scientific peer-review" rather than being measured against aspirational standards that current research practice is not guaranteed to live up to. This they call their 'conservative argument from consistency', the crux of which is that like cases should be treated alike:

> Critics have argued that donor-funding should be prohibited because of fundamental ethical concerns about scientific validity, social value, therapeutic misconception, exploitation and fair subject selection. But the nature of the concerns levelled at donor-funding models are not qualitatively, nor in many cases quantitatively, different from features of currently permitted health research.

As King and Ballantyne's article title suggests, this makes PP "permissible not perfect": it accords with current minimal, rather than ideal, ethical standards. Compared with other forms of donor-funding, they regarded the PP as most likely to reduce the potential ethical risks. Dal-Ré et al concur, concluding that PP is the most appropriate self-funding option for "early investigation of new orphan drugs".[9] They point out, however, that PP may be more complex to implement but suggest that, in Spain, the Spanish Federation of Rare Diseases could fulfil the role of the matching agency. Vayena[14] also defends PP, which she regards as addressing the ethical deficiencies of off-label usage and right-to-try approaches. She sees PP as continuous with increasingly patient-led research.

Given this cautiously favourable reception in the literature, it would be helpful to know how PP might be received by UK research ethics committees (RECs) and what concerns may arise during review. If it could be established that PP-funded studies may, with the right safeguards, be conducted in an

ethically permissible way, then identifying barriers to approval and mitigating these would remove a potential obstacle to this novel funding stream. Our study therefore aimed to identify and explore concerns that may be raised by RECs when reviewing PP-funded clinical trials.

Our study had three objectives:

1) To undertake an initial analysis of the ethical issues raised by PP in the light of Health Research Authority (HRA) policies and guidance to RECs, and to use this analysis to create a topic guide to explore the stakeholders' views;
2) To explore, using focus groups, the views and ethical concerns about PP for REC members, clinical researchers and potential research participants as key stakeholders in the research ethics review process;
3) To determine, based on objectives 1) and 2), what REC guidance around PP might be needed.

METHOD

An empirical ethics approach[15] was chosen to meet our aim. This enabled us to combine ethical analysis with the stakeholders' views about acceptability. Identifying and exploring issues philosophically enabled a systematic evaluation of ethical issues based on key features of the PP, the role and remit of RECs and broader principles of research ethics. We drew on Frith's symbiotic approach[16] to integrate our philosophical analysis into the empirical investigation. Philosophical analysis influenced the data collection (by informing the topic guide), our thematic analysis and, through the adoption of a philosophical lens, the way our results are discussed.

A topic guide was designed taking into account the small literature on the potential ethical objections to PP, and related aspects of the larger literature on research ethics. This literature was considered alongside published HRA policies and guidance for RECs and researchers making REC applications, to determine considerations that a REC should have in mind when reviewing research protocols.

The draft topic guide was piloted in February 2020 first with researchers (N=4) and REC members (N=2), and then with two research patient public involvement (PPI) group members, who also helped to shape the participant information for the study. The topic guide was revised and then finalised (supplemental1) based on the comments from each pilot group sequentially.

Three focus groups were convened, one for each of the stakeholder groups (REC chairs, clinical researchers and research PPI members, who were our proxy for potential study participants). The inclusion criteria were: role (clinical researcher, REC chair, PPI group member), availability (due to coronavirus (COVID-19) pandemic, ability to join Microsoft Teams meeting was added), and English speaking. There were no exclusion criteria.

REC chairs were recruited by email, using information in the public domain. Everyone approached and who was available on the date selected agreed to participate. Our intention was to recruit clinical researchers via published lists of REC-reviewed research for the period Jan-March 2020, (sampling for region and academic/hospital/industry based). The response rate was poor and only two participants were recruited. Four participants were recruited after UK Spine and two clinical trial units circulated information about the project. One researcher responded to our recruitment drive for PPI participants. Our PPI participants were recruited via PPI networks associated with clinical trials units and selected on the basis of availability and achieving gender balance and representation across the three groups approached.

Focus groups were held in September, October, and December 2020, using Microsoft Teams. Participants provided individual audio-recorded consent in advance. The consent process was an opportunity for the participants to familiarise themselves with Microsoft Teams, guided where needed

by the researchers gaining consent. One PPI participant was unable to participate due to microphone issues that we were unable to resolve during their consent meeting.

The focus groups were recorded and transcribed verbatim. Two participants (PPI and researcher) responded to the general invitation to send further reflections or comments by email. Each transcription was reviewed: identifying information was removed and participant identifiers allocated. Two researchers, working independently, manually coded the transcripts inductively, and independently organised the codes into categories. A thematic analysis was undertaken informed by the range of issues raised by the participants and our understanding of the ethical dimensions as suggested by Frith's[16] symbiotic approach. The resulting initial analysis was reviewed and then discussed with the remaining research team, and organised into themes that reflected our aim. The preliminary analysis was presented to, and discussed for validation purposes with, a 'user panel' drawn from each focus group.

When discussing our findings, we have adopted the "conservative argument from consistency" in line with King and Ballantyne's[11] evaluation of donor funding.

There was PPI involvement throughout (supplemental2).

RESULTS

Twenty-two participants attended three focus groups (table 1).

Table 1. Focus groups and participants.

Focus Group	Participant Type	Gender
1 (112 minutes)	REC Chairs (n = 7)	4 male; 3 female
2 (88 minutes)	Members of PPI groups (n = 8)	4 male; 4 female
3 (75 minutes)	Researchers (n = 7) Academic-based (n = 4) Hospital-based (n = 2) Industry-based (n = 1)	6 male; 1 female

Seven themes were identified from the coded data. Six were organised into two broad areas (table 2). Three themes represented concerns that fell outside of the remit of REC review in the UK, as established by the Governance Arrangements for RECs (GAfREC).[17] Three identified potential obstacles to favourable review in areas that are squarely within the purview of RECs. We will first start with the latter themes, before going on to reporting the participants' broader concerns about PP. We will conclude with the seventh theme, which reflected our participants 'all things considered' views. Illustrative quotations are provided (with further examples in supplementary3).

Table 2 The six themes organised according to established REC remit

Within established remit	Outside established remit
1. Good science 2. Concerns raised by donor gaining a place on the trial 3. Further funding from additional donors	4. Donors of bad character 5. Disrupting the research agenda/infrastructure 6. Matching agency governance and processes

1. Good science

Participants in all three focus groups highlighted the ethical importance of robust science and trial design for donor-funded research, which encompassed the need for independent expert review, with some participants acknowledging that all clinical trials would be subject to Medicines and Health Products Regulatory Agency (MHRA) review, and PPI input.

> We know that good science is good research, and that's good ethics. (RECP5)

The researcher groups expressed concerns about "crackpot" or "whacky" studies being conducted using interventions that lacked scientific basis.

The greatest fear raised in relation to the science was that donors might influence the study design. Many participants felt that a funder participating in a trial may be allowed to affect not only the conduct, but also the analysis or reporting of the results of the research. These participants expressed the view that the donor may feel invested in the product, creating a conflict of interest which may result in them lobbying for, for example, a 'softening' of the reported results.

> But I would be worried about the conduct and bias, perhaps, in analysis of the results, and do we bend rules for people who want to get into the trial? (PPIP5)

Some participants were concerned that a funder-participant could introduce bias or receive preferential treatment.

> [I]f the researchers do know who it is has provided the cash for this then there is going to be, however well intentioned, a tendency to treat that individual differently. (PPIP1)

2. Concerns raised by donor gaining a place on the trial

Three concerns relating to the donor gaining a place on the trial were identified: who would learn the identity of the donor, the therapeutic misconception (TM), and fairness.

The REC and PPI groups discussed whether the identity of the donor ought to be disclosed to the other trial participants. The PPI participants tended to transparency:

> Clearly this is of some concern to some people, of high concern to others, and of no concern to others, so I think you have to put the information in just morally. (PPIP7)

REC participants were concerned, though, that if donors' identities were known, and they publicised their participation on social media, this might influence trial recruitment, especially if the donors were celebrities.

Both groups recognised trial participants must be given information about the source of trial funding but some felt that disclosing the name and details of the matching agency would be sufficient:

> We don't go into lots of details about where money's come from through… We wouldn't ask who's donated to … what proportion of that donation has gone through to this project, but we'd just put "Cancer Research [UK]" at the top. (RECP6)

Members of both groups pointed out that potential participants are not in general very interested in details about funding.

The importance of donor-participants being sufficiently informed to avoid any TM was emphasised. First, that donors should be fully aware at the funding stage that no medical benefit is promised, nor even a place on the trial itself. Second, that as a participant giving consent to the trial, it should be clear them that no medical benefit is guaranteed.

> These people, one assumes, are very desperate, you know, they are really going to just want it for their own end initially. (PPIP6)

Core to PP is the idea that the funder secures a place on a trial subject to meeting its inclusion criteria at the time of recruitment. Some members of our PPI and researcher groups were concerned about fair participant selection, and ensuring that the risks and benefits of trial participation are distributed fairly.

> I have concerns around the fairness of participant selection. It should really be based on scientifically valid criteria not ability to pay and, and research risk and benefits should be fairly distributed, I think, in society. (ResP6)

Some in the PPI group felt that this potential unfairness could be remedied by the donor being supernumerary to the sample size required for the trial. They were unperturbed that the donor's data would be excluded from the trial as a consequence.

Others were less concerned about the potential unfairness, particularly in the REC group, and thought that wealthy individuals having an advantage was all-invasive fact of life.

Some participants acknowledged that allowing a donor to fund a trial, even where they gained one place on that trial, created opportunities for patients that would not otherwise exist.

> If you try to argue that it's not fair that that happens and, therefore, this shouldn't be a way of funding research you're then depriving all the other ten of being involved in a piece of research that may well be of benefit. (RECP4)

3. Further funding from additional donors

The REC and PPI groups discussed the possibility of further funding being sought from additional donor/s during a trial. There was no general agreement on how to reconcile increasing the number of donor-guaranteed places with potential objections that this may magnify any unfairness.

> It seems to be that there should be a limit, but I can't… choosing a number it would be entirely arbitrary, in the way I'm thinking about it. (RECP6)

Participants noted the importance, and difficulties, of ensuring studies were adequately costed beforehand, including funds for unforeseen difficulties and to avoid pauses in trial activity.

4. Donors of bad character

The consequences of some donors being bad people was only raised by the PPI group (though it was the principal objection to PP by a researcher in the pilot group). The concerns were two-fold: first that money from bad people was tainted, and this might, or should, put off potential trial participants, and second that the researchers' reputation would be at risk if the donor was later revealed to be immoral or criminal.

> PPIP6: And how ethical do we know the donor is, and, er, sort of, what, sort of, lifestyle do they lead, et cetera?
> PPIP5: That's a good point, would you want to be associated, now, with, er, [named individual convicted of sex trafficking] and, er, [their] friends?

5. Disrupting the research agenda/infrastructure

The researcher group expressed a strong (but not unanimous) view that existing structures ensured that research funding was channelled most effectively and that priority areas were researched. Some participants were concerned that PP might direct resources such as trained researchers away from traditionally-funded studies.

> You know, clinical research is an ecosystem, right? And it's, in some ways it's a closed ecosystem. Funding or taking part in some research means that resources and people and academics are deployed in something and it cannot be deployed somewhere else. (ResP7)

At the same time, it was recognised that more funding is needed: "you're not using the research resources most effectively but on the other hand you are adding to them." (ResP3)

6. Matching agency governance and processes

Participants in all three groups indicated that they might want to consider details of the operations and governance of the matching agency when reviewing a PP donor-funded research application.

> I just wanted to perhaps think about… how this matching agency is actually going to work…. how does the matching agency function with regard to tapping wealthy people for money? What sort of advertising is it going to have to do? How is it going to engage with people who are fantastically wealthy to promote itself? I think there are possibly issues around that, about how it actually… How the money actually comes to the agency, how the agency engages with donors, what it's putting forward as, 'this is what's in it for you,' and how it does that. (RECP3)

Added to these concerns were questions about how the agency would maintain a "firewall" (ResP5) between donor and research, and other considerations related to ensuring a robust research proposal. Some participants expressed the view that to be credible, the matching agency would need to replicate the processes found in existing funding organisations.

7. 'All things considered' opinions

There was a general feeling across the three groups that the PP is "fundamentally" (RECP6) acceptable but participants were also cautious: "no major objections … so long as we are able to maintain that scientific integrity and we do have these balances and checks in place." (ResP5). There was a recognition that donor-funding would generate more funding, and in turn facilitate more research, which was perceived positively.

Some participants stated that REC applications using PP should be treated like any other applications, and did not, for instance, require the HRA to establish a specialist committee.

> I don't see anything different in principle, really, between a pharma company funding research to a private individual, what's the difference? (PPIP7)

> [I]f it's going to work at all it's got to become normalised. (RECP3)

It was generally felt that each application could be considered on a case-by-case basis as opposed to, for example, the HRA issuing a formal broad-brush "Yes" or "No" approach, but that a framework outlining the relevant issues would be useful.

One participant felt very strongly that the PP was not acceptable but thought it was likely to happen regardless.

DISCUSSION

To meet our final objective of determining what specific REC guidance around PP may be required, and in line with the symbiotic approach, we identified the core ethical issues arising from our findings, which we organised into two broad groups (see table 3). In the first group are issues squarely within the REC purview as defined by the GAfREC. These are discussed according to whether they: (i) would be accounted for in a standard REC review or (ii) are specific to the PP, and therefore more likely to require REC guidance. The second group contains ethical issues that, whilst important, fall outside the usual purview of REC review, as defined by the GAfREC. We discuss these issues through the lens of King and Ballantyne's conservative consistency approach taking into account our participants 'all things considered' view that PP seems acceptable provided their concerns can be addressed in practice.

Table 3 Categorisation of ethical issues suggested by in our findings.

Issues falling within the established purview of REC review		**Issues outside the established purview of REC review**
Category (i): Issues covered in standard REC review	*Category (ii): Issues specific to the PP*	
Upholding scientific validity and rigour	Pre-empting any therapeutic misconception	Maximal use of research resources
Increasing the number of donors-participants	Transparency about funding vs donor privacy	Ensuring bad people are excluded as donors
	Fairness	Trustworthiness of matching agencies

Issues outside the established purview of REC review

We identified concerns that PP does not reflect how current funding and resources are currently allocated to meet priority areas and greatest need, that donors of bad character pose a reputational risk to researchers, and that RECs would want to know more about the processes and governance of matching agencies.

The REC remit does not include ensuring research resources are used maximally. A REC's primary obligation (GAfREC S3.2.1) is to protect the interests of research participants. Beyond this they should consider "the public interest in reliable evidence affecting health and social care and enable ethical and worthwhile research of benefit to participants or to science and society". Research does not have to meet the most urgent or widespread needs to be "worthwhile", and many studies receive favourable review that would not pass this threshold. Commercial research may, for example, direct researchers and research facilities towards work that is likely to prove profitable, rather than that which meets the greatest need.

GAfREC S3.2.2 states that RECs should consider the "safety and interests of researchers". Beyond excluding matters that are properly the responsibility of employers, the breadth of the responsibility to protect researchers' interests is not defined. The reputation of researchers and their employers is intertwined. Employing organisations – who are likely to be sponsors of the research – should consider organisational risks during the sponsorship review. Any perceived residual obligation could be discharged by RECs providing a general warning to researchers. The alternative is mandating RECs to undertake a detailed investigation into the character of all donors. RECs are not normally privy to detailed information about the characters of contributors to charities that fund research, nor their investment portfolios and tax returns etc. In order to take on this additional responsibility, REC would need not only access to such information, but also additional skills and resources, including centrally agreed benchmarks for moral decency applicable to all funders.

Details around the governance and operations of research funding bodies is not information that is currently collected via HRA Integrated Research Application Systems (IRAS) forms and made

available to RECs or participants. Our participants tended to the view that PP-funding should be normalised as far as REC review is concerned, which suggests that matching agencies should not be required to provide information that other bodies would not be expected to provide. On the other hand, PP-funding is novel and, as our findings reflect, matching agencies may lack the 'trusted brand' familiarity that other funding bodies have developed over time. Matching agencies would therefore be prudent as a minimum: i): commit to processes that demonstrably enforce their adherence to good science, including the transparent, robust peer-review of proposals and ensuring the adequacy of funding; ii) be open and transparent about these measures and other working practices, and direct RECs to this information even if the IRAS form does not routinely collect it.

(i) Issues covered in standard REC review

Upholding scientific validity and rigour

When outlining the PP, Masters and Nutt concentrated on existing protocols for promising therapeutic agents that had been shelved due to lack of funding. But the possibility of new protocols, designed with inclusion criteria that the donor would meet at least at the time of funding was left open. We found that donors having any influence over trial design could be perceived as undermining scientific rigour and therefore unacceptable. Accordingly, the prospects of PP-funded studies securing favourable review will be enhanced if matching agencies maintain a distance between researchers and donors rather than allowing specific characteristics of the donor to influence the design of putative studies. Arguably, however, a study designed to maximise the chances that a donor will be eligible could provide meaningful results, thereby meeting the GAfREC "worthwhile" threshold. Designing trials around donors, particularly those for neglected conditions, may therefore, be permissible provided they are scientifically robust, explore demonstrably promising interventions, are not disproportionately risky, and do not unfairly exclude groups who could potentially benefit.

Our study identified a perception that PP funding may encourage baseless studies, further reiterating the value of independent expert review to provide reassurance about the scientific basis and trial design. The HRA makes clear, however, that RECs are not expected to undertake their own scientific review of research; assessing the quality of the science is a responsibility that rests with the study sponsor. GAfREC S5.4.2.a states that a REC will be "satisfied with credible assurances that the research has an identified sponsor and that it takes account of appropriate scientific peer review". Accordingly, the REC's role is to *check* that sufficient scientific review has been obtained, not to conduct such a review themselves. As clinical trials, the studies funded using PP would require MHRA approval in addition to REC approval. MHRA review entails an expert review of the science and safety of clinical trials. GAfREC S5.4.2c states that RECs should not duplicate the work of another public body's regulatory duties. Concerns about the science and design of PP donor-funded research should therefore be resolved by the study sponsor ensuring that a robust, independent scientific review is provided to the REC, along with confirmation that the study has been submitted to the MHRA.

The inclusion of PPI in PP-funded studies was recommended by our participants. The HRA issued a joint briefing with INVOLVE endorsing the merits of PPI, particularly its beneficial impact on the ethical aspects of research,[18] and IRAS forms collect information on PPI. Accordingly, this is something RECs should already consider.

More than one donor-participant

Our participants seemed open to the idea of one or more other donors being added to a study on the same terms as the original funder. We found this surprising as one of the primary objections we found to PP-funding (see below) is that donors are guaranteed a place on the trial. Arguably, adding donors compounds the unfairness of the rich having greater access to potential research benefits than the poor because it would increase the proportion of wealthy participants in the trial. The inequities increase in proportion to the number of places on a trial given to those who can afford to pay for them. One of the

perceived ethical advantages of PP is its philanthropic nature, whereby wealth is redistributed.[14] This also distinguishes PP from pay-to-participate and pay-to-try models. The greater the proportion of wealthy donors required to fund a study, the closer that study will come to pay-to-participate, where participant selection is based on the ability to pay. This issue therefore warrants further philosophical research to establish the ethical tipping point between PP and pay-to-play. At least one trial where all the participants had to pay-to-play has, however, recently received favourable ethics review in the UK.[10] RECs may, therefore, be at least open to permitting PP-funded trials with more than one donor.

(ii) Issues specific to PP

In this section we discuss our findings about PP in relation to which guidance may be useful because the highlighted issues are novel or unique to PP. All relate to donors securing a place on a trial by virtue of funding it.

Pre-empting any therapeutic misconception

The TM arises when a research participant misunderstands the difference between clinical treatment and research and expects participation to result in medical benefit.[19] There are two points at which a donor might be affected by the TM in the PP.

First, at the funding stage. By agreeing to provide a significant amount of money for a trial, the donor might expect a medical benefit. It is, however, highly likely that the contracting process between donors and the matching agency would mitigate TM. As with any research funding, the terms and conditions and responsibilities of the donor and the matching agency would be set out in a legally binding agreement. Here it should and would be made explicit that agreeing to fund a trial may not result in a benefit. It may be prudent, therefore, for matching agencies to work with the HRA to agree a standard form of words for capturing this concern in contracts, which will facilitate easy REC checking and consistency of review.

Second, as a participant, the donor might be particularly vulnerable to the TM at the consent stage. King and Ballantyne suggest that donor-participants who are paying for a trial may be more likely to believe that the intervention will be medically beneficial, despite efforts to explain otherwise. However, as they point out, the TM is unfortunately prevalent in other clinical trials, and health research more widely. Much existing work demonstrates that research participants expect a benefit and cite this as a key factor in their decision to participate.[20-22] King and Ballantyne support Miller and Joffe's[23] contention that the TM should not prevent research where it is more likely to arise, but instead requires enhanced informed consent processes. Guidance would help RECs to assess whether proposed processes have been suitably enhanced for participating donors.

Transparency about funding vs donor privacy

Some evidence suggests that funding information makes little difference to research participants. Innes et al[24] found that information about funding was ranked amongst the least important pieces information included in an information sheet (29th out of 32 items ordered in terms of importance). The top-ranked items were potential side-effects, disadvantages/risks, what participation requires, and potential advantages. Confirmed scientific quality was ranked 11th. Similarly, in an observational study, Kirkby et al[25] found that information about funding was only viewed by a minority (23%) of participants.

Our PPI participants tended to think it important to disclose the identity of the donor in the interests of transparency. In PP, however, the funder is not an organisation but an individual, who may also be a participant. In being tasked with protecting participants' interests, RECs must consider the protection of the donor's privacy as a trial participant. Donors are likely to be very rich individuals, and given the types of trials amendable to PP (phase I or IIa), they (or nominated loved one) may also be very

unwell. To disclose their names in information sheets would render them more vulnerable by highlighting their financial and health status to other participants, and anyone else who can access participant information. Moreover, the potential influence of the funder as a rich person in a celebrity culture was raised by REC participants as something that may unduly influence whether people participate in a trial funded by a celebrity. To include the donor's name would also disclose their identity to the research team. This conflicts with the importance afforded by our participants to scientific rigour alongside their concerns that donors may influence results or gain preferential treatment.

RECs may therefore need to strike a balance between maintaining a distance between the donor and the researchers, protecting participant privacy, and transparency about the source of funding. When a charity funds research, participants are not provided with the names of the charity's individual donors. The matching agency is analogous to other organisations that sit between benefactors and the participants, controlling and administering research funding. Consistency therefore suggests that the matching agency rather than the donor should be named. This would provide parity with information participants typically receive about funding sources and ensure the privacy of donors is adequately protected.

Our study did not explore whether actual potential participants would be deterred from a trial funded by someone they thought reprehensible. Hypothetical studies with potential participants with orphan conditions would provide some insights into the relative weightings given to the donor's character and the paucity of participation opportunities. There is, however, evidence that studies of hypothetical behaviour are not good indicators of actual behaviour.[26] In the absence of reliable evidence, the temptation to err on the side of identifying the donor to safeguard fully informed consent, still needs to be weighed against protecting donor privacy and potential desirability of maintaining a virtual barrier between donors and researchers.

Fairness

A well-established ethical requirement is that the potential risks and benefits of research must be distributed fairly.[27] In PP, the donor secures a place on the trial by virtue of their wealth. Some participants thought it unfair that a donor can 'buy' potential benefits that others cannot afford, but others regarded differences in buying power as a fact of life. In considering these opposing findings, we offer two thoughts:

i). Rather than focussing on wider wealth disparities, we can concentrate on what is normal in research: this is the crux of the consistency approach. King and Ballantyne discussed three ways in which the current distribution of the benefits and risks of research are inequitable: the persistent problem of the TM which potentially leaves participants vulnerable to exploitation; the risks of research being 'outsourced' to poorer countries meaning the richer nations are able to benefit from research whilst dodging risk; and, the bulk of research effort and funding being spent tackling the diseases of wealthier nations, meaning that comparatively wealthy people already gain more benefits from research. King and Ballantyne argued that donor-funding models are not *more* commodifying than other research practices that are currently permitted. It would therefore be inconsistent, they argued, to prohibit work funded by a participating donor whilst tolerating these other practices. Acknowledging existing inequalities does not, however, justify multiplying them. King and Ballantyne offer two responses to this point: either donor-funded research and other sub-optimally ethical research practices should be prohibited (which they call a "radical conclusion") or the consistency approach must be rejected. The decision to reject the consistency approach should, however, be justified. Given that the solution to this conundrum impacts research practice beyond PP, it is one on which the HRA needs to form a view.

The HRA is committed to establishing what an acceptable level of inconsistency is between RECs, whilst accepting some level of variability.[28]. A pay-to-play trial has already received favourable review, so it would be reasonable for the applicant to be assured that responses to a PP-funded

proposal are consistent between RECs and between relevantly similar funding streams. A better situation may be for the HRA to adopt a position on PP-funding and make this position clear in its guidance to RECs and researchers. Our findings offer some empirical insights that may inform their deliberations.

ii). Blocking donor-funded research on the grounds of unfairness deprives both the donor and other eligible patients of the potential benefits of participation.

Some participants suggested the donor ought to be supernumerary to mitigate the potential unfairness. This would mean the donor would receive the trial drug or innovation, but their data would not be included in the study, thereby maximising the number of places available to others. This solution has its own ethical difficulties. Whilst the trialled innovations may be promising, there are still risks involved in trial participation. For this reason, to reduce risk it is generally considered unethical to recruit more participants than are statistically needed to meet the study aims. Moreover, PP was devised for phase I and IIa trials. In these small trials, data from each participant is likely to be statistically significant and of critical value in determining whether to suspend or close a trial due to adverse reactions. These are both considerations against making the donor supernumerary.

Furthermore, PP was developed in response to the paucity of research funding for rare or orphan diseases. As King and Ballantyne point out, these are diseases that do not attract funding from private or public sponsors because they are comparatively rare and are perceived as having low social utility and marketing potential. Opportunities for patients with these conditions to take part in research are limited or non-existent. Donor-funded research might therefore be the *only* funding model creating such opportunities for these patients. These inequalities also need to be factored into any decisions about PP on equity grounds.

Limitations and reflexivity

Two of the authors (AM, DN) devised PP. They have been actively involved in promoting this form of participant-funding. This project represents a continuation of this effort and as such their involvement is a potential source of bias. They were not, however, involved in the data-collection nor the initial coding. The other three researchers (HD – an academic specialising in ethics, SB – a researcher-clinician, KS – a PhD student with a background in research governance) were open-minded about whether PP is an acceptable funding model and alert to the potential for bias within the team.

Having a topic guide, particularly one developed on the back of our own analysis of the ethical issues, may have shaped the data collected. This risk was mitigated by starting with an open question. In each group this elicited a range of responses which either covered most areas in the remainder of the topic guide (REC and PPI groups) or led the discussion in a direction we had not anticipated (researcher group concerns about the disruption of the research agenda/infrastructure). Participants did not receive the questions in advance, and each focus group met only once for a relatively short amount of time given the complexity of some of the issues discussed. All participants were invited to email follow-up comments but only two did. However, our user panel agreed with our interpretation of the data, making only one change - to emphasise the potential for reputational damage over the risk of using tainted money as the predominant concern related to donors of bad character.

Our PPI group was a proxy for patients whose only access to novel therapeutics is through clinical trials. Such patients may have offered different perspectives.

A total of twenty-two participants took part, from three quite different stakeholder groups, which is a respectable size for an exploratory qualitative study. Nonetheless, given that the groups tended to focus on different concerns, with only some overlap between the groups, we cannot be confident that we achieved data saturation. Moreover, qualitative research is not intended to be generalisable. Our

study nevertheless offers new insights that may prompt policy development and inform further research.

Our project identified and explored concerns about PP from the perspective of REC review, taking account of current policies and practices, using the philosophical lens of King and Ballantyne's consistency argument. This located our discussion within the context of that which is considered permissible, as opposed to ideal, in current research practice.

CONCLUSIONS

We used focus groups to explore a novel potential source of research funding, the PP, where a donor funds an entire, single-arm phase I or IIa clinical trial in exchange for a place on that trial - subject to meeting inclusion and exclusion criteria at the time of recruitment. Using data collected from REC chairs, clinical researchers and PPI groups, we identified and explored ethical issues may be raised by RECs when reviewing PP-funded clinical trials. We have suggested areas where guidance related to PP-specific issues we identified would be helpful.

Next steps: further empirical research is needed to determine how prevalent in, and representative of, the relevant stakeholder groups our findings are. We have also highlighted areas where more philosophical work is needed, such as the incorporation of multiple donors. Participant-funding is evolving as a means of drawing more funding into areas that interest groups strongly feel warrant more attention. Masters and Nutt originally envisaged the PP being used only in single-arm interventions. Masters[13] has suggested an extension to the proposal that allows for randomised trials in neglected areas. Further research would be needed to determine if the principles behind PP can be applied to trials with more than one arm. It would be helpful for the HRA to consider its position on different forms of participant-funding. We have suggested areas where further guidance would support RECs in making independent but reasonably consistent judgements about PP-funded trials.

Data availability statement
Additional selected data are presented in Supplementary3. No other data are available.

Ethics statement
Patient consent for publication
Not applicable

Ethics approval
A favourable ethics opinion was received from the Biomedical & Scientific Research Ethics Committee of the University of Warwick [reference: BSREC 126/19-20].

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Author contributions
KS & HD were responsible for the first draft of this paper. AM, DN & SB provided comments on this and subsequent drafts. All authors approved the final version.

HD, AM, DN & SB designed the study.
HD designed the topic guide, and with KS gained participant consent, collected and coded the data.
HD, KS, SB, AM & DN decided how the data should be categorised and presented.
The corresponding author is guarantor and attests that all listed authors meet authorship criteria and no others meeting the criteria have been omitted.

Conflicts of interest

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/disclosure-of-interest/ and declare: funding for this project from UK Spine. HD is employed by the University of Warwick. KS was a doctoral researcher in receipt of a research stipend from the University of Warwick until September 2021 when she took up a post with the HRA but does not now represent their views. KS, DN, AM & HD received funding from UK Spine for time contributed to this study. In the past three years HD has received unrelated research funding from the Arts and Humanities Research Council, National Institute for Health Research and CIFAR, and is an unpaid member of DMS Ethics Committee, the Ethics Advisory Group of Birmingham Women's and Children's Hospitals Foundation Trust and NHS BT Deceased Donor Family Tissue Advisory Group; DN is a self-employed communications specialist currently working on an unrelated, fixed term contract as Head of Communications for the University of Warwick. In the past three years he has had contracts with Sutton Council, Newham Council, the Scouting Association, the London Assembly and Plymouth Council. He is retained by Sutton Council to develop the London Cancer Hub; AM is a free-lance writer, illustrator and teacher. Together AM & DN established and raised funds for iCancer, a not-for-profit patients support group; SB's salary is part-funded by the Birmingham Biomedical Research Centre and has provided paid consultancy in the field of Sjogren's clinical trial design in the past three years to Abbvie, Astra Zeneca, Galapagos and Novartis. No other relationships or activities that could appear have influenced the submitted work.

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Supplementary Material

1 Topic guide questions (prompts and probes not included)

Thinking as a researcher/potential participant/REC member, what are your thoughts about this funding model?

How could any concerns, questions or worries be addressed in the protocol, standard operating procedures or by other means?

One of the distinctive features of this funding model is that the donor (or their nominee) is guaranteed a place on the trial PROVIDED that they meet the inclusion/exclusion criteria at the time of recruitment. What concerns might this raise from your point of view?

As a general rule, no one should be excluded from research participation on economic grounds. To what extent does guaranteeing the donor (or their nominee) a place on a trial disadvantage other potential participants?

On occasions, researchers have to go back to funders for additional funding. This can happen, for example, if it takes them longer than expected to recruit sufficient participants or if there are other unanticipated and unavoidable delays. Funders do not always agree to additional funding. In the case of this model of funding, if for whatever reason, the original donor is unable or unwilling to fund an extension, what concerns, if any, might there be about an additional donor being sought on the same terms (i.e. being guaranteed a place on the trial PROVIDED they meet the inclusion/exclusion criteria at the time of recruitment)?

The Declaration of Helsinki states that potential participants should be told about the 'sources of funding' for clinical trials. Normally, this means including the name of the funding agency (e.g. Medical Research Council) in the participant information. In the case of the model we are exploring, this could be the actual name of the donor (e.g. Josephine Blogs). Or it could be the name of the matching agency, since they are responsible for the administration of the funding – like Cancer Research UK, which raises funds in a variety of ways and from a variety of sources. What are your thoughts about the information that should be provided to potential participants?

Taking all of our discussions into account, to what extent do you think that potential concerns RECs may have about this funding model can be satisfactorily addressed?

That's all of our questions, what else should we be considering from your point of view?

2. Statement of PPI involvement

Masters and Nutt are neither clinicians nor academics. They are lay people and in one case also a patient affected by the lack of funding for neglected drugs. They devised the Plutocratic Proposal for donor-funding that lies at the heart of this study. They were full co-applicants on the funding application and have been active co-investigators on the project. They have been remunerated for their contribution on an hourly basis in line with INVOLVE recommendations.

Masters and Nutt helped to design the project and their agenda forged the research questions and limited the scope of the study to REC review. They were involved in the categorisation of the findings and the drafting of this paper, on which they are co-authors.

In addition, PPI group members from a local clinical trials unit assisted with the evaluation of the topic guide and advised on the timing for the PPI focus group (to take account of the burdens of participation in terms of length and the need for regular breaks). They were instrumental in the design of the participant information sheet and we followed their advice about creating a video presentation to explain the Plutocratic Proposal in the context of research funding. One of our focus groups was comprised solely of PPI members. Members from this group were also members of our user panel and reviewed the summary of findings that will be distributed to all those who participated and post on our website, once our findings have been peer reviewed. They were remunerated for this work in line with INVOLVE recommendations.

Masters and Nutt are taking our findings forward in that they are working on ways to realise their aim of establishing a matching agency and using this (and other models of donor-funding) to fund clinical trials.

3. Table with additional quotations ordered as reported

Participants (P) were allocated an identifier according to focus group (REC, PPI and Res=researcher) and then order in which they spoke (P1, P2, P3 etc.).

Good science

1. 'We know that good science is good research, and that's good ethics.' (RECP5)
2. 'I think, you know, we've mentioned the word crackpot schemes a few times over the course of the past 20 minutes and it's clear that, that, that that is where the danger really lies and, and the concept, the idea really that this is gonna be funding areas of research which just shouldn't be funded.' (ResP5)
3. 'I would have grave concerns about creating a system which allowed donor-funded research to fund poor quality research…once you put a system in which doesn't have the safeguards of UKRI type panel, then it is gonna be vulnerable, I think, to having crackpot ideas funded.' (ResP3)

4. 'I have concern around scientific validity. I'd want to be convinced that the donor had no role or influence in the design, the conduct or the reporting of, of the research.' (ResP6
5. 'The potential for the donor to influence the science, which raises concerns and it's the same concern as if there's a pharmaceutical company that's funding. And, there's a conflict of interest there, and I can imagine there being all sorts of pressures.' (ResP1)
6. 'But I would be worried about the conduct and bias, perhaps, in analysis of the results, and do we bend rules for people who want to get into the trial?' (PPIP5)
7. 'It's certainly true in doing research with independent healthcare companies, I've done several studies that if they don't like the results they really come after you in a way. They want you to… there's pressure to, "Well, couldn't you just, sort of soften it down here?" or whatever. Instead of, you know, perhaps always facing what you've actually found out.' (RECP3)

8. '… there's a particular need for anyone involved in this expert review and RECs to be certain about the science and the background literature as it relates to a piece of research through this route.' (RECP4)
9. 'If they're clinical trials, they have to go through the MHRA, erm, in which case that is one independent review.' (RECP7)
10. 'I would have concerns about how you could have the same level of critical independent review in this parallel universe.' (ResP4)
11. '… and there must be PPI everywhere to ensure the views of the public are expressed and acted on at all levels.' (PPIP5)

12. 'if the researchers do know who it is has provided the cash for this then there is going to be, however well intentioned, a tendency to treat that individual differently.' (PPIP1)

Concerns raised by the donor gaining a place on the trial

Disclosing the identity of the donor

13. 'I think if somebody is, is prepared to put the money up for this then it should be known by everybody who's involved in the process.' (PPIP1)
14. 'Clearly this is of some concern to some people, of high concern to others, and of no concern to others, so I think you have to put the information in just morally.' (PPIP7)
15. 'In the documents that I've read, that perhaps CRUK fund this, I don't know how they're gonna write down, you know, "a donor," cos that will immediately raise suspicions in somebody's mind.' (PPIP6)

16. ‘I was thinking just now of the ways in which having a named donor might actually influence recruitment. You know, just thinking about, for example, Britney Spears and Kanye West, two people with long term severe mental health problems, and one of whom repeatedly is presented as mad and the other who’s presented very sympathetically as, “Oh, poor dear, she's struggling.” … Do those sort of images have a knock on effect if you see them on the participant information? You know, ‘I'm not going to sign up for something, you know, funded by him, but I might, you know, if it comes from her.” … There is an argument for that, that anonymity.’ (RECP3)
17. ‘That was one of the reasons why the ethics committee was so cross about it [piece of research proposed by a celebrity], because we thought there was someone who is using his celebrity to try and push through a piece of research and, indeed, get a head start on recruitment prior to even getting a review by the ethics committee.’ (RECP1)

18. ‘I mean, the alternative is you just say it's the matching agency, but I don't think that’s being transparent - sufficiently transparent.’ (PPIP7)
19. ‘To say that…a piece of research is funded by an anonymous donor, from…the very little I know of the Helsinki Agreement, is probably okay.’ (PPIP4)
20. ‘We don't go into lots of details about where money’s come from through…organisations that we generally tend to think are reputable, like Cancer Research. We wouldn’t ask who’s donated to that, you know, and what proportion of that donation has gone through to this project, but we'd just put “Cancer Research” at the top.’ (RECP6)
21. ‘There are good reasons not to tell participants who’s funding trials in some circumstances, and I have seen the ethics committee swayed by arguments that you shouldn’t tell participants who’s funding specific trials.’ (RECP1)

22. ‘I suspect that many potential participants would be more concerned about that [the science] than…they would be about who’s funding it.’ (RECP6)
23. ‘The evidence is that people aren't interested in funding.’ (RECP7)
24. ‘I mean, my experience of working with participants is that very few of them are concerned about who’s funding it, and, you know, as… comparing funding from drug companies, is it vastly different?’ (PPIP3)

The therapeutic misconception

25. ‘People think that if you throw enough money at something then in 18 months you might have a cure for any disease when in actuality that almost certainly is never likely to be true again.’ (ResP5)
26. ‘People [researchers] are convinced about their treatment, they will take money from many sources for it, and if somebody is charismatic and persuasive about their treatment, I’m not convinced that the donor is gonna be in a position to make an informed decision that that’s the treatment that they want to put their money into.’ (ResP1)
27. ‘These people, one assumes, are very desperate, you know, they are really going to just want it for their own end initially.’ (PPIP6)
28. ‘There's quite a difficulty, I think, isn't there, in how donor money is going to be used properly to fund good research without it becoming a ‘looking around for something that might help me. And those would have to be very clear to the people who are intending to give the money, the people who're in the matching agency, and the people doing the research.’ (RECP4)
29. ‘If at the end of the, of that consent process the patient says, “thanks, I’m delighted to go in as long as it’s going to help me,” at that point, that patient’s consent is not valid and therefore in a sense there is something implicit about this whole transactional relationship which is problematic.’ (ResP4)

30. ‘If I have an illness and I agree to participate in a trial, then I generally believe that that trial is happening because there’s been good review that it’s an appropriate thing to do, that the intervention is going to be likely to be successful, that, you know, it has been fully peer reviewed…they’re not gonna do it unless it’s likely to be successful, whether it’s got a good chance, or whether it’s by charity or government funding.’ (ResP1)

Donor benefit

31. ‘I have concerns around the fairness of participant selection. It should really be based on scientifically valid criteria not ability to pay and, and research risk and benefits should be fairly distributed, I think, in society.’ (ResP6)
32. ‘Are other participants going to know that it’s being funded for one particular person, with that person in mind, or that problem in mind? So, you know, other participants might feel aggrieved, if you like, that it's funded for this particular one person.’ (PPIP3)

33. ‘I haven't heard anything that says they need to be included in the analysis.’ (PPIP2)
34. ‘This is my lay suggestion, why do they have to actually be part of the analysis? Be part of the, the research…there’s a donor who’s… For which they get the treatment and that’s fine, that’s done, and nobody actually knows who they are. But when it comes to the analysis there’s some flag put into some system somewhere that says, “Don't include this person.” And as I say, I'm not very sure about the ethics of what I've just said but it seems to me pragmatic.’ (PPIP3)
35. ‘Well, my first reaction is that that [excluding donor from analysis] sounds a very good idea, as you say it means nobody’s losing their place. I haven’t thought, at the moment, of any disadvantage of that.’ (PPIP4)

36. ‘I would agree with RECP1’s point, you know, you know, my dear father, when I sat on his knee, said to me, “Life’s not fair,” and I haven't forgotten that one.’ (RECP7)
37. ‘It's the same thing as why can that person buy a Rolls Royce yet I can't? It's those sort of things, why can people have first class train fare or flight, when I can't?’ (PPIP7)

38. ‘If you try to argue that it's not fair that that happens and, therefore, this shouldn’t be a way of funding research you're then depriving all the other ten of being involved in a piece of research that may well be of benefit. So, you know, I think somebody using a lot of money, erm, to benefit others, and it also benefits them, seems entirely reasonable.’ (RECP4)

Further funding from additional donors

39. ‘Again, er, the fact that 100 people fund and it's 100 participants who are the funders, I've no issue… its benefit that’s what's, are what's important here, for the common good.’ (PPIP7)
40. ‘It seems to be that there should be a limit, but I can't… choosing a number it would be entirely arbitrary, in the way I'm thinking about it.’ (RECP6)
41. ‘I don't think this is a problem that is specific to this particular type of trial, I think it's something that would, would apply right across the board for any sorts of trials, and it's just part of good trial management that you make sure that the thing doesn’t run out… that sort of stuff shouldn’t happen no matter what type of trial it is.’ (RECP1)

Donors of bad character

and how ethical do we know the donor is, and, er, sort of, what, sort of, lifestyle do they lead, et cetera? (PPIP6) That’s a good point, would you want to be associated, now, with, er, [named individual convicted of sex trafficking] and, er, [their] friends? (PPIP5)

I don't have a problem with many people, but if they're offshoring money… Pharmacy and insurers have to make a profit, everybody has to make a profit to be able to live, if those are excessive then, perhaps, they're immoral, if they're offshored they're definitely immoral, if they don't pay their taxes they're immoral because the rest of us ordinary people suffer because of that, and some people are suffering more. And, I'm sorry, I really do think we should stick to basic principles because once they start eroding they go very quickly. (PPIP5)

[named individual convicted of sex trafficking] was a very generous contributor to science, … perhaps a background check would be useful, do they pay their taxes, do they, er, offshore their, er, profits? … the source of this cash may be very dubious indeed. (PPIP1)

Disrupting the research agenda/infrastructure

Picking up though on this issue of individual donors being able to skew the research landscape which another, er, er, group member, sort of, mentioned, I think that is really important. (ResP1)

'you're not using the research resources most effectively but on the other hand you are adding to them.' (ResP3)

You know, clinical research is an ecosystem, right? And it's, in some ways it's a closed ecosystem. Funding or taking part in some research means that resources and people and academics are deployed in something and it cannot be deployed somewhere else. (ResP7)

I think NIHR, [identifying information removed], would say the same, we'd set up an infrastructure, there's no point doing stuff in the BRCs if you don't have a mechanism to translate it and put it through. I mean, any, er, responsible research, national fund… funding a whole system, just different from charities, er, but even charities have to think if they produce something, what's that route? There's no point producing research that just stops. (ResP3)

There will always be some who are opposed to this 'new' model because either it represents a change and/or it deviates from the 'accepted' funding systems/pathways. Or it may be seen as a way of trying to circumvent established systems. (ResP6 - follow up email)

Matching agency governance and processes

I just wanted to perhaps think about…a little bit about how this matching agency is actually going to work…. how does the matching agency function with regard to tapping wealthy people for money? What sort of advertising is it going to have to do? How is it going to engage with people who are fantastically wealthy to promote itself? I think there are possibly issues around that, about how it actually… How the money actually comes to the agency, how the agency engages with donors, what it's putting forward as, 'this is what's in it for you,' and how it does that. (RECP3)

[The matching agency has] a big role to play which I don't really fully understand at the moment, but I think it's got to be, you know, all seeing, all doing, and, erm, I'm not quite sure how that all fits in with, sort of, legal things and statutory things, other research aspects, it all seems still a tad confusing to me (PPIP6)

and I think this firewall [between donor and researcher] and the integrity of this matching agency is where the success or failure of this initiative is really likely to lie. (ResP5)

All things considered opinions

42. 'I can't see any fundamental issue that would make me want to say, "No. Can't even consider it." I think there are lots of things to thrash out, but I think it's something that needs to be on the table.' (RECP6)
43. 'So I have no major objections to this model because it's already happening that the rich are accessing novel and experimental treatments. If we allow it to have donor-funded research, it may lead to some breakthroughs that will eventually be available to the public. And at the moment many things are being crowd funded, video games, et cetera, films, so I have no serious objections.' (PPIP8)
44. 'It would be something I'd be quite happy to sign up to so long as we are able to maintain that scientific integrity and we do have these balances and checks in place.' (ResP5)

45. 'I think it's an interesting subject, and it can be a novel way of funding research as well, because researchers who are applying for grant applications, what you mentioned, it's, kind of, becoming more and more difficult to get studies funded.' (RECP5)

46. 'I think having a separate committee to review these, these sort of studies, unless we actually demonstrate a need for it it surely just reinforces that this is a special case when, actually, erm, if it's going, if it's going to work at all it's got to be come normalised. I can see the argument for special committees that deal with defence or, er, defence projects, or, erm, certain other factors, but why should this be a separate category? If it's going to work it's just another funding stream.' (RECP3)
47. 'You know, an area that's not normally funded cos there's nothing in it for the pharma companies and I don't see anything different in principle, really, between a pharma company funding research to a private individual, what's the difference?' (PPIP7)
48. 'So many of these things are so study dependent, and it just depends upon the context of the study as to exactly what, what you come down to.' (RECP1)
49. 'There are specific considerations that come up, and what's needed, and might come from this sort of work is a, a framework of questions and considerations where… Of the particular issues in this type of trial.' (RECP7)

50. 'I've listened with interest and I think people have made some excellent points but I'm afraid they haven't really moved me from my initial position, that this is a bad thing, erm, and it may or may not have good results but, erm, in the lap of the gods. I suspect it's going to happen regardless of, er, of my personal feelings, as many other things happen. I don't like it.' (PPIP1)

SRQR checklist table

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Acceptability of donor-funding for clinical trials in the UK: a qualitative empirical ethics study using focus groups to elicit the views of research patient public involvement group members, research ethics committee chairs and clinical researchers.

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ABSTRACT

Objectives The Plutocratic Proposal is a novel method of funding early phase, clinical trials where a single donor funds the entire trial and in so doing secures a place on it. The aim of this study was to identify and explore concerns that may be raised by UK RECs when reviewing clinical trials funded in this way.

Design Empirical ethics combining ethical analysis and qualitative data from three focus groups held online using Frith's symbiotic approach. Data were analysed using inductive thematic approach informed by the study aims and ethical analysis.

Participants 22 participants were recruited: eight research patient public involvement group members, seven research ethics committee chairs and seven clinical researchers. All were based in the UK.

Results With one exception, participants thought the Plutocratic Proposal may be 'all things considered' acceptable, providing their concerns were met, primary of which was upholding scientific integrity. Other concerns discussed related to the acceptability of the donor securing a place on the trail including: whether this was unfair distribution of benefits, disclosing the identity of the donor as the funder, protecting the donor from exploitation, and funding a single study with multiple donors on the same terms. Some misgivings fell outside the usual REC purview: detrimental impact of donors of bad character, establishing the trustworthiness of matching agency and its processes, and optimising research funding and resources. Despite their concerns, participants recognised that because the donor funds the whole trial, others would also potentially benefit from participating.

Conclusions We identified concerns about the Plutocratic Proposal. UK RECs may be open to approving studies if these can be addressed. Existing governance processes will do some of this work, but additional REC guidance, particularly in relation to donors securing a place on the trial, may be necessary to help RECs navigate ethical concerns consistently.

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ARTICLE SUMMARY: STRENGTHS AND LIMITATIONS OF THIS STUDY

- The Plutocratic Proposal has received a cautiously favourable reception in the literature, but this is the first study to explore whether studies funded using this model may be deemed acceptable by UK RECs.
- Empirical ethics, which combines philosophical analysis and empirically obtained insights, is a recognised methodology for understanding and evaluating ethical issues that affect policy in healthcare services and research.
- Focus groups are a useful qualitative tool for exploring potentially controversial topics, as they permit participants to engage with each other's views but we cannot be confident that we reached data saturation in this study.
- Qualitative findings are not generalisable beyond the study sample.

INTRODUCTION

Many promising clinical interventions do not progress to early clinical trials due to a lack of funding, and some that do may fail for commercial reasons.[1, 2] The 'valley of death' in which promising therapies may flounder, is a persisting, multi-faceted and international problem.[3, 4] One solution to this funding shortfall in the initial stages of development proposed by two patient-advocates, Masters and Nutt,[5] is that a single, very wealthy individual commits to funding an entire single-arm phase I or phase IIa clinical trial in exchange for the guarantee of a place on the trial. Importantly, this guarantee is subject to the inclusion and exclusion criteria being met at the point of recruitment. Their 'Plutocratic Proposal' (PP) envisages a 'matching agency' that 'pairs' donors and researchers without exploiting the donor or interfering with normal and accepted research review and governance procedures. This they describe as 'committed philanthropy' because one donor commits to funding the trial fully aware that they may not meet the inclusion criteria. Masters' and Nutt's proposal grew out of their experience of crowd-funding a clinical trial for a friend with metastatic pancreatic neuroendocrine cancer. They argue there is a moral imperative to explore new, acceptable avenues for research funding, especially for potential therapeutic responses to rarer diseases that would otherwise be shelved.

The idea of patients funding novel treatments is not new, particularly in relation to small-scale, single-arm trials and off-label use. It has been seen, for instance, in regenerative cell treatment[6-8] and oncology,[9, 10] where it has been noted that large scale randomised control trials, especially against placebo, might not be the most ethical or economical way of gathering data on clinical effectiveness.[10] More recently, crowd-funding has been considered as a potential source of finance for clinical trials on rare diseases.[9]

PP presents ethical challenges. These were evaluated by King and Ballantyne[11] against current research practices and also other forms of funding by participants – pay-to-play,[12] where individuals pay to participate in a trial, and pay-to-try,[13] where individuals pay for access to a promising intervention but not obviously as part of any trial. They concluded that there is "nothing inherently unethical" about PP. Donor-funding should, they argue, be assessed against "real-world ethical standards" and "standard health research legislation/guidelines and undergo [institutional review board/research ethics committee] and scientific peer-review" rather than being measured against aspirational standards that current research practice is not guaranteed to live up to. This they call their 'conservative argument from consistency', the crux of which is that like cases should be treated alike:

> Critics have argued that donor-funding should be prohibited because of fundamental ethical concerns about scientific validity, social value, therapeutic misconception, exploitation and fair subject selection. But the nature of the concerns levelled at donor-funding models are not qualitatively, nor in many cases quantitatively, different from features of currently permitted health research.

As King and Ballantyne's article title suggests, this makes PP "permissible not perfect": it accords with current minimal, rather than ideal, ethical standards. Compared with other forms of donor-funding, they regarded the PP as most likely to reduce the potential ethical risks. Dal-Ré et al concur, concluding that PP is the most appropriate self-funding option for "early investigation of new orphan drugs".[9] They point out, however, that PP may be more complex to implement but suggest that, in Spain, the Spanish Federation of Rare Diseases could fulfil the role of the matching agency. Vayena[14] also defends PP, which she regards as addressing the ethical deficiencies of off-label usage and right-to-try approaches. She sees PP as continuous with increasingly patient-led research.

Given this cautiously favourable reception in the literature, it would be helpful to know how PP might be received by UK research ethics committees (RECs) and what concerns may arise during review. If it could be established that PP-funded studies may, with the right safeguards, be conducted in an

ethically permissible way, then identifying barriers to approval and mitigating these would remove a potential obstacle to this novel funding stream. Our study therefore aimed to identify and explore concerns that may be raised by RECs when reviewing PP-funded clinical trials.

Our study had three objectives:

1) To undertake an initial analysis of the ethical issues raised by PP in the light of Health Research Authority (HRA) policies and guidance to RECs, and to use this analysis to create a topic guide to explore the stakeholders' views;
2) To explore, using focus groups, the views and ethical concerns about PP for REC members, clinical researchers and potential research participants as key stakeholders in the research ethics review process;
3) To determine, based on objectives 1) and 2), what REC guidance around PP might be needed.

METHOD

An empirical ethics approach[15] was chosen to meet our aim. This enabled us to combine ethical analysis with the stakeholders' views about acceptability. Identifying and exploring issues philosophically enabled a systematic evaluation of ethical issues based on key features of the PP, the role and remit of RECs and broader principles of research ethics. We drew on Frith's symbiotic approach[16] to integrate our philosophical analysis into the empirical investigation. Philosophical analysis influenced the data collection (by informing the topic guide), our thematic analysis and, through the adoption of a philosophical lens, the way our results are discussed.

A topic guide was designed taking into account the small literature on the potential ethical objections to PP, and related aspects of the larger literature on research ethics. This literature was considered alongside published HRA policies and guidance for RECs and researchers making REC applications, to determine considerations that a REC should have in mind when reviewing research protocols.

The draft topic guide was piloted in February 2020 first with researchers (N=4) and REC members (N=2), and then with two research patient public involvement (PPI) group members, who also helped to shape the participant information for the study. The topic guide was revised and then finalised (supplemental1) based on the comments from each pilot group sequentially.

Three focus groups were convened, one for each of the stakeholder groups (REC chairs, clinical researchers and research PPI members, who were our proxy for potential study participants). The inclusion criteria were: role (clinical researcher, REC chair, PPI group member), availability (due to coronavirus (COVID-19) pandemic, ability to join Microsoft Teams meeting was added), and English speaking. There were no exclusion criteria.

REC chairs were recruited by email, using information in the public domain. Everyone approached and who was available on the date selected agreed to participate. Our intention was to recruit clinical researchers via published lists of REC-reviewed research for the period Jan-March 2020, (sampling for region and academic/hospital/industry based). The response rate was poor and only two participants were recruited. Four participants were recruited after UK Spine and two clinical trial units circulated information about the project. One researcher responded to our recruitment drive for PPI participants. Our PPI participants were recruited via PPI networks associated with clinical trials units and selected on the basis of availability and achieving gender balance and representation across the three groups approached.

Focus groups were held in September, October, and December 2020, using Microsoft Teams. Participants provided individual audio-recorded consent in advance. The consent process was an opportunity for the participants to familiarise themselves with Microsoft Teams, guided where needed

by the researchers gaining consent. One PPI participant was unable to participate due to microphone issues that we were unable to resolve during their consent meeting.

The focus groups were recorded and transcribed verbatim. Two participants (PPI and researcher) responded to the general invitation to send further reflections or comments by email. Each transcription was reviewed: identifying information was removed and participant identifiers allocated. Two researchers, working independently, manually coded the transcripts inductively, and independently organised the codes into categories. A thematic analysis was undertaken informed by the range of issues raised by the participants and our understanding of the ethical dimensions as suggested by Frith's[16] symbiotic approach. The resulting initial analysis was reviewed and then discussed with the remaining research team, and organised into themes that reflected our aim. The preliminary analysis was presented to, and discussed for validation purposes with, a 'user panel' drawn from each focus group.

When discussing our findings, we have adopted the "conservative argument from consistency" in line with King and Ballantyne's[11] evaluation of donor funding.

Patient and public involvement (PPI)

Masters and Nutt (who are not academic or clinicians) were involved throughout. PP is their concept and they approached and worked with Draper to design and secure funding for the project. They had input into the research questions, the categorisation of the findings and are full authors on this paper. In addition, further input from PPI groups was sought to develop the topic guide, and potential patients formed one of our focus groups and reviewed our initial results. All participants were asked if we could retain their contact information to receive a summary of our results once published. (See Supplementary materials 2 for further details).

RESULTS

Twenty-two participants attended three focus groups (table 1).

Table 1. Focus groups and participants.

Focus Group	Participant Type	Gender
1 (112 minutes)	REC Chairs (n = 7)	4 male; 3 female
2 (88 minutes)	Members of PPI groups (n = 8)	4 male; 4 female
3 (75 minutes)	Researchers (n = 7) Academic-based (n = 4) Hospital-based (n = 2) Industry-based (n = 1)	6 male; 1 female

Seven themes were identified from the coded data. Six were organised into two broad areas (table 2). Three themes represented concerns that fell outside of the remit of REC review in the UK, as established by the Governance Arrangements for RECs (GAfREC).[17] Three identified potential obstacles to favourable review in areas that are squarely within the purview of RECs. We will first start with the latter themes, before going on to reporting the participants' broader concerns about PP. We will conclude with the seventh theme, which reflected our participants 'all things considered' views. Illustrative quotations are provided (with further examples in supplementary3).

Table 2 The six themes organised according to established REC remit

Within established remit	Outside established remit

1. Good science 2. Concerns raised by donor gaining a place on the trial 3. Further funding from additional donors	4. Donors of bad character 5. Disrupting the research agenda/infrastructure 6. Matching agency governance and processes

1. Good science

Participants in all three focus groups highlighted the ethical importance of robust science and trial design for donor-funded research, which encompassed the need for independent expert review, with some participants acknowledging that all clinical trials would be subject to Medicines and Health Products Regulatory Agency (MHRA) review, and PPI input.

> We know that good science is good research, and that's good ethics. (RECP5)

The researcher groups expressed concerns about "crackpot" or "whacky" studies being conducted using interventions that lacked scientific basis.

The greatest fear raised in relation to the science was that donors might influence the study design. Many participants felt that a funder participating in a trial may be allowed to affect not only the conduct, but also the analysis or reporting of the results of the research. These participants expressed the view that the donor may feel invested in the product, creating a conflict of interest which may result in them lobbying for, for example, a 'softening' of the reported results.

> But I would be worried about the conduct and bias, perhaps, in analysis of the results, and do we bend rules for people who want to get into the trial? (PPIP5)

Some participants were concerned that a funder-participant could introduce bias or receive preferential treatment.

> [I]f the researchers do know who it is has provided the cash for this then there is going to be, however well intentioned, a tendency to treat that individual differently. (PPIP1)

2. Concerns raised by donor gaining a place on the trial

Three concerns relating to the donor gaining a place on the trial were identified: who would learn the identity of the donor, the therapeutic misconception (TM), and fairness.

The REC and PPI groups discussed whether the identity of the donor ought to be disclosed to the other trial participants. The PPI participants tended to discuss transparency:

> Clearly this is of some concern to some people, of high concern to others, and of no concern to others, so I think you have to put the information in just morally. (PPIP7)

REC participants were concerned, though, that if donors' identities were known, and they publicised their participation on social media, this might influence trial recruitment, especially if the donors were celebrities.

Both groups recognised trial participants must be given information about the source of trial funding but some felt that disclosing the name and details of the matching agency would be sufficient:

> We don't go into lots of details about where money's come from through… We wouldn't ask who's donated to … what proportion of that donation has gone through to this project, but we'd just put "Cancer Research [UK]" at the top. (RECP6)

Members of both groups pointed out that potential participants are not in general very interested in details about funding.

The importance of donor-participants being sufficiently informed to avoid any TM was emphasised. First, that donors should be fully aware at the funding stage that no medical benefit is promised, nor even a place on the trial itself. Second, that as a participant giving consent to the trial, it should be clear them that no medical benefit is guaranteed.

> These people, one assumes, are very desperate, you know, they are really going to just want it for their own end initially. (PPIP6)

Core to PP is the idea that the funder secures a place on a trial subject to meeting its inclusion criteria at the time of recruitment. Some members of our PPI and researcher groups were concerned about fair participant selection, and ensuring that the risks and benefits of trial participation are distributed fairly.

> I have concerns around the fairness of participant selection. It should really be based on scientifically valid criteria not ability to pay and, and research risk and benefits should be fairly distributed, I think, in society. (ResP6)

Some in the PPI group felt that this potential unfairness could be remedied by the donor being supernumerary to the sample size required for the trial. They were unperturbed that the donor's data would be excluded from the trial as a consequence.

Others were less concerned about the potential unfairness, particularly in the REC group, and thought that wealthy individuals having an advantage was all-invasive fact of life.

Some participants acknowledged that allowing a donor to fund a trial, even where they gained one place on that trial, created opportunities for patients that would not otherwise exist.

> If you try to argue that it's not fair that that happens and, therefore, this shouldn't be a way of funding research you're then depriving all the other ten of being involved in a piece of research that may well be of benefit. (RECP4)

3. Further funding from additional donors

The REC and PPI groups discussed the possibility of further funding being sought from additional donor/s during a trial. There was no general agreement on how to reconcile increasing the number of donor-guaranteed places with potential objections that this may magnify any unfairness.

> It seems to be that there should be a limit, but I can't… choosing a number it would be entirely arbitrary, in the way I'm thinking about it. (RECP6)

Participants noted the importance, and difficulties, of ensuring studies were adequately costed beforehand, including funds for unforeseen difficulties and to avoid pauses in trial activity.

4. Donors of bad character

The consequences of some donors being bad people was only raised by the PPI group (though it was the principal objection to PP by a researcher in the pilot group). The concerns were two-fold: first that money from bad people was tainted, and this might, or should, put off potential trial participants, and second that the researchers' reputation would be at risk if the donor was later revealed to be immoral or criminal.

PPIP6: And how ethical do we know the donor is, and, er, sort of, what, sort of, lifestyle do they lead, et cetera?
PPIP5: That's a good point, would you want to be associated, now, with, er, [named individual convicted of sex trafficking] and, er, [their] friends?

5. Disrupting the research agenda/infrastructure

The researcher group expressed a strong (but not unanimous) view that existing structures ensured that research funding was channelled most effectively and that priority areas were researched. Some participants were concerned that PP might direct resources such as trained researchers away from traditionally-funded studies.

> You know, clinical research is an ecosystem, right? And it's, in some ways it's a closed ecosystem. Funding or taking part in some research means that resources and people and academics are deployed in something and it cannot be deployed somewhere else. (ResP7)

At the same time, it was recognised that more funding is needed: "you're not using the research resources most effectively but on the other hand you are adding to them." (ResP3)

6. Matching agency governance and processes

Participants in all three groups indicated that they might want to consider details of the operations and governance of the matching agency when reviewing a PP donor-funded research application.

> I just wanted to perhaps think about… how this matching agency is actually going to work…. how does the matching agency function with regard to tapping wealthy people for money? What sort of advertising is it going to have to do? How is it going to engage with people who are fantastically wealthy to promote itself? I think there are possibly issues around that, about how it actually… How the money actually comes to the agency, how the agency engages with donors, what it's putting forward as, 'this is what's in it for you,' and how it does that. (RECP3)

Added to these concerns were questions about how the agency would maintain a "firewall" (ResP5) between donor and research, and other considerations related to ensuring a robust research proposal. Some participants expressed the view that to be credible, the matching agency would need to replicate the processes found in existing funding organisations.

7. 'All things considered' opinions

There was a general feeling across the three groups that the PP is "fundamentally" (RECP6) acceptable but participants were also cautious: "no major objections … so long as we are able to maintain that scientific integrity and we do have these balances and checks in place." (ResP5). There was a recognition that donor-funding would generate more funding, and in turn facilitate more research, which was perceived positively.

Some participants stated that REC applications using PP should be treated like any other applications, and did not, for instance, require the HRA to establish a specialist committee.

> I don't see anything different in principle, really, between a pharma company funding research to a private individual, what's the difference? (PPIP7)

> [I]f it's going to work at all it's got to become normalised. (RECP3)

It was generally felt that each application could be considered on a case-by-case basis as opposed to, for example, the HRA issuing a formal broad-brush "Yes" or "No" approach, but that a framework outlining the relevant issues would be useful.

One participant felt very strongly that the PP was not acceptable but thought it was likely to happen regardless.

DISCUSSION

To meet our final objective of determining what specific REC guidance around PP may be required, and in line with the symbiotic approach, we identified the core ethical issues arising from our findings, which we organised into two broad groups. The first group contains ethical issues that, whilst important, fall outside the usual purview of REC review, as defined by the GAfREC . In the second group are issues squarely within the REC purview as defined by the GAfREC. These are further grouped according to whether they: (i) would be accounted for in a standard REC review or (ii) are specific to the PP, and therefore more likely to require REC guidance. We discuss these issues through the lens of King and Ballantyne's conservative consistency approach taking into account our participants 'all things considered' view that PP seems acceptable provided their concerns can be addressed in practice.

Issues outside the established purview of REC review

We identified concerns that PP does not reflect how current funding and resources are currently allocated to meet priority areas and greatest need, that donors of bad character pose a reputational risk to researchers, and that RECs would want to know more about the processes and governance of matching agencies.

The REC remit does not include ensuring research resources are used maximally. A REC's primary obligation (GAfREC S3.2.1) is to protect the interests of research participants. Beyond this they should consider "the public interest in reliable evidence affecting health and social care and enable ethical and worthwhile research of benefit to participants or to science and society". Research does not have to meet the most urgent or widespread needs to be "worthwhile", and many studies receive favourable review that would not pass this threshold. Commercial research may, for example, direct researchers and research facilities towards work that is likely to prove profitable, rather than that which meets the greatest need.

GAfREC S3.2.2 states that RECs should consider the "safety and interests of researchers". Beyond excluding matters that are properly the responsibility of employers, the breadth of the responsibility to protect researchers' interests is not defined. The reputation of researchers and their employers is intertwined. Employing organisations – who are likely to be sponsors of the research – should consider organisational risks during the sponsorship review. Any perceived residual obligation could be discharged by RECs providing a general warning to researchers. The alternative is mandating RECs to undertake a detailed investigation into the character of all donors. RECs are not normally privy to detailed information about the characters of contributors to charities that fund research, nor their investment portfolios and tax returns etc. In order to take on this additional responsibility, REC would need not only access to such information, but also additional skills and resources, including centrally agreed benchmarks for moral decency applicable to all funders.

Details around the governance and operations of research funding bodies is not information that is currently collected via HRA Integrated Research Application Systems (IRAS) forms and made available to RECs or participants. Our participants tended to the view that PP-funding should be normalised as far as REC review is concerned, which suggests that matching agencies should not be required to provide information that other bodies would not be expected to provide. On the other hand, PP-funding is novel and, as our findings reflect, matching agencies may lack the 'trusted brand' familiarity that other funding bodies have developed over time. Matching agencies would therefore be prudent as a minimum: i): commit to processes that demonstrably enforce their adherence to good science, including the transparent, robust peer-review of proposals and ensuring the adequacy of

funding; ii) be open and transparent about these measures and other working practices, and direct RECs to this information even if the IRAS form does not routinely collect it.

(i) Issues covered in standard REC review

Upholding scientific validity and rigour

When outlining the PP, Masters and Nutt concentrated on existing protocols for promising therapeutic agents that had been shelved due to lack of funding. But the possibility of new protocols, designed with inclusion criteria that the donor would meet at least at the time of funding was left open. We found that donors having any influence over trial design could be perceived as undermining scientific rigour and therefore unacceptable. Accordingly, the prospects of PP-funded studies securing favourable review will be enhanced if matching agencies maintain a distance between researchers and donors rather than allowing specific characteristics of the donor to influence the design of putative studies. Arguably, however, a study designed to maximise the chances that a donor will be eligible could provide meaningful results, thereby meeting the GAfREC "worthwhile" threshold. Designing trials around donors, particularly those for neglected conditions, may therefore, be permissible provided they are scientifically robust, explore demonstrably promising interventions, are not disproportionately risky, and do not unfairly exclude groups who could potentially benefit.

Our study identified a perception that PP funding may encourage baseless studies, further reiterating the value of independent expert review to provide reassurance about the scientific basis and trial design. The HRA makes clear, however, that RECs are not expected to undertake their own scientific review of research; assessing the quality of the science is a responsibility that rests with the study sponsor. GAfREC S5.4.2.a states that a REC will be "satisfied with credible assurances that the research has an identified sponsor and that it takes account of appropriate scientific peer review". Accordingly, the REC's role is to *check* that sufficient scientific review has been obtained, not to conduct such a review themselves. As clinical trials, the studies funded using PP would require MHRA approval in addition to REC approval. MHRA review entails an expert review of the science and safety of clinical trials. GAfREC S5.4.2c states that RECs should not duplicate the work of another public body's regulatory duties. Concerns about the science and design of PP donor-funded research should therefore be resolved by the study sponsor ensuring that a robust, independent scientific review is provided to the REC, along with confirmation that the study has been submitted to the MHRA.

The inclusion of PPI in PP-funded studies was recommended by our participants. The HRA issued a joint briefing with INVOLVE endorsing the merits of PPI, particularly its beneficial impact on the ethical aspects of research,[18] and IRAS forms collect information on PPI. Accordingly, this is something RECs should already consider.

More than one donor-participant

Our participants seemed open to the idea of one or more other donors being added to a study on the same terms as the original funder. We found this surprising as one of the primary objections we found to PP-funding (see below) is that donors are guaranteed a place on the trial. Arguably, adding donors compounds the unfairness of the rich having greater access to potential research benefits than the poor because it would increase the proportion of wealthy participants in the trial. The inequities increase in proportion to the number of places on a trial given to those who can afford to pay for them. One of the perceived ethical advantages of PP is its philanthropic nature, whereby wealth is redistributed.[14] This also distinguishes PP from pay-to-participate and pay-to-try models. The greater the proportion of wealthy donors required to fund a study, the closer that study will come to pay-to-participate, where participant selection is based on the ability to pay. This issue therefore warrants further philosophical research to establish the ethical tipping point between PP and pay-to-play. At least one trial where all the participants had to pay-to-play has, however, recently received favourable ethics

review in the UK.[10] RECs may, therefore, be at least open to permitting PP-funded trials with more than one donor.

(ii) Issues specific to PP

In this section we discuss our findings about PP in relation to which guidance may be useful because the highlighted issues are novel or unique to PP. All relate to donors securing a place on a trial by virtue of funding it.

Pre-empting any therapeutic misconception

The TM arises when a research participant misunderstands the difference between clinical treatment and research and expects participation to result in medical benefit.[19] There are two points at which a donor might be affected by the TM in the PP.

First, at the funding stage. By agreeing to provide a significant amount of money for a trial, the donor might expect a medical benefit. It is, however, highly likely that the contracting process between donors and the matching agency would mitigate TM. As with any research funding, the terms and conditions and responsibilities of the donor and the matching agency would be set out in a legally binding agreement. Here it should and would be made explicit that agreeing to fund a trial may not result in a benefit. It may be prudent, therefore, for matching agencies to work with the HRA to agree a standard form of words for capturing this concern in contracts, which will facilitate easy REC checking and consistency of review.

Second, as a participant, the donor might be particularly vulnerable to the TM at the consent stage. King and Ballantyne suggest that donor-participants who are paying for a trial may be more likely to believe that the intervention will be medically beneficial, despite efforts to explain otherwise. However, as they point out, the TM is unfortunately prevalent in other clinical trials, and health research more widely. Much existing work demonstrates that research participants expect a benefit and cite this as a key factor in their decision to participate.[20-22] King and Ballantyne support Miller and Joffe's[23] contention that the TM should not prevent research where it is more likely to arise, but instead requires enhanced informed consent processes. Guidance would help RECs to assess whether proposed processes have been suitably enhanced for participating donors.

Transparency about funding vs donor privacy

Some evidence suggests that funding information makes little difference to research participants. Innes et al[24] found that information about funding was ranked amongst the least important pieces information included in an information sheet (29th out of 32 items ordered in terms of importance). The top-ranked items were potential side-effects, disadvantages/risks, what participation requires, and potential advantages. Confirmed scientific quality was ranked 11th. Similarly, in an observational study, Kirkby et al[25] found that information about funding was only viewed by a minority (23%) of participants.

Our PPI participants tended to think it important to disclose the identity of the donor in the interests of transparency. In PP, however, the funder is not an organisation but an individual, who may also be a participant. In being tasked with protecting participants' interests, RECs must consider the protection of the donor's privacy as a trial participant. Donors are likely to be very rich individuals, and given the types of trials amendable to PP (phase I or IIa), they (or nominated loved one) may also be very unwell. To disclose their names in information sheets would render them more vulnerable by highlighting their financial and health status to other participants, and anyone else who can access participant information. Moreover, the potential influence of the funder as a rich person in a celebrity culture was raised by REC participants as something that may unduly influence whether people participate in a trial funded by a celebrity. To include the donor's name would also disclose their identity to the research team. This conflicts with the importance afforded by our participants to

scientific rigour alongside their concerns that donors may influence results or gain preferential treatment.

RECs may therefore need to strike a balance between maintaining a distance between the donor and the researchers, protecting participant privacy, and transparency about the source of funding. When a charity funds research, participants are not provided with the names of the charity's individual donors. The matching agency is analogous to other organisations that sit between benefactors and the participants, controlling and administering research funding. Consistency therefore suggests that the matching agency rather than the donor should be named. This would provide parity with information participants typically receive about funding sources and ensure the privacy of donors is adequately protected.

Our study did not explore whether actual potential participants would be deterred from a trial funded by someone they thought reprehensible. Hypothetical studies with potential participants with orphan conditions would provide some insights into the relative weightings given to the donor's character and the paucity of participation opportunities. There is, however, evidence that studies of hypothetical behaviour are not good indicators of actual behaviour.[26] In the absence of reliable evidence, the temptation to err on the side of identifying the donor to safeguard fully informed consent, still needs to be weighed against protecting donor privacy and potential desirability of maintaining a virtual barrier between donors and researchers.

Perceived potential unfairness

A well-established ethical requirement is that the potential risks and benefits of research must be distributed fairly.[27] In PP, the donor secures a place on the trial by virtue of their wealth. Some participants thought it unfair that a donor can 'buy' potential benefits that others cannot afford, but others regarded differences in buying power as a fact of life. In considering these opposing findings, we offer two thoughts:

i). Rather than focussing on wider wealth disparities, we can concentrate on what is normal in research: this is the crux of the consistency approach. King and Ballantyne discussed three ways in which the current distribution of the benefits and risks of research are inequitable: the persistent problem of the TM which potentially leaves participants vulnerable to exploitation; the risks of research being 'outsourced' to poorer countries meaning the richer nations are able to benefit from research whilst dodging risk; and, the bulk of research effort and funding being spent tackling the diseases of wealthier nations, meaning that comparatively wealthy people already gain more benefits from research. King and Ballantyne argued that donor-funding models are not *more* commodifying than other research practices that are currently permitted. It would therefore be inconsistent, they argued, to prohibit work funded by a participating donor whilst tolerating these other practices. Acknowledging existing inequalities does not, however, justify multiplying them. King and Ballantyne offer two responses to this point: either donor-funded research and other sub-optimally ethical research practices should be prohibited (which they call a "radical conclusion") or the consistency approach must be rejected. The decision to reject the consistency approach should, however, be justified. Given that the solution to this conundrum impacts research practice beyond PP, it is one on which the HRA needs to form a view.

The HRA is committed to establishing what an acceptable level of inconsistency is between RECs, whilst accepting some level of variability.[28]. A pay-to-play trial has already received favourable review, so it would be reasonable for the applicant to be assured that responses to a PP-funded proposal are consistent between RECs and between relevantly similar funding streams. A better situation may be for the HRA to adopt a position on PP-funding and make this position clear in its guidance to RECs and researchers. Our findings offer some empirical insights that may inform their deliberations.

ii). Blocking donor-funded research on the grounds of unfairness deprives both the donor and other eligible patients of the potential benefits of participation.

Some participants suggested the donor ought to be supernumerary to mitigate the potential unfairness. This would mean the donor would receive the trial drug or innovation, but their data would not be included in the study, thereby maximising the number of places available to others. This solution has its own ethical difficulties. Whilst the trialled innovations may be promising, there are still risks involved in trial participation. For this reason, to reduce risk it is generally considered unethical to recruit more participants than are statistically needed to meet the study aims. Moreover, PP was devised for phase I and IIa trials. In these small trials, data from each participant is likely to be statistically significant and of critical value in determining whether to suspend or close a trial due to adverse reactions. These are both considerations against making the donor supernumerary.

Furthermore, PP was developed in response to the paucity of research funding for rare or orphan diseases. As King and Ballantyne point out, these are diseases that do not attract funding from private or public sponsors because they are comparatively rare and are perceived as having low social utility and marketing potential. Opportunities for patients with these conditions to take part in research are limited or non-existent. Donor-funded research might therefore be the *only* funding model creating such opportunities for these patients. These inequalities also need to be factored into any decisions about PP on equity grounds.

Limitations and reflexivity

Two of the authors (AM, DN) devised PP. They have been actively involved in promoting this form of participant-funding. This project represents a continuation of this effort and as such their involvement is a potential source of bias. They were not, however, involved in the data-collection nor the initial coding. The other three researchers (HD – an academic specialising in ethics, SB – a researcher-clinician, KS – a PhD student with a background in research governance) were open-minded about whether PP is an acceptable funding model and alert to the potential for bias within the team.

Having a topic guide, particularly one developed on the back of our own analysis of the ethical issues, may have shaped the data collected. This risk was mitigated by starting with an open question. In each group this elicited a range of responses which either covered most areas in the remainder of the topic guide (REC and PPI groups) or led the discussion in a direction we had not anticipated (researcher group concerns about the disruption of the research agenda/infrastructure). Participants did not receive the questions in advance, and each focus group met only once for a relatively short amount of time given the complexity of some of the issues discussed. All participants were invited to email follow-up comments but only two did. However, our user panel agreed with our interpretation of the data, making only one change - to emphasise the potential for reputational damage over the risk of using tainted money as the predominant concern related to donors of bad character.

Our PPI group was a proxy for patients whose only access to novel therapeutics is through clinical trials. Such patients may have offered different perspectives.

A total of twenty-two participants took part, from three quite different stakeholder groups, which is a respectable size for an exploratory qualitative study. Nonetheless, given that the groups tended to focus on different concerns, with only some overlap between the groups, we cannot be confident that we achieved data saturation. Moreover, qualitative research is not intended to be generalisable. Our study nevertheless offers new insights that may prompt policy development and inform further research.

Our project identified and explored concerns about PP from the perspective of REC review, taking account of current policies and practices, using the philosophical lens of King and Ballantyne's

consistency argument. This located our discussion within the context of that which is considered permissible, as opposed to ideal, in current research practice.

CONCLUSIONS

We used focus groups to explore a novel potential source of research funding, the PP, where a donor funds an entire, single-arm phase I or IIa clinical trial in exchange for a place on that trial - subject to meeting inclusion and exclusion criteria at the time of recruitment. Using data collected from REC chairs, clinical researchers and PPI groups, we identified and explored ethical issues may be raised by RECs when reviewing PP-funded clinical trials. We have suggested areas where guidance related to PP-specific issues we identified would be helpful.

Next steps: further empirical research is needed to determine how prevalent in, and representative of, the relevant stakeholder groups our findings are. We have also highlighted areas where more philosophical work is needed, such as the incorporation of multiple donors. Participant-funding is evolving as a means of drawing more funding into areas that interest groups strongly feel warrant more attention. Masters and Nutt originally envisaged the PP being used only in single-arm interventions. Masters[13] has suggested an extension to the proposal that allows for randomised trials in neglected areas. Further research would be needed to determine if the principles behind PP can be applied to trials with more than one arm. It would be helpful for the HRA to consider its position on different forms of participant-funding. We have suggested areas where further guidance would support RECs in making independent but reasonably consistent judgements about PP-funded trials.

Data availability statement
Additional selected data are presented in Supplementary3. No other data are available.

Ethics statement
Patient consent for publication
Not applicable

Ethics approval
A favourable ethics opinion was received from the Biomedical & Scientific Research Ethics Committee of the University of Warwick [reference: BSREC 126/19-20].

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Author contributions
KS & HD were responsible for the first draft of this paper. AM, DN & SB provided comments on this and subsequent drafts. All authors approved the final version.
HD, AM, DN & SB designed the study.
HD designed the topic guide, and with KS gained participant consent, collected and coded the data.
HD, KS, SB, AM & DN decided how the data should be categorised and presented.
The corresponding author is guarantor and attests that all listed authors meet authorship criteria and no others meeting the criteria have been omitted.

Conflicts of interest

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/disclosure-of-interest/ and declare: funding for this project from UK Spine. HD is employed by the University of Warwick. KS was a doctoral researcher in receipt of a research stipend from the University of Warwick until September 2021 when she took up a post with the HRA but does not now represent their views. KS, DN, AM & HD received funding from UK Spine for time contributed to this study. In the past three years HD has received unrelated research funding from the Arts and Humanities Research Council, National Institute for Health Research and CIFAR, and is an unpaid member of DMS Ethics Committee, the Ethics Advisory Group of Birmingham Women's and Children's Hospitals Foundation Trust and NHS BT Deceased Donor Family Tissue Advisory Group; DN is a self-employed communications specialist currently working on an unrelated, fixed term contract as Head of Communications for the University of Warwick. In the past three years he has had contracts with Sutton Council, Newham Council, the Scouting Association, the London Assembly and Plymouth Council. He is retained by Sutton Council to develop the London Cancer Hub; AM is a free-lance writer, illustrator and teacher. Together AM & DN established and raised funds for iCancer, a not-for-profit patients support group; SB's salary is part-funded by the Birmingham Biomedical Research Centre and has provided paid consultancy in the field of Sjogren's clinical trial design in the past three years to Abbvie, Astra Zeneca, Galapagos and Novartis. No other relationships or activities that could appear have influenced the submitted work.

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Supplementary Material

1 Topic guide questions (prompts and probes not included)

Thinking as a researcher/potential participant/REC member, what are your thoughts about this funding model?

How could any concerns, questions or worries be addressed in the protocol, standard operating procedures or by other means?

One of the distinctive features of this funding model is that the donor (or their nominee) is guaranteed a place on the trial PROVIDED that they meet the inclusion/exclusion criteria at the time of recruitment. What concerns might this raise from your point of view?

As a general rule, no one should be excluded from research participation on economic grounds. To what extent does guaranteeing the donor (or their nominee) a place on a trial disadvantage other potential participants?

On occasions, researchers have to go back to funders for additional funding. This can happen, for example, if it takes them longer than expected to recruit sufficient participants or if there are other unanticipated and unavoidable delays. Funders do not always agree to additional funding. In the case of this model of funding, if for whatever reason, the original donor is unable or unwilling to fund an extension, what concerns, if any, might there be about an additional donor being sought on the same terms (i.e. being guaranteed a place on the trial PROVIDED they meet the inclusion/exclusion criteria at the time of recruitment)?

The Declaration of Helsinki states that potential participants should be told about the 'sources of funding' for clinical trials. Normally, this means including the name of the funding agency (e.g. Medical Research Council) in the participant information. In the case of the model we are exploring, this could be the actual name of the donor (e.g. Josephine Blogs). Or it could be the name of the matching agency, since they are responsible for the administration of the funding – like Cancer Research UK, which raises funds in a variety of ways and from a variety of sources. What are your thoughts about the information that should be provided to potential participants?

Taking all of our discussions into account, to what extent do you think that potential concerns RECs may have about this funding model can be satisfactorily addressed?

That's all of our questions, what else should we be considering from your point of view?

2. Statement of PPI involvement

Masters and Nutt are neither clinicians nor academics. They are lay people and in one case also a patient affected by the lack of funding for neglected drugs. They devised the Plutocratic Proposal for donor-funding that lies at the heart of this study. They were full co-applicants on the funding application and have been active co-investigators on the project. They have been remunerated for their contribution on an hourly basis in line with INVOLVE recommendations.

Masters and Nutt helped to design the project and their agenda forged the research questions and limited the scope of the study to REC review. They were involved in the categorisation of the findings and the drafting of this paper, on which they are co-authors.

In addition, PPI group members from a local clinical trials unit assisted with the evaluation of the topic guide and advised on the timing for the PPI focus group (to take account of the burdens of participation in terms of length and the need for regular breaks). They were instrumental in the design of the participant information sheet and we followed their advice about creating a video presentation to explain the Plutocratic Proposal in the context of research funding. One of our focus groups was comprised solely of PPI members. Members from this group were also members of our user panel and reviewed the summary of findings that will be distributed to all those who participated and post on our website, once our findings have been peer reviewed. They were remunerated for this work in line with INVOLVE recommendations.

Masters and Nutt are taking our findings forward in that they are working on ways to realise their aim of establishing a matching agency and using this (and other models of donor-funding) to fund clinical trials.

3. Table with additional quotations ordered as reported

Participants (P) were allocated an identifier according to focus group (REC, PPI and Res=researcher) and then order in which they spoke (P1, P2, P3 etc.).

Good science

1. 'We know that good science is good research, and that's good ethics.' (RECP5)
2. 'I think, you know, we've mentioned the word crackpot schemes a few times over the course of the past 20 minutes and it's clear that, that, that that is where the danger really lies and, and the concept, the idea really that this is gonna be funding areas of research which just shouldn't be funded.' (ResP5)
3. 'I would have grave concerns about creating a system which allowed donor-funded research to fund poor quality research…once you put a system in which doesn't have the safeguards of UKRI type panel, then it is gonna be vulnerable, I think, to having crackpot ideas funded.' (ResP3)

4. 'I have concern around scientific validity. I'd want to be convinced that the donor had no role or influence in the design, the conduct or the reporting of, of the research.' (ResP6
5. 'The potential for the donor to influence the science, which raises concerns and it's the same concern as if there's a pharmaceutical company that's funding. And, there's a conflict of interest there, and I can imagine there being all sorts of pressures.' (ResP1)
6. 'But I would be worried about the conduct and bias, perhaps, in analysis of the results, and do we bend rules for people who want to get into the trial?' (PPIP5)
7. 'It's certainly true in doing research with independent healthcare companies, I've done several studies that if they don't like the results they really come after you in a way. They want you to… there's pressure to, "Well, couldn't you just, sort of soften it down here?" or whatever. Instead of, you know, perhaps always facing what you've actually found out.' (RECP3)

8. '… there's a particular need for anyone involved in this expert review and RECs to be certain about the science and the background literature as it relates to a piece of research through this route.' (RECP4)
9. 'If they're clinical trials, they have to go through the MHRA, erm, in which case that is one independent review.' (RECP7)
10. 'I would have concerns about how you could have the same level of critical independent review in this parallel universe.' (ResP4)
11. '… and there must be PPI everywhere to ensure the views of the public are expressed and acted on at all levels.' (PPIP5)

12. 'if the researchers do know who it is has provided the cash for this then there is going to be, however well intentioned, a tendency to treat that individual differently.' (PPIP1)

Concerns raised by the donor gaining a place on the trial

Disclosing the identity of the donor

13. 'I think if somebody is, is prepared to put the money up for this then it should be known by everybody who's involved in the process.' (PPIP1)
14. 'Clearly this is of some concern to some people, of high concern to others, and of no concern to others, so I think you have to put the information in just morally.' (PPIP7)
15. 'In the documents that I've read, that perhaps CRUK fund this, I don't know how they're gonna write down, you know, "a donor," cos that will immediately raise suspicions in somebody's mind.' (PPIP6)

16. ‘I was thinking just now of the ways in which having a named donor might actually influence recruitment. You know, just thinking about, for example, Britney Spears and Kanye West, two people with long term severe mental health problems, and one of whom repeatedly is presented as mad and the other who’s presented very sympathetically as, “Oh, poor dear, she's struggling.” … Do those sort of images have a knock on effect if you see them on the participant information? You know, ‘I'm not going to sign up for something, you know, funded by him, but I might, you know, if it comes from her.” … There is an argument for that, that anonymity.’ (RECP3)
17. ‘That was one of the reasons why the ethics committee was so cross about it [piece of research proposed by a celebrity], because we thought there was someone who is using his celebrity to try and push through a piece of research and, indeed, get a head start on recruitment prior to even getting a review by the ethics committee.’ (RECP1)

18. ‘I mean, the alternative is you just say it's the matching agency, but I don't think that’s being transparent - sufficiently transparent.’ (PPIP7)
19. ‘To say that…a piece of research is funded by an anonymous donor, from…the very little I know of the Helsinki Agreement, is probably okay.’ (PPIP4)
20. ‘We don't go into lots of details about where money’s come from through…organisations that we generally tend to think are reputable, like Cancer Research. We wouldn’t ask who’s donated to that, you know, and what proportion of that donation has gone through to this project, but we'd just put “Cancer Research” at the top.’ (RECP6)
21. ‘There are good reasons not to tell participants who’s funding trials in some circumstances, and I have seen the ethics committee swayed by arguments that you shouldn’t tell participants who’s funding specific trials.’ (RECP1)

22. ‘I suspect that many potential participants would be more concerned about that [the science] than…they would be about who’s funding it.’ (RECP6)
23. ‘The evidence is that people aren't interested in funding.’ (RECP7)
24. ‘I mean, my experience of working with participants is that very few of them are concerned about who’s funding it, and, you know, as… comparing funding from drug companies, is it vastly different?’ (PPIP3)

The therapeutic misconception

25. ‘People think that if you throw enough money at something then in 18 months you might have a cure for any disease when in actuality that almost certainly is never likely to be true again.’ (ResP5)
26. ‘People [researchers] are convinced about their treatment, they will take money from many sources for it, and if somebody is charismatic and persuasive about their treatment, I’m not convinced that the donor is gonna be in a position to make an informed decision that that’s the treatment that they want to put their money into.’ (ResP1)
27. ‘These people, one assumes, are very desperate, you know, they are really going to just want it for their own end initially.’ (PPIP6)
28. ‘There's quite a difficulty, I think, isn't there, in how donor money is going to be used properly to fund good research without it becoming a ‘looking around for something that might help me. And those would have to be very clear to the people who are intending to give the money, the people who're in the matching agency, and the people doing the research.’ (RECP4)
29. ‘If at the end of the, of that consent process the patient says, “thanks, I’m delighted to go in as long as it’s going to help me,” at that point, that patient’s consent is not valid and therefore in a sense there is something implicit about this whole transactional relationship which is problematic.’ (ResP4)

30. ‘If I have an illness and I agree to participate in a trial, then I generally believe that that trial is happening because there’s been good review that it’s an appropriate thing to do, that the intervention is going to be likely to be successful, that, you know, it has been fully peer reviewed…they’re not gonna do it unless it’s likely to be successful, whether it’s got a good chance, or whether it’s by charity or government funding.’ (ResP1)

Donor benefit

31. ‘I have concerns around the fairness of participant selection. It should really be based on scientifically valid criteria not ability to pay and, and research risk and benefits should be fairly distributed, I think, in society.’ (ResP6)
32. ‘Are other participants going to know that it’s being funded for one particular person, with that person in mind, or that problem in mind? So, you know, other participants might feel aggrieved, if you like, that it's funded for this particular one person.’ (PPIP3)

33. ‘I haven't heard anything that says they need to be included in the analysis.’ (PPIP2)
34. ‘This is my lay suggestion, why do they have to actually be part of the analysis? Be part of the, the research…there’s a donor who’s… For which they get the treatment and that’s fine, that’s done, and nobody actually knows who they are. But when it comes to the analysis there’s some flag put into some system somewhere that says, “Don't include this person.” And as I say, I'm not very sure about the ethics of what I've just said but it seems to me pragmatic.’ (PPIP3)
35. ‘Well, my first reaction is that that [excluding donor from analysis] sounds a very good idea, as you say it means nobody’s losing their place. I haven’t thought, at the moment, of any disadvantage of that.’ (PPIP4)

36. ‘I would agree with RECP1’s point, you know, you know, my dear father, when I sat on his knee, said to me, “Life’s not fair,” and I haven't forgotten that one.’ (RECP7)
37. ‘It's the same thing as why can that person buy a Rolls Royce yet I can't? It's those sort of things, why can people have first class train fare or flight, when I can't?’ (PPIP7)

38. ‘If you try to argue that it's not fair that that happens and, therefore, this shouldn’t be a way of funding research you're then depriving all the other ten of being involved in a piece of research that may well be of benefit. So, you know, I think somebody using a lot of money, erm, to benefit others, and it also benefits them, seems entirely reasonable.’ (RECP4)

Further funding from additional donors

39. ‘Again, er, the fact that 100 people fund and it's 100 participants who are the funders, I've no issue… its benefit that’s what's, are what's important here, for the common good.’ (PPIP7)
40. ‘It seems to be that there should be a limit, but I can't… choosing a number it would be entirely arbitrary, in the way I'm thinking about it.’ (RECP6)
41. ‘I don't think this is a problem that is specific to this particular type of trial, I think it's something that would, would apply right across the board for any sorts of trials, and it's just part of good trial management that you make sure that the thing doesn’t run out… that sort of stuff shouldn’t happen no matter what type of trial it is.’ (RECP1)

Donors of bad character

and how ethical do we know the donor is, and, er, sort of, what, sort of, lifestyle do they lead, et cetera? (PPIP6) That’s a good point, would you want to be associated, now, with, er, [named individual convicted of sex trafficking] and, er, [their] friends? (PPIP5)

I don't have a problem with many people, but if they're offshoring money… Pharmacy and insurers have to make a profit, everybody has to make a profit to be able to live, if those are excessive then, perhaps, they're immoral, if they're offshored they're definitely immoral, if they don't pay their taxes they're immoral because the rest of us ordinary people suffer because of that, and some people are suffering more. And, I'm sorry, I really do think we should stick to basic principles because once they start eroding they go very quickly. (PPIP5)

[named individual convicted of sex trafficking] was a very generous contributor to science, … perhaps a background check would be useful, do they pay their taxes, do they, er, offshore their, er, profits? … the source of this cash may be very dubious indeed. (PPIP1)

Disrupting the research agenda/infrastructure

Picking up though on this issue of individual donors being able to skew the research landscape which another, er, er, group member, sort of, mentioned, I think that is really important. (ResP1)

'you're not using the research resources most effectively but on the other hand you are adding to them.' (ResP3)

You know, clinical research is an ecosystem, right? And it's, in some ways it's a closed ecosystem. Funding or taking part in some research means that resources and people and academics are deployed in something and it cannot be deployed somewhere else. (ResP7)

I think NIHR, [identifying information removed], would say the same, we'd set up an infrastructure, there's no point doing stuff in the BRCs if you don't have a mechanism to translate it and put it through. I mean, any, er, responsible research, national fund… funding a whole system, just different from charities, er, but even charities have to think if they produce something, what's that route? There's no point producing research that just stops. (ResP3)

There will always be some who are opposed to this 'new' model because either it represents a change and/or it deviates from the 'accepted' funding systems/pathways. Or it may be seen as a way of trying to circumvent established systems. (ResP6 - follow up email)

Matching agency governance and processes

I just wanted to perhaps think about…a little bit about how this matching agency is actually going to work…. how does the matching agency function with regard to tapping wealthy people for money? What sort of advertising is it going to have to do? How is it going to engage with people who are fantastically wealthy to promote itself? I think there are possibly issues around that, about how it actually… How the money actually comes to the agency, how the agency engages with donors, what it's putting forward as, 'this is what's in it for you,' and how it does that. (RECP3)

[The matching agency has] a big role to play which I don't really fully understand at the moment, but I think it's got to be, you know, all seeing, all doing, and, erm, I'm not quite sure how that all fits in with, sort of, legal things and statutory things, other research aspects, it all seems still a tad confusing to me (PPIP6)

and I think this firewall [between donor and researcher] and the integrity of this matching agency is where the success or failure of this initiative is really likely to lie. (ResP5)

All things considered opinions

42. 'I can't see any fundamental issue that would make me want to say, "No. Can't even consider it." I think there are lots of things to thrash out, but I think it's something that needs to be on the table.' (RECP6)

43. 'So I have no major objections to this model because it's already happening that the rich are accessing novel and experimental treatments. If we allow it to have donor-funded research, it may lead to some breakthroughs that will eventually be available to the public. And at the moment many things are being crowd funded, video games, et cetera, films, so I have no serious objections.' (PPIP8)

44. 'It would be something I'd be quite happy to sign up to so long as we are able to maintain that scientific integrity and we do have these balances and checks in place.' (ResP5)

45. 'I think it's an interesting subject, and it can be a novel way of funding research as well, because researchers who are applying for grant applications, what you mentioned, it's, kind of, becoming more and more difficult to get studies funded.' (RECP5)

46. 'I think having a separate committee to review these, these sort of studies, unless we actually demonstrate a need for it it surely just reinforces that this is a special case when, actually, erm, if it's going, if it's going to work at all it's got to be come normalised. I can see the argument for special committees that deal with defence or, er, defence projects, or, erm, certain other factors, but why should this be a separate category? If it's going to work it's just another funding stream.' (RECP3)

47. 'You know, an area that's not normally funded cos there's nothing in it for the pharma companies and I don't see anything different in principle, really, between a pharma company funding research to a private individual, what's the difference?' (PPIP7)

48. 'So many of these things are so study dependent, and it just depends upon the context of the study as to exactly what, what you come down to.' (RECP1)

49. 'There are specific considerations that come up, and what's needed, and might come from this sort of work is a, a framework of questions and considerations where… Of the particular issues in this type of trial.' (RECP7)

50. 'I've listened with interest and I think people have made some excellent points but I'm afraid they haven't really moved me from my initial position, that this is a bad thing, erm, and it may or may not have good results but, erm, in the lap of the gods. I suspect it's going to happen regardless of, er, of my personal feelings, as many other things happen. I don't like it.' (PPIP1)

SRQR checklist table

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