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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 research ethics committees (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: 8 research patient public involvement group members, 7 REC chairs and 7 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 trial including: whether this was an 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 the 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.

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 research ethics committees.
⇒ 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, multifaceted 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 crowdfunding 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, crowdfunding 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 (REC)) 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 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 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 RECs 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 (online supplemental file 1) 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 January–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 potential 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

Masters and Nutt (who are not academics 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 online supplemental file 2 for further details).

Table 1 Focus groups and participants

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

PPI, patient public involvement; REC, research ethics committee.

RESULTS

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

Seven themes were identified from the coded data. Six were organised into two broad areas (table 2). Three themes represented concerns that fell outside 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 report 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 online supplemental file 3).

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 should be subject to Medicines and Health Products Regulatory Agency (MHRA) review, and PPI input.

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

REC, research ethics committee.

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

The researcher group 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)

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 to 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 an 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)

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.

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 twofold: 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?

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)

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.

'All things considered' opinions

There was a general feeling across the three groups that 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 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, while 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: (1) would be accounted for in a standard REC review or (2) 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, RECs 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 to: (1): 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; (2) 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.

Issues covered in standard REC review

Upholding scientific validity and rigour

When outlining 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 an 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.

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 TM

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 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 any 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 versus 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 among the least important pieces of 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 is 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 amenable 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:

(1) 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 while 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 while 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 suboptimally 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, while 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.

(2) 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. While 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 and 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 and 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 22 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, 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 that may be raised by RECs when reviewing PP-funded clinical trials. We have suggested areas where guidance related to the 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 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.

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Contributors KS and HD were responsible for the first draft of this paper. AM, DN and SB provided comments on this and subsequent drafts. All authors approved the final version. HD, AM, DN and SB designed the study. HD designed the topic guide, and with KS gained participant consent, collected and coded the data. HD, KS, SB, AM and 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.

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Competing interests 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 and 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 3 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 freelance writer, illustrator and teacher. Together, AM and 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.

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