Optimising equity of access: how should we allocate slots to the most competitive trials in Cystic Fibrosis (CF)?

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ABSTRACT

Background

Trial participation can allow people with CF early access to CFTR modulator therapies, with high potential for clinical benefit. Therefore, the number of people wishing to participate can substantially exceed the number of slots available. We aimed to understand how the CF community thinks slots to competitive trials should be allocated across the UK and whether this should be driven by clinical need, patients' engagement/adherence or be random. For the latter, we explored site-level versus registry-based, national randomisation processes.

Methods

We developed an online survey, recruiting UK-based stakeholders through social media, newsletters and personal contacts. Closed questions were analysed for frequencies and percentages of responses. Free-text questions were analysed using thematic analysis.

Results

We received 203 eligible responses. Overall, 75% of stakeholders favoured allocation of slots to individual sites based on patient population size, although pharma favoured allocation based on previous metrics. Currently, few centres have defined strategies for allocating slots locally. At face-value, stakeholders believe all eligible participants should have an equal chance of getting a slot. However, further questioning reveals preference for prioritisation strategies, primarily perceived treatment adherence, although healthcare professionals were less likely to favour this strategy than other stakeholder groups. The majority of stakeholders would prefer to allocate slots and participate in trials locally but 80% said if necessary, they would engage in a system of national allocation.

Conclusions

Fair allocation to highly competitive trials does not appear to have a universally acceptable solution. Therefore, transparency and empathy remain critical to negotiate this uncertain territory.

INTRODUCTION

New drug developments in CF make this an exciting time to be involved in trials. Nearly 100 drugs are in the pipeline, including multiple cystic fibrosis transmembrane conductance regulator (CFTR) modulators[1], molecules restoring function of the defective CFTR protein rather than targeting symptoms and complications. Positive data from modulator trials have been widely discussed within the UK CF community, but post-approval funding has frequently required complex and time-consuming negotiation. For many people with CF (pwCF), trial participation has thus been a route to accessing these drugs more rapidly. Therefore, securing a place on some trials, particularly those with open-label phases, can be highly competitive and the number of people keen to participate far exceeds the available slots[2]. As an example, at Royal Brompton and Harefield Trust, a site with a large number of patients, we have recently completed feasibility forms on which the number of potentially eligible patients exceeded the number of slots eventually offered by a factor of over 50. Despite a recent UK funding breakthrough for the latest modulator, Kaftrio™, these issues remain acutely relevant for children and young adolescents with CF and those with genetic mutations without approved modulator therapies and may become relevant to novel therapeutic approaches taken in the future such as gene therapy trials.

Some research sites, including our own, have developed approaches to allocate trial places in a way we think is most fair[2]. However, there is no consensus on what defines “fair” in this regard as was demonstrated by a series of communications in J Cyst Fibrosis in 2019[2–4]. In addition to differences of opinion between sites, not all CF care centres deliver trials. Some centres have few trials running and others may have large numbers of patients but few slots. Therefore, there is significant variability in how likely a patient is to get access to a trial depending

on where they receive their clinical care. We were challenged to consider whether a fairer system could be developed, e.g. one based on a national registry rather than a site/network's own patient pool[4].

In negotiating this unchartered territory, we propose that the CF community should have the opportunity to help define "fair" and shape any systems to be implemented. Therefore, we set out to better understand how stakeholders think slots to highly competitive trials should be allocated across the UK.

AIMS

We aimed to capture opinions on the scale and impact of this issue, to identify any site-specific allocation strategies currently in use for competitive clinical trials and to seek stakeholders' views on 1) how the pharmaceutical industry should allocate slots to individual research sites, 2) how individual sites should allocate slots to their population, 3) referral to trials at sites other than the participant's clinical care centre and 4) whether slots would most fairly be allocated at a national level e.g. through a patient registry.

METHODS

We designed and administered an online survey to capture stakeholders' views (included in online supplement). The survey contained a mix of multiple-choice (MCQs) and free-text questions. The questionnaire was piloted with three HCPs and four pwCF prior to release. Skip logic was employed so respondents were only presented questions relevant to their role to minimise unanswered questions and drop-out rates. The MCQs were analysed for frequencies and percentages of responses. Differences in responses between the four major stakeholder groups (pwCF, parents/carers, healthcare professionals (HCPs) and pharma) were compared using Chi-square analysis. Questionnaires were excluded when <50% of questions were completed. We collected simple demographics from the participant to understand our sample make-up, but no personal identifiable data was collected. Free-text questions were analysed by thematic analysis to identify recurring themes, allowing respondents to explain or clarify answers and provide information not prospectively asked by the study team[5].

Inclusion criteria

- Invested stakeholder (as defined by the participant)
- Able to read and write English
- Willing to consent to participation

We planned to open the survey for 3 weeks, aiming for a pragmatic sample size of 200 with no maximum sample size and no formal stratification. The survey link was shared on Twitter and the CF Trust's Clinical Trials Accelerator Platform (CTAP) newsletter, which flags developments about CF trials in the UK. The team made

professional contacts aware of the survey via email and WhatsApp. Participants could only access the survey once from any given device, however we were unable to ensure participants did not answer twice on different devices. Ethical approval was obtained from the Joint Research Compliance Office (JRCO) at Imperial College London.

RESULTS

We opened the survey on June 3rd and closed on June 24th 2020. We received 231 responses; 28 were excluded as <50% of the questions were completed. Only 1 participant defined themselves within the "other" group and as such their data could not be analysed as a major stakeholder group and their individual responses have not been included in the data displays.

ELIGIBLE RESPONSES (n=203)			
People with CF (n=52)	Age (years)	<18	0 (0%)
		18-24	7 (13%)
		25-34	18 (35%)
		35-44	21 (40%)
		45-54	5 (10%)
		55-64	1 (2%)
		65+	0 (0%)
	Location of clinical care	UK excluding London	37 (71%)
		London	15 (29%)
	Does your clinical centre run trials?	Yes	38 (73%)
		No	3 (6%)
		Don't know	11 (21%)
	Previous trial participation	Yes	22 (42%)
		No	30 (58%)
Parents and Carers of Children with CF (n=86)	Age of child (years)	Under 1	1 (1%)
		1-2	4 (5%)
		3-5	16 (19%)
		6-11	26 (30%)
		12-17	21 (24%)
		18+	19 (22%)
	Location of clinical care	UK excluding London	54 (63%)
		London	32 (37%)
	Does your child's clinical centre run trials?	Yes	59 (69%)
		No	8 (9%)
		Don't know	19 (22%)
	Previous trial participation	Yes	28 (33%)
		No	58 (67%)
Healthcare Professionals (n=49)	Role	Allied health professional	24 (49%)
		Doctor	17 (35%)
		Nurse	8 (16%)
	Paediatric/adult practice?	Mostly paediatrics	21 (43%)
		Mostly adults	24 (49%)
		Mixed	3 (6%)
		Not answered	1 (2%)

	Location of centre	UK excluding London	34 (69%)
		London	15 (31%)
	Does your centre run trials?	Yes	40 (82%)
		No	4 (8%)
		Don't know	5 (10%)
Pharmaceutical industry (n=15)			
Other (n=1)	Role	CF Trust Representative	

Table 1: Respondent characteristics

The scale and impact of the issue

70% of HCPs were aware of patients being unable to access trials due to lack of slots. 50% felt this had significantly impacted patients' psychological wellbeing and 30% felt it impacted on patients' relationships with clinical teams. One HCP described the phenomenon in the free text section "*Patients not getting places on trials can have a really significant impact on their mood that is often underestimated. The impact is more severe for those with more advanced disease or surrounding significant life events*."

Views on allocation of slots to research sites by commercial sponsors

We asked all stakeholders, "*When pharmaceutical companies open trials at several centres in the UK, they need to decide how many slots to give each centre. Which of these most closely matches your opinion on how slots to very popular trials should be allocated to centres across the UK?".* MCQ responses were:

- "*Slots should be allocated according to metrics such as experience and how well they have performed previously"* (18/203, 9%)
- *"All centres should be allocated the same number of slots*" (32/203, 16%)
- *"Centres should be allocated slots according to the size of their population"* (152/203, 75%)

There was a significant difference between how major stakeholder groups answered this question ($p<0.001$, Chi square analysis).

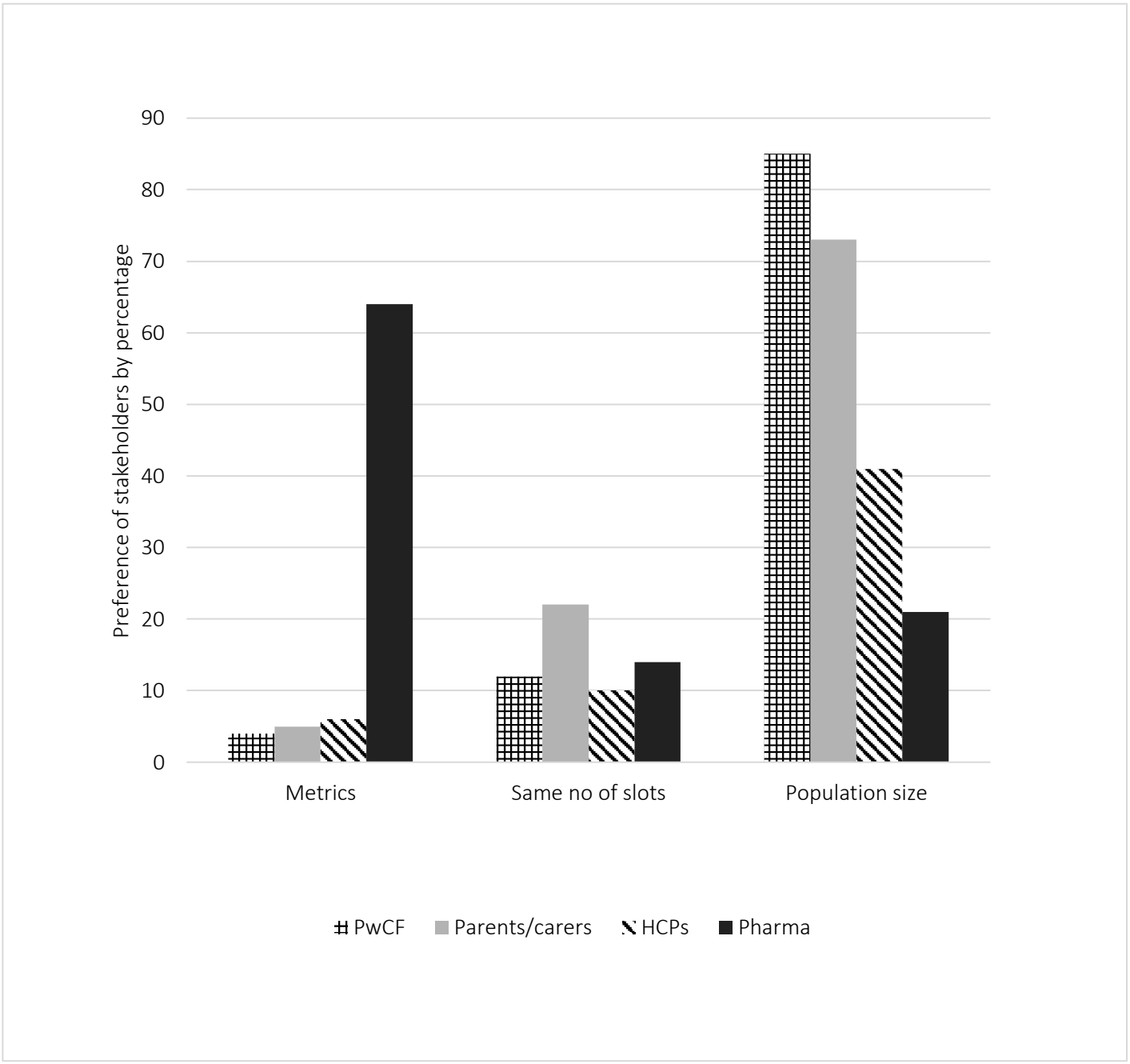

Figure 1a: Preferred method of allocation of slots for popular clinical trials: based on a site's previous metrics, allocated equally or based on a site's size (percentage breakdown by major stakeholder group).

Identification of site-specific allocation strategies in use

We asked the HCPs, *"Does your site have a standard approach to allocating slots on competitive trials?"*. 17/49 (35%) selected "*No*", and 17/49 (35%) "*Don't know*". 15/49 (30%) selected "*Yes*" and were prompted to specify their strategy. Analysis revealed: randomisation (n = 8 (drawing numbers from a hat 2, number generator 3, unspecified 3), prioritisation based on clinical need (n=4) and prioritisation based on likely protocol adherence (n=3).

Views on how sites should allocate slots to their population

We asked all stakeholders to respond *"Yes"*, *"No"* or *"Don't know"* to the statement "*I think every person meeting the entry requirements should have exactly the same chance of getting a slot on a trial*".

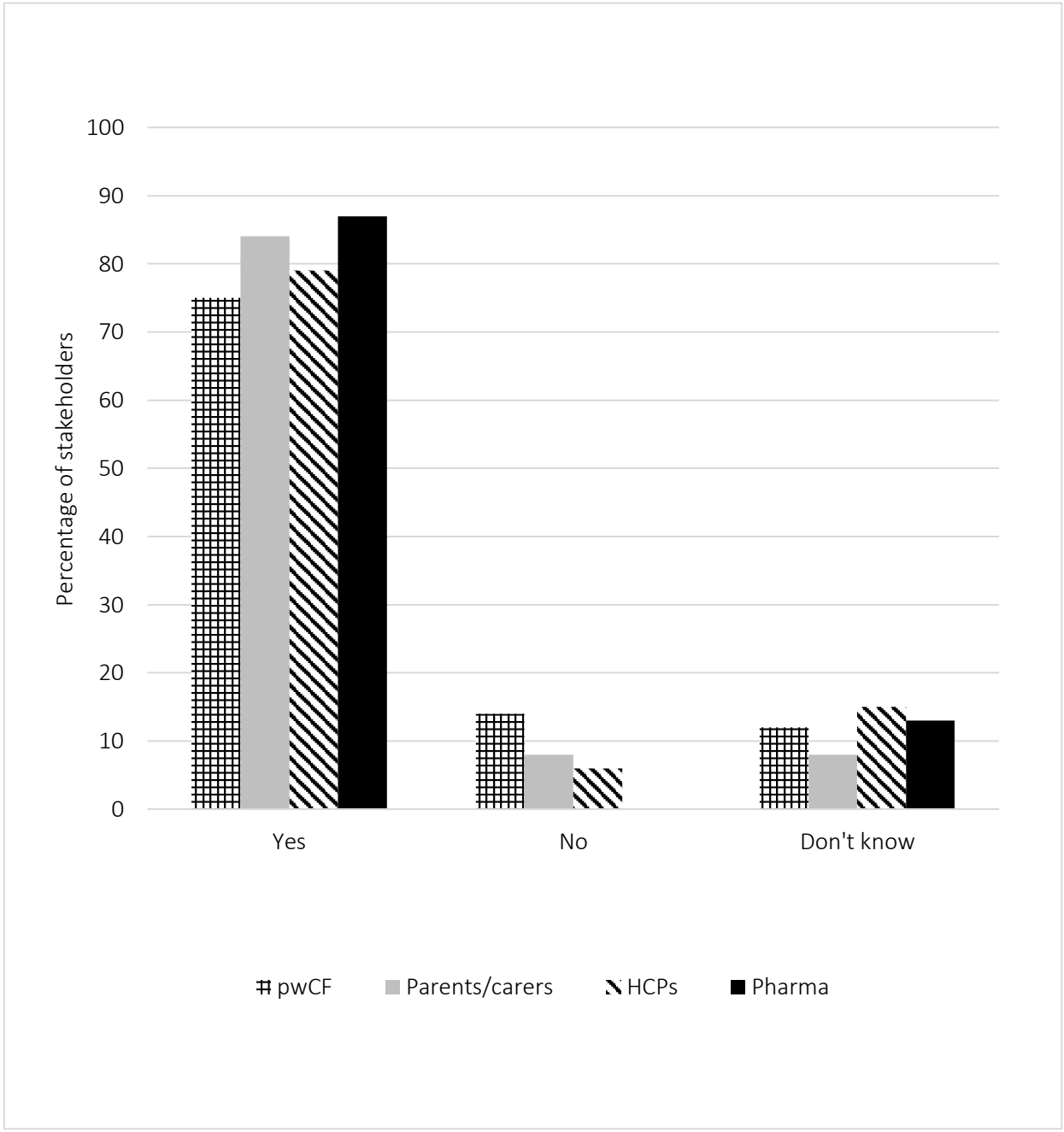

Figure 1b: Agreement with the statement *"I think that every person who meets the entry requirements should have exactly the same chance of getting a slot on a trial*", percentage breakdown by major stakeholder group

80% of participants responded "*Yes*", 11% "*Don't know*" and 9% "*No*"; there was no significant difference in responses between the major stakeholder groups, although any comparison is likely underpowered by small group sizes apart from "Yes". However, further questioning about specific prioritisation strategies revealed inconsistencies between this initial statement and subsequent expressed preferences.

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree	Difference between major stakeholder group responses (Chi square)
People with poorer health should be prioritised for enrolment						
All stakeholders combined (n=203)	**33 (16%)**	**68 (33%)**	**68 (33%)**	**31 (15%)**	**3 (1%)**	
pwCF (n= 52)	8 (15%)	17 (33%)	18 (35%)	8 (15%)	1 (2%)	p=0.991
Parents/Carers (n= 86)	14 (16%)	29 (34%)	29 (34%)	12 (14%)	2 (2%)	
HCPs (n= 49)	8 (16%)	16 (33%)	16 (33%)	9 (18%)	0 (0%)	
Pharma (n= 15)	3 (20%)	5 (33%)	5 (33%)	2 (13%)	0 (0%)	
People who have taken part in previous trials should be prioritised for enrolment						
All stakeholders combined	**24 (12%)**	**60 (30%)**	**79 (39%)**	**29 (11%)**	**11 (5%)**	
pwCF	11 (22%)	14 (29%)	14 (29%)	10 (19%)	3 (6%)	p=0.057
Parents/Carers	7 (8%)	28 (33%)	30 (35%)	16 (19%)	5 (10%)	
HCPs	5 (12%)	12 (24%)	28 (33%)	3 (6%)	1 (2%)	
Pharma	1 (7%)	5 (33%)	7 (47%)	0 (0%)	2 (13%)	
People who contact the team first should be prioritised for enrolment						
All stakeholders combined	**5 (2%)**	**25 (12%)**	**52 (26%)**	**88 (43%)**	**33 (16%)**	
pwCF	1 (2%)	7 (13%)	10 (19%)	18 (35%)	16 (31%)	p=0.119
Parents/Carers	2 (2%)	10 (12%)	18 (20%)	45 (52%)	11 (13%)	
HCPs	1 (2%)	6 (12%)	18 (37%)	20 (49%)	4 (5%)	
Pharma	1 (7%)	2 (13%)	5 (33%)	5 (33%)	2 (13%)	
People who are strongly adherent with therapies should be prioritised for enrolment						
All stakeholders combined	**46 (23%)**	**88 (43%)**	**44 (22%)**	**20 (10%)**	**6 (2%)**	
pwCF	14 (27%)	35 (67%)	1 (2%)	1 (2%)	1 (2%)	**p<0.001**
Parents/Carers	25 (29%)	41 (48%)	19 (22%)	1 (1%)	0 (0%)	
HCPs	2 (4%)	5 (10%)	19 (39%)	18 (37%)	5 (10%)	
Pharma	5 (33%)	6 (40%)	4 (27%)	0 (0%)	0 (0%)	

Table 2: Extent of agreement with statements outlining prioritisation strategies for each stakeholder group and all respondents combined.

Views on referral to trials at sites other than the participant's clinical care centre

	Respondent group/s (n)	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
I would prefer to take part in a trial at my usual clinical centre	pwCF and parents of children with CF (138)	25%	38%	20%	16%	1%
In my clinical role, I would be more comfortable if a patient participated in a trial that was run at our centre rather than referring them to a different centre?	HCPs (49)	12%	29%	39%	11%	6%
In my research role, I would be more comfortable seeing a patient who receives their clinical care at the centre rather than a referral from another centre?	HCPs (49)	2%	12%	25%	43%	16%
I would prefer sites to allocate trial slots to patients who receive their clinical care at that site, rather than referring patients between centres?	Pharma (15)	6%	7%	27%	40%	20%

Table 3: Stakeholders' views on referral between sites for trial participation

We followed the question to pwCF/parents with the statement *"If necessary, if I/my child were offered a place to take part in a popular trial at a different centre from the one where I/my child receive usual clinical care, I/my child would still take part?".* MCQ responses were:

- *"Yes"* (112/138, 81%)
- *"No"* (9/138, 7%)
- *"Maybe"* (16/138, 12%)
- Not answered (1/138, <1%)

Stakeholders' views on allocating slots at a national level (e.g. through the patient registry) and pitfalls to using this process

We asked, *"Assuming that an individual met the inclusion/exclusion criteria of a trial, and the clinical team felt that person would be safe to take part, which of these systems do you think would be the best way to allocate slots on popular trials?*" MCQ responses were:

- *"Every centre (or network) is allocated its slots and all eligible patients at that centre or network have exactly the same chance of getting a place on a trial"* (40/203, 20%)

- *"Every centre (or network) is allocated its slots and the individual teams select patients from their centre to participate based on a number of factors (such as disease severity, adherence to current therapy, previous participation in early phase trials etc)"* (111/203, 55%)
- *"Nationally, all eligible patients are included in a process of random (by chance) selection. Those selected are referred to their nearest available trial centre. This would ensure that everyone in the UK has the same chance of taking part regardless of which CF centre they attend for clinical care"* 48/203 (24%)
- *"Other"* (4/203, 2%)

There was no significant difference between responses from the stakeholder groups.

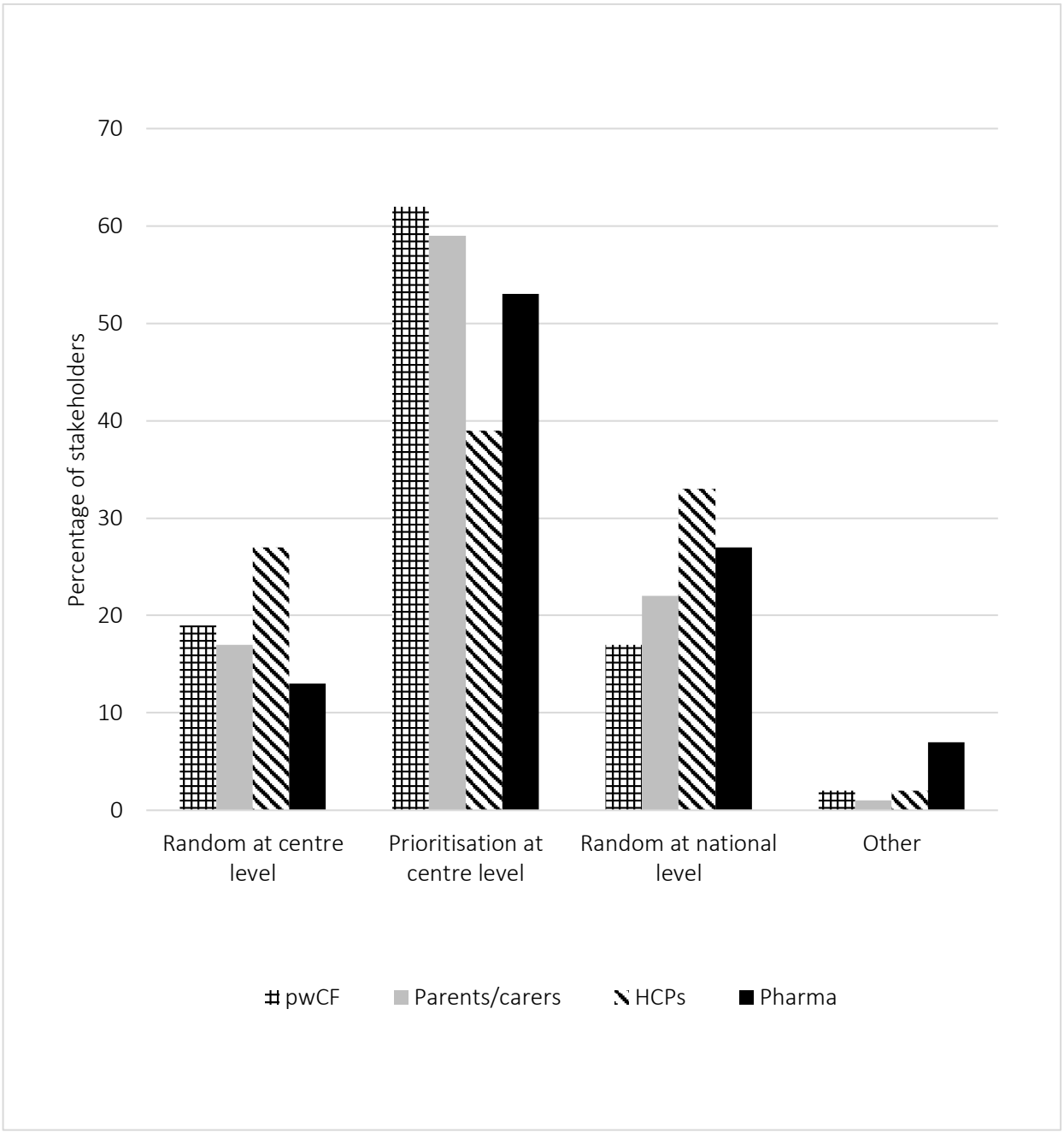

Figure 1c: Distribution of responses to the statement "Assuming that an individual met the inclusion/exclusion criteria of a trial, and the clinical team felt that person would be safe to take part, which of these systems do you think would be the best way to allocate slots on popular trials", percentage breakdown by major stakeholder group

Despite previous indication of preference for local allocation, 80% of stakeholders selected *"Yes"*, when asked *"If a national approach to allocating slots were adopted, would you support using the CF Registry to randomly select potential participants according to the total number of slots available across the UK (eligibility would then be confirmed with CF centre)?".* We asked "*Are there particular problems or challenges that you anticipate associated with using the CF Registry to randomly identify participants for popular trials*?". The results of thematic analysis of the free-text are shown in Table 4.

Theme	Example quotation(s)
Expressed dislike of the use of randomisation +/- proposal for specific prioritisation strategies	"Severe cases should be offered first" (person with CF) "CF patients with lower lung function should be prioritised" (person with CF) "CF centres know their patients better than a random database, they know who may benefit from additional help of a trial drug. Having been on a trial, it is a long commitment and my team knew that I would do all that was requested of me. I think they must play a role in the selection process" (person with CF) "Not all patients may be suitable for a trial, and the CF Registry would just see a number and not a person. If someone was selected that had poor compliance or did not look after themselves, it makes it very unfair for those that have worked hard and proactively asked about trials" (person with CF) "People who currently are not on any modulators should be prioritised for new trials (person with CF)
Preference to attend visits at own trial centre	"Would prefer to do a trial at my own centre" (person with CF) "I would only want to do a trial at our centre. I trust the team to look after us and to know our background well" (parent)
Accuracy/ integrity of data on the registry and the right to opt out*	"My kid is not on the registry, we have never been asked. How many other people have been missed off?" (parent) "Not everybody wants to share their data with the Trust, it shouldn't exclude them from participating in trials. Smacks of the tail wagging the dog" (person with CF) "Data accuracy and completeness in the registry could be an issue. But I believe the registry is fairly accurate and complete. Clinicians may be more motivated to ensure the data they enter into the registry is accurate and complete if it could affect patients (sic) ability to be considered for clinical trials" (HCP)
Additional time and resources required to implement	"Difficult to administer for sites" (HCP) "It can be harder to coordinate when patients come from other centres. There are lots of other things to think about and communication can be a problem" (HCP)

	"May be hard for the study team. Who would regulate? May be harder for monitoring, although if appropriate systems in place this could be mitigated" (HCP) "Using the registry would be appropriate as long as the information is current, but it seems this would require a lot of extra screening work to get to the right participant" (HCP)
*The UK CF Registry has multiple checks in place to ensure quality control[6], which individual patients may not be aware of. Increasing education around these issues may be required if a national approach were to be adopted.	

Table 4: Thematic analysis of free text data regarding views on using random allocation through the CF Registry to select patients for competitive clinical trials

DISCUSSION

This snapshot demonstrates that the allocation of slots to competitive clinical trials is an emotive issue, with potential consequences for patients' psychological wellbeing and relationships with clinical teams.

Overall, three quarters of stakeholders supported population size as the primary determinant of number of slots allocated by the pharmaceutical industry to individual research sites. Subgroup analysis revealed a statistically significant difference between stakeholder groups, with pharma differing from others and favouring metrics-based allocation. Whilst it is easy to understand why the pharmaceutical industry favour allocating sites based on how well a site has performed previously, it disadvantages sites with less trials experience. A proportional representation system would mean that patients at large centres are not disadvantaged by increased competition to access slots and this system is favoured by pwCF, parents/carers and HCPs alike.

Most individual sites do not have a standard approach to slot allocation and there is no consensus on how to allocate slots. Of those who initially stated that "*All participants who meet the eligibility criteria should have exactly the same chance of enrolment*", 92% (149/162) went on to favour prioritisation based on additional criteria. This discrepancy reveals one of the major pitfalls of discussing controversial issues and the bias that can be presented through a desire to give a 'public account' where respondents give what they see to be the 'correct' answer rather than their true opinion. It also demonstrates the benefits of further questioning within surveys to tease out deeper seated preferences[7].

Equality can be achieved by identifying all eligible patients and randomly allocating slots e.g. using a number generator. However, equality is not necessarily equivalent to fairness or equity. For example, many argue it is more equitable to prioritise sicker patients, but others consider this to result in a suboptimally representative sample entering trials. Some suggest that patients who committed time and accepted the higher-risk of early-phase trial participation have "earned" easier passage into competitive later-phase trials and fear that removal

of this incentive will halt drug development earlier in the pipeline with knock-on impacts for the whole CF population[2]. Traditional pragmatic models e.g. selecting patients who contact the team first, or who engage effectively with clinical care represent popular options as they ensure rapid recruitment and adherence to the protocol. However, adherence and research knowledge have been shown to correlate with socioeconomic status and educational opportunities[8–10]. Similar factors influence opportunities in health research and health outcomes for patients[11,12]. Targeted selection of highly adherent or knowledgeable patients may plausibly drive this phenomenon. We presented four potential prioritisation models as options to all stakeholders (Table 2): 66% supported priority being given to those who were more adherent with standard therapy, 50% to those with poor health status, 41% to those who had taken part in early phase trials and 14% to those contacting the team first. Whilst these groupings are not completely mutually exclusive, the sum of 'agree/strongly agree' responses across the 4 questions greatly exceeded 100%, demonstrating that individual respondents were agreeing to multiple reasons for priority. Overall, the highest ranked prioritisation strategy was adherence. Interestingly, of the four proposed prioritisation strategies, this is the only one for which significant differences between stakeholder groups was demonstrated; HCPs were less likely to favour adherence-based prioritisation than pwCF, parents/carers and pharma. We propose several potential reasons for this. The first is sample selection bias - we are likely to have reached an engaged group of patients who may value adherence more highly than the general CF population[13]. It may also reflect the oversight HCPs have of the correlation between sociodemographic variables and adherence. However, it may reveal a true discrepancy between the way HCPs and patients regard this issue. The disconnect between the mutually exclusive assertions that all eligible participants should have an equal chance of getting a place on a trial and the expressed preferences for prioritisation strategies, combined with the discrepancies in opinions between HCPs and patients on which prioritisation strategies to use highlights that there is unlikely to be a universally acceptable solution.

Amongst pwCF and parents/carers, 63% would prefer to take part in a trial at their usual clinical centre, with only 1% strongly disagreeing that they would prefer to participate at their usual centre (Table 3). Comfort and familiarity with teams and physical environment and convenience of using local centres are cited examples in the literature of why patients prefer to take part in trials at their usual centre[14–16]. Despite this, when asked *"If necessary, if I/my child were offered a place to take part in a popular trial at a different centre from the one where I/my child receive usual clinical care, I/my child would still take part?"* only 7% selected *"No"*. It is critical to recognise the potential power imbalance this topic has created- whereby a substantial percentage of stakeholders are expressing a preference for one model but stating that they would support a non-favoured system to access competitive trials. 41% of clinical HCPs felt more comfortable with patient participation at their

own centre, however research teams appear comfortable with referrals with only 2% strongly agreeing that they would prefer to see patients who receive their clinical care at the research centre (Table 3).

Less than a quarter of stakeholders favoured allocating slots at a national rather than local level, with no statistical differences between stakeholder groups (Figure 1c). Concerns about national allocation were multiple, ranging from administrative concerns to further expressed dislike of random slot allocation and preference to continue to deliver trials locally (Table 4). Despite their reservations, 80% of stakeholders stated that, if necessary, they would support a national approach to registry allocation if it were adopted, again perhaps highlighting how desperate some patients are to access trials. In this section there was further support for prioritisation rather than randomisation strategies providing internal validity that, despite the initial 'face-value' statement that all eligible participants should have equal chances of getting a place on a trial, deeper questioning reveals quantitative and qualitative support for prioritisation strategies.

STRENGTHS AND LIMITATIONS

It is important to avoid assumptions and be precise with language when developing surveys, particularly when exploring subjective concepts like 'fairness'. One of the key strengths of this work is the team's extensive experience of CF trial delivery, as well as pretesting with pwCF and HCPs. The anonymity of the survey was another important strength.

One of the limitations with all online voluntary surveys is an inevitable selection bias towards more engaged patients[13]. We tried to minimise this by recruiting through multiple sources including social media forums and having inclusive eligibility criteria, however the potential bias must be acknowledged. We were able to obtain a broad geographical spread across the UK, and the majority of pwCF and parents of children with CF had not previously taken part in a trial. As the trials landscape and reimbursement decisions are country specific, we chose to explore this issue only with people in the UK. Therefore, whilst some of the findings are clearly transferable to other countries, at this stage they are most relevant to UK-based sites.

As highlighted, there are areas where the provision of a public account may have introduced bias. However, we were able to gently explore in more depth, challenge underlying assumptions and use qualitative data to better develop our understanding of these issues which strengthens our work[5,7]. To our knowledge, this is the first piece of work to formally explore these issues with a large group of stakeholders and provides unique insights into how the issues are viewed by the UK CF community.

PRACTICE IMPLICATIONS

This study demonstrates that ensuring fair allocation to competitive trials is an emotive issue that is considered to impact patients' wellbeing and their relationships with clinical teams. In general, there is a preference for the pharmaceutical industry to allocate slots to individual sites based on the size of the clinical population at that site. Stakeholders are prepared to engage in referral between sites for trial visits but would prefer not to. Stakeholders agree they would use a system of national allocation through the registry if necessary, but the majority would prefer local allocation of slots. We identify a potentially worrying power imbalance, whereby pwCF are prepared to accept unfavourable conditions to secure slots onto highly competitive trials. Currently, few centres have defined strategies for allocating slots locally and there does not appear to be a universally acceptable solution. At face value, stakeholders believe all eligible participants should have an equal chance of getting a place on a trial. However, in depth questioning reveals a preference for prioritisation strategies, primarily based on adherence and health status. It becomes clear there are no definitive answers.

We consider that this project has demonstrated insufficient stakeholder support for a system overhaul with national, rather than local, slot allocation. Whilst we acknowledge that there may be a preference for using prioritisation strategies rather than random allocation, the potential sample selection bias combined with the lack of consensus on what those prioritisation strategies should be mean we are not planning to move away from our current system at this stage, nor to suggest to other sites that there is an optimal model. Our model is one of randomised ranking followed by consultation with the multidisciplinary team (MDT); only under exceptional circumstances would someone be deemed unsuitable to be offered a screening slot. We have been pleasantly surprised on occasions when individuals we might not have approached under a different system have proved willing, fully compliant and highly-appreciative participants. This project reinforces the potential for trial access issues to impact patients' well-being and highlights the necessity of transparency, tact and empathy in supporting the CF population without whose involvement, future clinical trials would be unable to progress.

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CONFLICT OF INTEREST STATEMENT

RD, KP, LA, RB and KB have no conflicts to declare. GD reports personal fees from Chiesi Limited, outside the submitted work. SC reports personal fees from Chiesi Pharmaceuticals, personal fees and non-financial support from Vertex, personal fees from Zambon and personal fees from Insmed, outside the submitted work. NJS has participated in advisory boards for Vertex, Chiesi, Pulmocide and Roche. He has received payments for speaking engagements from Vertex, Gilead, Chiesi, Teva and Zambon. JCD has served on advisory boards and participated in clinical trial leadership, educational activities and grant review board activities for a number of pharma companies active in CF clinical trials: Vertex, PTI, Galapagos, AbbVie, AlgiPharma, Chiesi, Enterprise, Teva, Ionis, Eloxx, Roche, Gilead.

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