

Letter to the editor

Fair selection of participants in clinical trials: the challenge to push the envelope further

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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. RD and SS have no declarations of interest. NJS has consulted for Vertex Pharmaceuticals, Chiesi, Roche, Pulmocide, PTC Therapeutics and Gilead.

The pipeline of new drugs being developed for cystic fibrosis (CF) is both exciting and challenging, perhaps in equal measure. Issues related to the large number of trials being conducted, some of these competing for the same group of patients, the need to ensure that more traditional drugs such as anti-infectives/ anti-inflammatories can still be trialled whilst CFTR modulators are 'stealing the show' and the inequity of access remain paramount. The CF Foundation's Therapeutic Development Network (TDN) and the European CF Society Clinical Trials Network (ECFS CTN) are actively engaged in tackling these issues and the ECFS Task Force's strategic plan to speed up access to medicines has recently published its first papers proposing solutions related to trial design¹ and rare mutations².

In response to some of the challenges at our site, we recently reported on the development of our Standard Operating Procedure (SOP) allowing random- rather than selective- allocation of trials slots in highly competitive studies. This issue is of particular relevance in the UK currently as access to licensed CFTR modulators is limited, so participation in a trial with an open-label extension is one of the few ways of receiving drug. We are pleased that our letter generated some much-needed dialogue, including a response from Ms. Camila Strassle at the National Institutes of Health³. We are encouraged by her positive comments on our letter and would like to respond to suggestions she made that have influenced our next steps.

Her primary point is very well taken: even if study sites implement fairness strategies such as our SOP, the fact that certain sites participate in trials and others do not, creates inequalities in individuals' access to new drugs and the other benefits of research participation. Recognising this,

the UK Cystic Fibrosis Trust, with funding support from the CF Foundation, has launched the Clinical Trials Accelerator Platform (CTAP, <https://www.cysticfibrosis.org.uk/the-work-we-do/clinical-trials-accelerator-platform>). Funding for research co-ordinators across 20 CF centres, as well as a shared network of expertise, has rapidly expanded the number of people living with CF able to access trials. It is estimated that x% of the UK population receives their CF clinical care at a CTAP trial site.

However, even if sites offer to open for trials, sponsors will select only certain of these for a given study; often this number is large (although rarely all-inclusive) and each site only has a small number of screening slots which are filled fast and competitively. Other times, the number of sites is small and recruitment thus regionally heterogeneous. We are somewhat uniquely placed in London, with a high concentration of people (~20% of the CF UK population) in a relatively small geographic location with good transport links. Teams in different CF centres work closely on both clinical training issues and research, the latter largely through the London CF Collaboration (<https://www.ucl.ac.uk/child-health/research/infection-immunity-inflammation/respiratory-critical-care-and-anaesthesia/respiratory-23>). Building on this foundation and in light of concerns around both fairness and efficiency of the current trials system, we have recently established a new working model: the four London CTAP sites make rational and joint decisions about which of them will offer to take on a trial, rather than all being in competition with each other and duplicating workload. Sites at which the trial does not open are offered slots into which they can refer their patients. There are also two smaller sites, not trial-active, who can act in this way as 'Participant Identification Centres (PICs)'. Although not mentioned in our original letter, our new SOP has in fact been applied across this referral network, ensuring a fairer and wider distribution of opportunity; we plan to publish a detailed report on this working model, its successes and challenges towards the start of 2020.

Undoubtedly, recruiting an unknown participant from another centre to a drug trial involves more work for the trial team: getting to know the patient/ family; communication; requesting and collating copies of 'source' documentation etc. Some referring clinicians may have understandable concerns, particularly if they are new to such a system eg. lack of familiarity with processes such as GCP, time required for safe communication, the need to comply with reporting adverse events in a timely fashion. Delays in agreements which allow them access to detailed protocols, inclusion/exclusion criteria are another challenge. We have also heard fears of 'losing' patients to another centre. Certain of these issues can be addressed up front by agreements between referring and study sites: we are always clear that trial participants from another clinic come to our centre only for study visits and that clinical care is not provided, except in a rare emergency when we would communicate promptly with the lead centre. The system does mean more of a time commitment is required from the person with CF or their family, which will be acceptable to some and not others. In terms of the professional time involved, we feel strongly that referring a patient to participate in a clinical trial and maintaining high standards of communication with the trial team throughout is not trivial. It should both be compensated financially and attract credit for the referring site's research metrics system. We are working with sponsors on the former and propose that some standardisation of costs and processes would be helpful, an issue CTAP will work on.

In her letter, Ms Strassle however goes further, suggesting that slots could be *allocated at a national level* through the registry. This is a really interesting idea, and not one we have considered previously. We have used the UK registry to locate very small groups of patients, for example young children with gating mutations^{4,5} and to identify sites with older patients with rare *CFTR* mutations for HIT-CF (<https://www.hitcf.org/>). In these cases, following a data search, the registry team (who do not know the identity of the patient, only their code number) contacts the relevant clinic and

informs them they have one or more patients fulfilling the main inclusion criteria. If the local clinical team feel it is appropriate, these subjects/ parents are then approached, and if interested, referred to their nearest or preferred trial site for screening. This is rather different from the scenario proposed by Ms Strassle, in which the registry actually *generates the ranking sequence* of people to be contacted with the offer of involvement. It is true that in a large trial, particularly one which was extremely popular meaning people were prepared to travel, this could be the fairest approach nationally. However, it could easily result in a site filling the trial with participants from outside. Whether teams would feel this detracted from their motivations in running studies- which could include providing the best care to their own patient population- is unknown, as is their view on the increased workload that would ensue.

The questions raised by this helpful correspondence have led us to propose a survey across the UK of people with CF, parents of children with CF and clinical teams (both research active and not) to assess their views on a registry-based allocation system such as this. We acknowledge the role of Ms Strassle's letter in catalysing this piece of work and would be pleased to communicate further on this issue either with her or anyone else with suggestions to improve our working practice.

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