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Title: Working in partnership with the patient community to develop outline trial designs in CF.

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Dear Editors

In a collaboration between health professionals and the patient community, we previously identified the Top 10 priorities for clinical research in CF(1). Here, we have used a similar approach to explore four of these priorities further and suggest outline designs of clinical trials to address them.

We selected the following four priorities: simplifying treatment burden (Treatment Burden); relieving gastrointestinal symptoms (GI); improving and sustaining treatment adherence (Adherence); and exercise as a replacement for chest physiotherapy (Exercise). We had 2,018 responses across the four online surveys sent out between April 2018 and April 2019 (1,321 (66%) patient community, 697 (34%) health care professionals (HCP)). Outline trial designs were developed from the results of these and reviewed by 547 respondents to our final acceptability survey with 234 (43%) from the patient community and 313 (57%) from HCPs. The majority of responses to all surveys were from the UK but we also had responses from Europe, USA and Canada, and Australia (mean UK percentage 65% (242/375), range 59% (270/446) to 87% (389/445)). Table 1 shows the trial suggestions, the overall rank of perceived importance reflecting the common priorities of the patient and clinical community and their acceptability in terms of willingness to take part.

Research priority	Trial suggestion	Perceived importance	Willingness to participate	
			Yes	Possibly
Treatment Burden	Can we reduce treatment burden by stopping one or more treatments for adults or children on CFTR modulators (eg Orkambi, Kalydeco, Symkevi)?	**1**	68%	24%
Exercise	Can we replace one airway clearance session a day with exercise of a person's choice?	2	67%	26%
Treatment Burden	Can shared goal setting and personalised care plans support adolescents transitioning into adult care and reduce their treatment burden?	3	71%	24%
Adherence	Can we support treatment motivation through engagement with a mobile app, with phone calls from the CF team when engagement drops?	4	61%	30%
GI	Can probiotics improve gut symptoms?	5	64%	30%
Adherence	Can a mobile app improve motivation and sustain accurate measuring of nutritional content of meals and setting PERT (pancreatic enzyme) doses?	6	58%	32%
Exercise	Can we replace some airway clearance sessions with an online exercise class?	7	53%	33%
GI	Can psychological (talking) therapy improve gut symptoms?	8	43%	38%

Table 1 Trial suggestions generated by the process. Acceptability of the trial and overall rank in importance out of the eight trial suggestions generated. The left hand column relates the trial

suggestion to the original top ten priority it was developed from; Priority 1: Simplifying treatment burden; Priority 2: Relieving gastrointestinal symptoms; Priority 6: Improving and sustaining treatment adherence; Priority 7: Exercise as a replacement for chest physiotherapy

This is a process which has given a voice to the CF community in setting research priorities and now in defining trials to act on these priorities. We have taken the broad insight generated by a James Lind Alliance (JLA) Priority Setting Partnership (PSP) and refined to the point where a research group can further develop the priorities for funding. We had good representation from the professional and lay communities in both the designing of the study and participation. Our work has generated eight defined trial ideas which have been ranked in terms of acceptability and importance by the CF community.

To the best of our knowledge, this is the first time that JLA priorities have been developed into testable trial hypotheses in a collaborative process, involving both the patient and clinical community. Patient and Public involvement is a key requirement from most clinical research funders but this usually involves a focus group around a preconceived trial idea(2). We describe a process of true co-production of research ideas.

Our work benefits from having a global reach and a large number of participants from the CF community. The surveys were anonymous and promoted via social media to encourage honest responses. Whilst we had a good response, this still only represents a small proportion of the total population of people with CF and some participants will have responded to more than one survey. We cannot be sure that the views expressed by survey respondents are fully representative of the wider CF population. We undertook these surveys before triple CFTR modulator therapy was approved for use in the UK and it is possible that different priorities would be identified by participants for whom modulators were available.

There are currently around 70,000 people with CF worldwide which means that the pool of people who are eligible and willing to take part in research trials is relatively small. Trials are often demanding on participants' time and it is therefore vital to make sure that they are relevant and timely. In 2018 the UK CF Trust carried out a survey to assess the burden of CF treatment and impact on everyday life of living with CF. When asked what one thing would improve their lives, 10% of respondents said prioritisation of research(3).

The trial idea ranked number one in our study related to the possibility of stopping one or more concurrent treatments (such as nebulised therapy) when adults or children commence CFTR modulators (e.g. Orkambi™, Kalydeco™, Symkevi™) in order to reduce treatment burden. Most (92%) of the respondents said they would definitely or possibly be happy to take part in such a trial.

Reducing treatment burden was the top priority for CF research in the original JLA PSP and our current work has identified that testing the marginal contribution of specific medications is one way to help achieve this(4, 5). With the advent of CFTR modulator drugs, the treatment landscape is rapidly changing. There is a growing body of research underway, testing the continued need for specific maintenance therapies for pwCF on modulators. This includes the CF SIMPLIFY trial in the US (NCT04378153) and CF STORM in the UK, (ISRCTN14081521).

Listening to and encouraging participation by the CF community in all stages of the chain of evidence-based medicine is vital to ensure good quality and relevant research. This consultation was

undertaken at a time of rapid therapeutic advances in CF which will transform clinical outcomes, demographics and expectations of the global CF population. Already some of these trial questions have led to funded research. We hope that more will be funded and acknowledge that priorities will be dynamic, evolve, and need refreshing over time.

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Conflicts of interest:

GD reports personal fees from Chiesi Ltd and Vertex, outside the submitted work

AS reports a research grant and personal fees from Vertex. These activities are outside the submitted work. In addition, Prof. Smyth has a patent *alkyl quinolones as biomarkers of pseudomonas aeruginosa infection and uses thereof issued*.

TD reports personal fees from Vertex, Gilead & Chiesi. She has spoken at meetings supported by Teva, Zambon and Vertex. These activities are outside the submitted work.