Curating the Patient Voice (BSA 2024) Julia Frost and Catherine Pope

This paper is about how the patient voice gets curated for people with a rare disease, in the development of a new drug.

Background

We began this project by working with a physician who works with patients who have a rare disease called Idiopathic Pulmonary Fibrosis, or IPF. The physician suggested that some patients struggle to access clinical trials, which is often the only way that they can receive drugs that are in the development phase and pre-licence, for their condition. This physician acted as a gatekeeper to a pharmaceutical company who were undertaking trials of a new molecule for IPF, where I have subsequently been embedded as part of an MRC funded Innovation Fellowship, where I have been exploring how they *do* Patient Engagement.

We were also mindful of the disconnect in the literature between industry practices and more critical social science perspectives *on* patient engagement:

Twenty years ago, **Guston and Sarewitz** (2002) identified the need for innovative scientific technologies to include not just instrumental assessments, but also **discursive assessments of a new technology**, **so that the lay public are involved in deliberative processes.** They saw this as important because the consequences of science don't evolve from a static or complete technology, but from co-production that creates both the technology *and* its social context. Central to their mid-range methodology is what they call **front-end social judgement research** – to assess 'public concerns about and aspirations for the development and application of an innovation'- which they believe can enhance the societal value of research-based innovation.

However, what we see in the industry design literature now, is the identification of **Patient-Centric Drug Product (PCDP) design** (Stegmann et al 2022), **but this is premised on reviewing the available literature and industry perspectives, without engaging patients in the process.**

Methods

The wider objectives of the project are to explore ways in which patients and other members of the public experience engaging with the process of orphan drug development (or drugs for rare diseases), and how engagement might be optimised?

And this is through 3 overlapping research activities:

Firstly, working with Patient and Public Involvement (PPI) representatives. These are people with IPF, who informed the research design, and who I meet with regularly to inform my observations of pharmaceutical practice.

Secondly, in terms of empirical data I have conducted 32 **in-depth interviews with IPF patients,** and 19 **healthcare professionals** who care for them and that recruit patients to drug trials.

And thirdly, through the project I have been seconded to a pharmaceutical company, who *were* developing drugs for IPF, but also embedding a patient engagement framework throughout their practices, which involves gathering patient insights (*the* 'Patient Voice') at key junctures in the drug development lifecycle. The company have since disinvested in the drug for IPF, but have allowed me access and analyse a set of historical Patient Voice Reports about IPF, which I identified during my secondment, with two objectives - in the spirit of knowledge exchange:

Firstly, so that the company can understand the value of social science methods and critical appraisal of market research, and

Secondly, to share learning from (now redundant) reports about the experience of a rare disease with my patient collaborators – which has not been allowed before, but which has the potential to re-use primary data which companies no longer have use for, but which may be of benefit to patients.

Regulatory Authorities

Patient engagement is legitimated by **Guidance from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)** which clearly mandates for the inclusion of patient perspectives in the drug development process, which can potentially lead to the development of 'better drugs'. The guidance requires

pharmaceutical companies to include patient input in their drug development practices, and makes clear that this can be achieve by open dialogue throughout the study design process. But this guidance, and similar ones from the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) make clear that drug companies are not permitted to approach individual patients directly - which constitutes marketing or drug promotion.
A recent **Reflections Paper produced by the ICH** (2021) **acknowledges that the current practice of collecting the 'Patient Voice' has significant room for improvement.** The paper *does* reflect upon the 'key areas where incorporation of the patient's perspective could improve the quality, relevance, safety and efficiency of drug development and inform regulatory decision making'. However, having *'reflected*' the paper notes that the incorporation of patient perspectives in the drug development lifecycle is indeed a challenge, which now requires *further* stakeholder consultation.
This means that while the Guidance is being further refined, industry have to look to third party organisations to work with patients on their behalf.

Contract Research Organisations

Since the 1930's Contract Research Organisations (CROs) have been employed by pharmaceutical companies to complete their clinical trial-related functions, including the producing the '**patient voice**' report, to inform the development of new medicines.
When a new molecule has been identified from **Phase II**, and a pharmaceutical team wants to undertake a pivotal trial in humans (A **Phase III** randomised controlled trial that provides evidence of effectiveness), a CRO is employed to provide a Patient Voice to inform the protocol design – e.g. to clarify unmet needs and optimise trial recruitment and retention.
The CROs recruit *to* the Patient Voice reports from Patient *Organisations*, where patient and caregiver *representatives* advocate for a wider community with a specific medical condition (and are readily available), or recruit the clinical staff who typically care for them.
These illustrations are from publicly available CRO products (rather than the ones that I have analysed), but illustrate:

- The **emphasis on 'patient-centric data**' for the pre-trial Patient Voice, but they typically only detail the number of patients recruited and the Country (or market)

that they were recruited from (e.g. 3 per country), and no demographic details are provided.

- Sometimes the CROs provide the methods of data collection, but this tends to be a description or method **without rationale**, and the data is either left to speak for itself, or is analysed with **descriptive statistics** (e.g. 33% of the 3 recruited from a country).
- The market facing Patient Voice (also called the Target Product Profile), is constructed with *physicians*, and concerns the **promissory nature of the new drug** (to identify under what conditions the drug can be sold). However, company websites also have patient facing content that is made with members of the Patient Organisations, who may have been involved in the recruitment of patients to the earlier report that informed the protocol.

'Independent guidance' for the conduct of patient engagement may be cited in the Patient Voice, but the guidance is created by boundary spanning organisations that are underwritten by pharmaceutical collaborations. For example:

- EUPATI – European Patients' Academy on Therapeutic Innovation, funded by the European Commission and the European Federation of Pharmaceutical Industries (EFPIA).
- PARADIGM - Patients Active in Research and Dialogues for an Improved Generation of Medicine, also funded by EFPIA and inkind by the Innovative Medicines Initiative (IMI).

Fabbri (2020) has suggested that the symbiotic relationships between pharmaceutical companies and patient organisations might 'encourage' the patient voice to align with industry priorities.

The Patient Voice

The industry sponsored literature, for example TransCelerate 2020, suggests that the Patient Voice is necessary to develop 'high-quality, safe, and effective fit-for-patient medicines'. Researchers for Pfizer suggest that it is sufficient to interview 6-8 patients with a rare disease, to capture adequate patient experience to inform the development of new treatments for the condition; and they propose that "*drug developers keep the patient voice*

up front and present in all communications with regulatory authorities" (Deal et al 2016). That objective can be seen here in an Editorial for Clinical Leader - an industry newsletter – which advocates the collection of the **Patient Voice (not voices), to inform the regulatory authorities that patients (and caregivers) have been involved in medical product development.**

It is noteworthy though, that the **Target Product Profile (or TPP)** is conducted to identify the market to which the drug will be launched, but much like the Patient-Centric Drug Product (PCDP) design mentioned earlier**,** is only **conducted with physicians** (rather than patients), because **physicians are considered to be the end –users and consumers.** It is also interesting to note that a TPP can shorten regulatory review by 30 days (Breder et al 2017), while the inclusion of the Patient Voice does not seem to have this benefit.

Patient 'Themes'

To engage with the reflections of the ICH, we analysed a set of (anonymous) patient voice reports that have been conducted by several CROs, for IPF.

We identified 7 reports by 5 different CROs.

As we would expect with a series of reports conducted by *different* specialist CROs, these were conducted at various phases of the drug development lifecycle. For example, we identified one online ethnography with patients at the pre-clinical trial protocol development, and a Target Product Profile with physicians pre-market. Interestingly, we identified that a key patient insight report was conducted in one country (or one market), while the commercial focused TPP was conduced with a more heterogenous sample of physicians across 10 markets.

Topics explored in the Patient Voice exercises, focused on: diagnosis, treatments, and unmet need.

The reports that include physicians, tended to focus more on a wide repertoire of trial practices, such as: physician engagement, awareness/expectations of new therapy, clinical endpoints, appeal of a trial, and recommendations for study development.

When synthesised, they comprised interviews with 77 patient, 15 caregivers, 102 physicians; and observations with 37 patients, and 15 caregivers – which is a significant

dataset of patients for one rare disease, when compared to the current evidence base in the public domain.

Where/how the patient gets lost

But, we are not suggesting that in their current form The Patient Voice necessarily represents *patients*, and we have identified sites where the patients get lost in current CRO practice:

Rabeharisoa (2014) has written about the 'politics of numbers' in rare disease research, whereby patients pool their knowledge and political resources to engage pharmaceutical organisations, to meet their challenges and unmet needs. By doing so they provide a **ready sample of patients** for recruitment by CROs to Patient Voice exercises, but this reification means that other demographic variables become redundant, such that the CROs only need to sample a given number of patients with a condition because that is the only variable of interest. Therefore, other patient characteristics are lost as they become the representative of the condition (Frankish et al 2002).

A corollary is that patients become one dimensional, and the reports often constructed an **average patient**, rather than a more multi-dimensional person. Thus, patients with IPF are represented *as* male, frail, and likely to have met many specialists before being diagnosed, and this 'patient persona' becomes the standard for the population.

Zovareva (2023) notes that because business is premised upon efficiency, it is unsurprising **that tools are standardised** to optimise their re-use and scalability. But while standardised data collection tools might optimise the return on the time invested in an interview, they limit the extent to which a patient can raise and discuss the issues that are more important to them, but which fall outside of the remit of the CRO's brief.

Where patients from multiple markets were engaged, the results were presented in that format (as the unit of business), which could lead to slippage into **cultural stereotypes**, and here we saw the cynical or stoic UK citizen, the freemarket favouring American, and the heavily smoking Italian.

Brown and Michael (2003) identified that expectations for a technology are mediated by an **actors' involvement and proximity to the technology.** In the Total Product Profile, it is the physicians closest to the innovation, by virtue of being the specialist physicians in a given

rare disease who have an established relationship with a pharmaceutical company, or who have been involved in clinical trials of near-market products who are recruited. They tend to support the 'moonshot' product with the most speculative and ambitious profile (the most disruptive), rather than the 'minimal scenario' which is more likely to provide a small incremental (and less risky) scenario for patients.

Prioritise deliberation with patients

We contrast these findings with our own, gathered from sociological research with more marginalised people who have IPF: they are older people with multiple co-morbidities, living in rural settings, who are not engaged with Patient Organisations, and may or may not have experience of participation in clinic trials – but who CROs would consider 'difficult to engage'.

These patients identified *themselves* as 'different' from patients who attend Patient Organisations, who they typified as either evangelical about new drugs, or miserable once they are too sick to participate in trials. The patients that we interviewed suggested that they were not 'smart enough' to take part in research or they could not imagine mechanisms that would enable them to work with drug companies on an even footing. Without having an understanding of the value of their contribution they thought it was best left to doctors to advocate on their behalf.

When we gave discussed these findings with our patient involvement group, who as members of local IPF support groups sit at the interface of naive patients and professional Patient Organisations, they were clear that any **recommendations need to be directed to drug companies,** as it should not be the responsibility of individual patients to work out how they might have *a voice*. They suggest that the legislative guidance, designed to protect patients from drug companies is out of date, as it inhibits effective dialogue between them, but perceive that industry has a duty to work with legislators to find solutions that would enable a wider demographic of patients to have a better stake in the drug development process.

The next phase in our research in to undertake a **Citizen's Jury**, with our invested stakeholders, to co-design accessible resources to share with UK industry leads and other stakeholders. We had envisaged that these would be to resources for recruiting a wider

group of patients to clinical trials, but have identified that the challenge is further **upstream**, in that key voices are absent when clinical trials are designed.
Deliberation is also required on the whether any flaws in the current Patient Voice documents undermine their value to both patients and other pharmaceutical companies, or whether an open access repository might be useful place for pharmaceutical companies to pool their learning of how to work more effectively and ethically with patients.

Conclusion:

We conclude that:
There is *crisis* in the current representation of patients in drug development. Our analysis leads us to agree with Zvonareva (2023), that a participatory turn in drug development is taking place, but without shifting the established concentration in epistemic power".
Patients and health professionals have participated in the Patient Voice exercises but with a limited role in curating how they are represented.

Continuity of pharmaceutical practice obfuscates wider patient perspectives, in a way that continues to put the needs of business, or patients with existing relationships with business, before those of *other* patients – limiting the potential for the development of personalised medicines.
Change in methodological practices, would enable wider patient engagement, required to better inform the development of personalised medicines.

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