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The role of patient organisations in research and development: Evidence from rare diseases

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ABSTRACT

Patient organisations play an increasingly crucial role in the pharmaceutical sector, yet their impact on innovation remains unexplored. We estimate the impact of patient organisations on R&D activity in the context of rare diseases in Europe using a proprietary dataset that maps clinical trials from discovery to phase III across 29 countries, 1893 indications, and 30 years (1990–2019). By applying difference-in-differences and event study methodologies to a panel of 1,646,910 unique R&D observations, we find that country-indication pairs with at least one operating patient organisation have a higher rate of R&D activity compared to those without, with stronger effect in more prevalent rare diseases compared to ultra-rare conditions. We observe a lag in effects from patient organisation introduction, suggesting it takes approximately five years for these organisations to affect R&D activity. Overall, our work suggests that patient organisations play an important role in steering R&D efforts in rare diseases. Further research is needed to better understand mechanisms driving this effect and the potential impact of patient organisations on existing health inequities.

1. Introduction

Therapeutic innovation is critical in reducing mortality and morbidity. In recent decades, we have observed an increase in the intensity of the discovery and development of new therapies (Brown and Wobst, 2021; European Medicines Agency, 2022a). However, this productivity growth is not uniform across all disease areas, and there is a persistent mismatch between the burden of disease and medical innovation across diseases and countries (Barrenho et al., 2022; Barrenho et al., 2019; Davis et al., 2017; Miraldo et al., 2021). For example, Alzheimer's disease affects approximately 7 people in 1000 in Europe, while only 2/1000 are affected by rheumatoid arthritis (Vos et al., 2020). Nevertheless, there are 19 authorised medicines to treat arthritis in Europe, compared to only 10 for Alzheimer's disease (European Medicines Agency, 2022b).

There are multiple factors associated with heterogeneity of innovation across different disease areas. On the supply side, factors such as technological specialization, firm experience, and internal know-how are crucial for successful innovation (Danzon et al., 2005). The understanding of the basic science underlying diseases also varies significantly across areas, making it more challenging to innovate in some areas than others (Toole, 2012). This uncertainty also implies that some therapeutic areas are characterized by higher risks of failure in the R&D process and are therefore less commercially attractive targets for R&D investment by pharmaceutical companies (Arora et al., 2021; Wong et al., 2019). Expected returns and availability of internal funds determine innovation performance (Grootendorst and Matteo, 2007; Shaikh et al., 2021; Vandoros, 2014). Therefore, even when safe and efficacious drugs exist, pharmaceutical companies might avoid launching or delay launch in markets that are riskier and/or offer lower returns on investment (Kanavos et al., 2017). Finally, public policy can also stimulate innovation via both financial and non-financial incentives (Gamba et al., 2021; Yin, 2008).

On the demand side, market size is one of the most important determinant of R&D efforts, with larger markets (in volume and/or value) attracting more investments (Agarwal and Gaule, 2022; Blume-Kohout and Sood, 2013; Civan and Maloney, 2006; Dubois et al., 2015). Disease prevalence and payers willingness to pay for innovation, are two key factors driving pharmaceutical innovation, with recent evidence showing that innovation has focused on more profitable conditions such as neoplasms and cardiovascular diseases, neglecting other equally burdensome conditions and ultimately posing a serious

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challenge to achieving health equity (Barrenho et al., 2019, 2022). Procurement fragmentation, affordability issues and lack of policies and regulations that incentivise affordable innovation in certain under-looked areas, further exacerbate inequalities in access to innovation (Nemzoff et al., 2019).

The extent of these effects are intrinsically linked to buyers' countervailing bargaining power, through which buyers' concentration and coordinated action can enable market power over sellers (Galbraith, 1952).

Countervailing bargaining power has been shown to result in welfare gains across various contexts (Jacobson and Dorman, 1991; Loertscher and Marx, 2019; Noll, 2005). In healthcare, given the high levels of concentration on the supply side in many provision areas, countervailing buyer power can play an important role. For example, empirical studies have shown that larger insurers and insurers operating in more concentrated markets are able to negotiate lower hospital prices through bilateral negotiations with hospitals (Ho and Lee, 2017). Additionally, the literature on non-profit lobbying suggests how informed and invested users can help transform policies from profit-driven and paternalistic to more equitable and user-centric through their organised efforts (Sherraden et al., 2002; Shier and Handy, 2015).

In pharmaceutical markets, coordination and articulation among demand-side stakeholders, such as patients, physicians, state regulatory agencies, and payers, have been posited as being instrumental as a countervailing response to high prices, risk of capture by the pharmaceutical industry, and inequalities in innovation (Ellison and Snyder, 2010; Grepperud and Pedersen, 2020; Senier et al., 2017; Sorenson and Kanavos, 2011). Yet, the impact of buyers' power on pharmaceutical markets and innovation dynamics has been largely overlooked in the literature. Previous studies on the determinants of R&D have mostly focused on supply-side factors (e.g. firm and industry level factors) and policy and regulations (e.g. pricing and reimbursement, intellectual property rights, R&D incentives) (Chorniy et al., 2021; Kourouklis, 2021; Roberts, 1999; Shaikh et al., 2021; von der Schulenburg et al., 2011). On the demand side effects the literature has mostly focused on the role of unmet need (Bhattacharya and Packalen, 2011) and associated market size as shaping factors for R&D investment (see Barrenho and Miraldo, 2018 for an overview on the determinants of pharmaceutical R&D). To the best of our knowledge no contribution has assessed the role of demand countervailing power on innovation.

Our research aims at filling this gap by exploring whether organised demand side in the form of patient organisations (hereinafter referred to POs) translates to an increase in R&D activity in the disease areas they operate and in the countries they have been established. While previous literature has explored the roles of various demand-side stakeholders, POs have received relatively less attention, making them the focus of our analysis. We use data on R&D activity for rare diseases as given their low prevalence, highly fragmented demand side, as well as, low levels of innovation and diminished prospects of profitability to industry, it is an area where there is scope for buyers' power to play a role in shaping innovation. To do so, we leverage a unique proprietary dataset of clinical trials activity and POs-level characteristics in Europe between 1990 and 2019. Exploiting variation in PO introduction across countries, diseases, and time we deploy difference-in-difference and event study methodologies, we compare pre and post POs-introduction R&D activity in country-indication pairs where POs were present versus those where they were not, which enables us to infer the effect of POs' activities.

There are four main findings from our analyses. First, we find that country-indication pairs with at least a PO have a higher rate of R&D activity compared country-indication pairs with no PO. Second, a higher number of POs in a country-indication pair is associated to an increasing thought non-linear R&D activity. Third, this effect is found to be smaller for ultra-rare versus non-ultra-rare diseases. Fourth, there is a lag in effects from PO introduction, suggesting that it takes approximately five years from their creation for POs to affect R&D activity. Overall, our results show that POs have an important role in steering R&D activity in the rare disease context. If equitable innovation is a priority, our results suggest that advocacy is unlikely to be not sufficient in promoting innovations and needs to be complemented with other policies.

The paper is structured as follows. Section 2 illustrates the institutional framework and the peculiarities that make the rare diseases a good case study to understand the potential role of organised demand in pharmaceutical innovation. Sections 3 and 4 describe, respectively, data and methodology for the empirical analysis, with results presented in Section 5. Section 6 concludes and discusses policy implications.

2. Institutional framework

Patient organisations (POs) play an increasingly crucial role in the pharmaceutical sector. As the primary users of medical innovation, patients are uniquely positioned to provide insight into their unmet needs, disease symptoms, and the impact of their condition on their quality of life (Aymé et al., 2008; Bedlington et al., 2017). The success of HIV/AIDS advocacy campaigns in the 1980s, where POs managed to pressure policymakers and garner media support to secure access to innovative medicines (Edwards, 2017; Rose, 2014), has led to an unprecedented level of involvement in health decision-making by these organisations. Regulatory bodies in Europe and the United States have prioritised patient engagement, with the European Medicines Agency (EMA) including patients and patient groups in scientific advice procedures, and the US Congress recently passing a bill mandating the Food and Drug Administration (FDA) to consider patient experience data in their drug approval process (Edwards, 2019; Murphy et al., 2022). Similarly, in the UK, a government report on the healthcare system's response to safety concerns highlighted the need for engagement with patients throughout the regulatory lifecycle of medicinal products (Haskell, 2020).

Beyond articulating the demand, POs play a crucial role in the overall innovation model. A small but growing body of the literature has focused on how patients can play a role in research priority settings, highlighting its importance and potential to drive innovation (Davies--Teye et al., 2021; Gill et al., 2022; Lavallee et al., 2020; Zwaan et al., 2023). For example, the presence of POs and the mobilisation of rare disease patients are fundamental prerequisites for conducting clinical research. In recent years, POs have taken on increasingly active roles in the R&D landscape. They have not only provided financial support and resources for clinical research, but have also become advocates for improved access to treatments and have engaged with various stakeholders, including pharmaceutical companies (Dunkle et al., 2010; Fleurence et al., 2013; Hoffman et al., 2011; Koay and Sharp, 2013; Menon and Stafinski, 2014; Polich, 2012). By engaging directly with the patients community, POs can facilitate recruitment and compliance during clinical trials (Geissler et al., 2017). In research design and planning, POs can provide valuable support by helping to identify patient-relevant outcomes and facilitating the collection of real-world data through patient registries (Aymé et al., 2008; Fleurence et al., 2013; Polich, 2012). Furthermore, they can advance the knowledge base of disease pathophysiology by conducting disease history studies (Boulanger et al., 2020). These initiatives can de-risk the development of medicines, making it easier for pharmaceutical companies to innovate in this area. Finally, as shown by the HIV/AIDS activism, POs can also play an important role in advocacy for access to and funding of innovation as well as being on the frontline of efforts to educate patient communities and raise awareness about overlooked diseases (Bedlington et al., 2017; Geissler et al., 2017). Although organised demand in the form of POs may not directly impact high medicine prices, it can effectively generate public and media attention, exerting pressure on the industry to re-evaluate and revise their pricing strategies (Kmietowicz, 2019). Furthermore, it is worth noting that POs frequently participate in drug assessments, which can influence reimbursement decisions to some extent (Gagnon et al., 2011; Menon and Stafinski, 2014; Norburn & Thomas). By doing so, POs play a pivotal role in shaping the innovation

process, contributing in multifaceted ways that extend beyond their primary mission of advocating for patient needs and ultimately signal to manufacturers and policymakers areas where innovation is needed the most. Fig. 1 illustrates the various activities in which POs are involved across drugs development and commercialization timeline.

While active across many therapeutic areas, the role of POs has been particularly important in the context of rare diseases (Aymé et al., 2008; Mavris and Le Cam, 2012), which in Europe are defined as diseases that affect 5 or less people in 10,000 (European Commission, 2000). As medical knowledge on rare diseases is usually scarce and complicated to understand and access, patients and families affected by these conditions came together to provide each other with support and medical expertise (Aymé et al., 2008). In the United States and in Europe, POs have been instrumental in advocating for scientific support and economic incentives to stimulate innovation in rare diseases, that ultimately led to the passing of the Orphan Drug Act in 1983 in the USA and the EU Regulation on Orphan Medicinal Products in Europe in 2000 (European Commission, 2000; Waxman, 2009). Furthermore, in many European countries, decision-makers seek patient inputs in health technology appraisals (HTA), especially in the context of rare diseases, where evidence is often scarce. For example, in appraisals for extremely rare diseases, NICE places particular importance on patients' testimonies, as they can help with defining target populations and determining treatment benefits (Livingstone, 2018). The market for rare diseases lends itself well to understand the role organised demand can play in innovation. By definition, this market is very small and fragmented, with more than 6000 unique rare diseases of which 85% have a prevalence point below 1/1,000,000 (Nguengang Wakap et al., 2020). While it is true that some medicines for rare diseases have proven to be a lucrative asset for pharmaceutical companies and the number of such drugs approved from regulators is increasing over time, also thanks to existing regulations, the majority of drugs have modest revenues (European Commission, 2019). In this context, POs can help counteracting the market power of pharmaceutical companies, ultimately leading to innovation that serves patients better.

While there seems to be consensus on the role of POs in adding value to the R&D process, empirical evidence is missing. Our study contributes to the literature on determinants of pharmaceutical innovation by quantifying the impact of POs presence and size on R&D efforts in the rare disease context. Previous studies on the role of POs in the R&D process have almost exclusively been descriptive and qualitative in nature, providing examples of successful collaborations between industry and patient organisations or of activities that POs carry out to support innovation, such as founding start-up companies, initiating clinical trials, funding registries and natural history databases, and sharing information with industry and researchers to support medicines development (Crossnohere et al., 2020; Koay and Sharp, 2013; Mikami and Sturdy, 2017). Our analysis adds to this literature by assessing the impact of POs' on rare disease R&D activity.

3. Data

In line with most of the literature on pharmaceutical innovation, we use the number of clinical trials, from discovery to phase III, as a measure of R&D activity (Agarwal and Gaule, 2022). We construct a unique panel dataset that maps clinical trials in rare diseases from basic discovery to phase III trials regardless of their funding source (i.e., public or private) matched with indication data from Orphanet and PO-level data from Eurordis. The panel comprises 1,646,910 unique R&D observations, nested within 29 European countries (EU27, UK and Switzerland), 1893 ORPHAcodes (hereinafter referred to as indications), and across 30 years (1990–2019).

The panel builds on the IQVIA pipeline intelligence database, which contains global R&D events in rare diseases. In the pipeline intelligence data, events are coded at country, indication, date, and event type level, and include all phases in the drug development process such as discovery, pre-clinical R&D, and phase I-III clinical trials. In the IQVIA dictionary, discovery refers to the initial stages of pharmaceutical research where no lead compounds have been identified, while pre-clinical trials include early studies and in vitro/in vivo experiments. The dataset, as well as our analysis, captures any form of R&D activity, whether it involves first-in-class products or incremental improvements within a specific indication. Events in diseases that did not match the European definition of rare disease (i.e., diseases that affect more than 5 people per 10,000), were removed from the dataset. Each rare event in the dataset was matched to the corresponding ORPHAcode – a numerical identifier of rare disease indications, retrieved from the Orphanet database – with the objective of fine tuning the indications for rare disease products in the dataset. Where discrepancies of indications were found, such as differences in ORPHAcodes, data entries were cleaned manually, and indications as coded in Orphanet prevailed. This event data was used to build a panel that records total R&D activity for each country, indication and year.

These data were merged at country, indication and year level with PO-level data obtained from Eurordis' list of member organisations and individual application forms submitted by the PO. Data extracted include the creation date of a PO in a specific country, the average size of the PO – proxied by its budget – and the disease(s) targeted by each

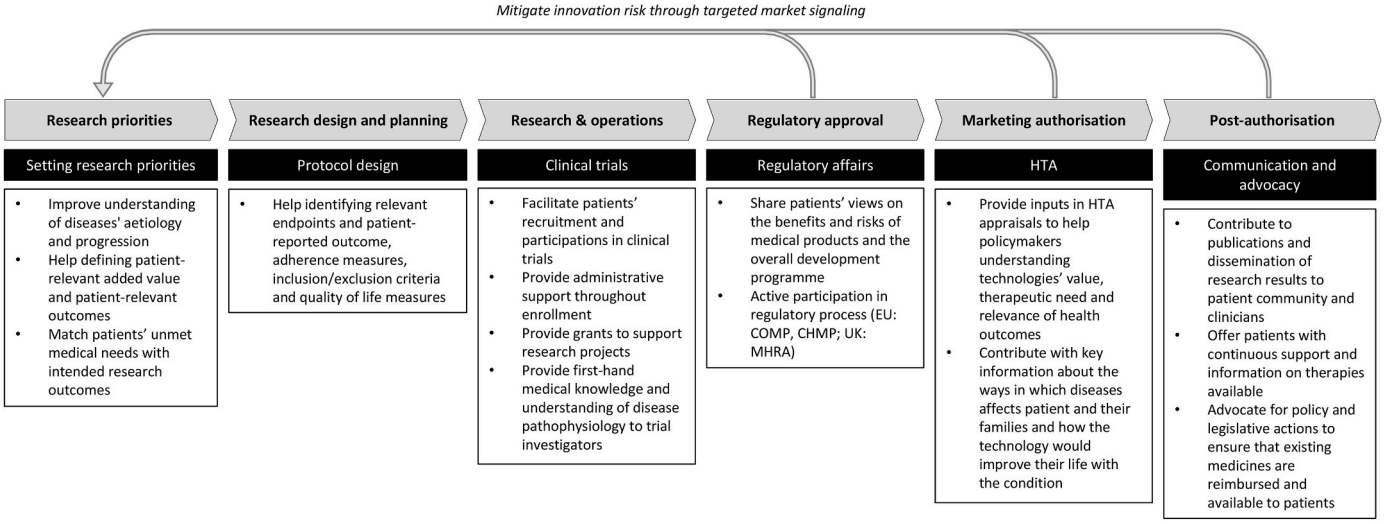

Fig. 1. POs involvement across drugs development and commercialization timeline. Notes: Adapted from Geissler et al. (2017); Aymé et al., 2008.

patient organisation.

The panel was complemented with data on healthcare expenditure (per capita) retrieved from OECD Data, prevalence at the European level and disease burden collected from the Orphanet and Institute for Health Metrics and Evaluation Global Burden of Disease datasets, respectively (OECD, 2022; Orphanet, 2022; Vos et al., 2020). Finally, each disease was matched to its corresponding Anatomical Therapeutic Chemical (ATC) first level class to explore trends at the therapeutic area level (World Health Organisation, 2022). Table 1 illustrates descriptive statistics of key variables used in the analyses. Further detail on the data sources, cleaning and merging of variables and panel construction can be found in the Supplementary Material. Ethical approval was not required as no human subjects were involved in this study.

4. Empirical model

Using event study and difference-in-difference (DID) methodologies, we exploit the variation of the creation of POs over time and across country-indication pairs to measure the effect of the presence of POs on the number of R&D activities of drugs targeting rare diseases. The key dependent variable - Y_{cit} - is the total number of R&D activities (i.e. discovery, preclinical, phase I, II and III trials) in country *c,* indication *i* and year *t*. The role of POs is captured by two variables of interest. The first, PO^{b}_{cit}, indicates the presence of at least one PO and is coded as 1 if at least a PO existed in a country-indication pair in a given year and 0 otherwise (Model 1.1, *Baseline regression*). Our second variable of interest, PO^{c}_{cit}, is the extent of presence of POs in a certain country-indication pair, proxied by the cumulative number of POs in a certain country-indication pair (Model 1.2).

We use a Poisson regression model with multiple high-dimensional fixed effects to analyse Y_{cit}, which is a non-negative count that exhibits a significant proportion of zeros (Correia et al., 2020).

The empirical specification for the main regression (Model 1.1) is as follows:

$$E(Y_{cit}) = \exp\left(\beta_1 PO^{b}_{cit} + size_{ci} + \delta_{ci} + \gamma_t\right) \quad (1)$$

Where the variable PO^{b}_{cit}, is equal to 1 from the time when the first PO was created in a certain country-indication pair and 0 before. It is always 0 for country-indication pairs where POs were never created. In Model 1.2, we use the same specification as in (1) but we use PO^{c}_{cit} rather than PO^{b}_{cit}, which is a categorical variable coded as 1 if there is no PO in a certain country-indication for a given year, 1 is there is only one PO and 2 if there is more than one PO.

In both models we control for country-indication fixed effects (δ_{ci}), to capture country and indication-specific time invariant unobservable heterogeneity that may be associated with different levels of innovation across countries and diseases (e.g., disease pathophysiology, availability of diagnostic testing, and R&D infrastructure). We also control for year fixed effects (γ_t) that capture time varying factors common across countries and diseases that may be associated with R&D activity such as technological changes over time that might make easier for companies to innovate, or policies and regulations such as the EU-wide orphan-specific incentives. Finally, to account for the potential role of financial support from industry in shaping the activities of POs, we control for $size_{ci}$, which is a time-invariant variable indicating the size of the PO, proxied by its membership fees paid to Eurordis.

In Models 1.3 and 1.4, we control for country and ATC class-specific trends, by interacting the abovementioned variables with a year trend variable. ATC class was chosen over indications as the high number of the latter led to an incidental parameters issue when attempting the interaction. Model 1.5 includes country-specific year fixed-effects. These allow to capture time-varying effects across countries and ATC classes, such as the introduction of country-specific policies. Finally, to account for time-invariant disease specific cofounders we have included an additional specification where we include indication fixed-effects, which allow to control for global level demand factors (see Table 3 in Supplementary Materials).

We also assess the heterogeneity of the main effect across different types of rare diseases and across different sizes of POs. Namely, we first explore differences of PO effects between rare and ultra-rare diseases by interacting the main effect PO^{b}_{cit} with a dummy variable taking a value of 1 if the disease is ultra-rare and 0 otherwise (Model 2.1). Diseases were defined as ultra-rare if they affect up to 1 in 50,000 people, i.e., if their prevalence as reported in the Orphanet database was up to that threshold (NICE, 2004; Scottish Medicines Consortium, 2022). This was explored under the assumption that more common diseases might benefit from larger POs that have more resources and funding to advocate and direct research efforts.

Table 1
Descriptive statistics of key variables.

Variable	N	Mean	Std. Dev.	Min	Max
PO-related variables					
Presence of at least a PO = 1; 0 otherwise	1,646,910	0.134	0.340	0	1
Cumulative number of POs	1,646,910	1.140	0.365	0	3
POs budget					
1st quartile	80,199	6756	2387	5000	10,000
2nd quartile	61,583	100,000	0	100,000	100,000
3rd quartile	52,144	249,972	1179	200,000	250,000
4th quartile	26,088	3,137,439	5,676,879	500,000	2.00e+07
R&D events (phase I-III trials)	1,646,910	0.053	0.307	0	15
Year	1,646,910	2005	8.655	1990	2019
Country-related variables					
Health expenditure (per capita)	1,421,643	2447	1397	302.3	7138
Pharmaceutical expenditure (% of health expenditure)	162,798	17.13	6.770	6.329	36.97
Disease-related variables					
Prevalence (min)	1,461,600	1.347	5.167	1.28e-05	48.55
Prevalence (max)	1,461,600	2.206	7.991	1.28e-05	50
Prevalence (mean)	1,461,600	1.776	6.221	1.28e-05	48.55
DALYs (level 1)	1,397,452	4,220,240	5,479,735	5454	2.351e+07
DALYs (level 2)	1,396,640	381,098	680,475	7.615	7.138e+06
DALYs (level 3)	1,263,472	26,606	57,451	0	1.590e+06
DALYs (level 4)	183,512	12,668	30,985	0.00285	885,664

Abbreviations: POs (patient organisations); DALYs (disability-adjusted life years); R&D (research and development).
Notes: Minimum and maximum prevalence refer to the minimum and the maximum prevalence estimate points per 100,000 people for a specific indication, respectively. As the analysis is conducted at the country-indication-year level, if there were more than a PO in a country X, targeting indication Y in year T, the budget was estimated cumulatively for all existing POs.

Secondly, since the visibility and influence of POs may be influenced by their size, we include an interaction term between PO_{cit} and a variable indicating the quartile of the POs' membership fees, as they are paid according to the organisations' budget, which was used as a proxy for size. In Model 2.2, we create a categorical variable indicating the quartile the PO's budget falls into in a certain country-indication for a specific year. Table 1 shows the observations and the budget range included in each of the n quartiles. As the analysis is conducted at the country-indication-year level, if there were more than a PO in a country *c*, targeting indication *i* in year *t*, the budget was estimated cumulatively for all existing POs. All analyses were performed on STATA 16.

4.1. Event study design

To explore dynamic effects and pre-treatment trends, we deployed an event study design (Clarke and Tapia-Schythe, 2021), where we interacted the treatment, namely the presence of at least a PO in a country-indication pair, with multiple indicators of time before and after treatment(Clarke and Tapia-Schythe, 2021). This strategy allowed us to assess pre-treatment trend differences between treated and control groups, which if non-significant, increases our confidence on the identified causal impact of the policy (Clarke and Tapia-Schythe, 2021). The event study design specification is as follows:

$$E(Y_{cit}) = \beta_0 + \sum_{k=2}^{K} \beta_k \,(\text{PO lag k})_{\text{cit}} + \sum_{h=1}^{H} \beta_h (\text{PO lead h})_{\text{cit}} + \delta_{ci} + \gamma_t + \varepsilon_{cit} \tag{2}$$

Where *ci* represents the country-indication pair, *t* represents the year of the R&D event, and δ_{ci} and γ_t are country-indication and year fixed effects. In equation (2), leads and lags to PO introduction are defined as:

$$(\text{PO lag K})_{\text{cit}} = [\text{t} \leq PO_{ci} - \text{K}\,], \tag{3}$$

$$(\text{PO lag k})_{\text{cit}} = [\text{t} = \text{P}\,PO_{ci} - \text{k}\,] \text{ for k} \in \{1, \ldots., \text{K} - 1\}, \tag{4}$$

$$(\text{PO lead h})_{\text{cit}} = [\text{t} = PO_{ci} + \text{h}\,] \text{ for h} \in \{1, \ldots., \text{H} - 1\}, \tag{5}$$

$$(\text{PO lead H})_{\text{cit}} = [\text{t} \geq PO_{ci} + \text{H}\,]. \tag{6}$$

Lags and leads are binary variables that indicate that a given county-indication pair is a number of periods before or after from the event of interest, namely PO introduction. K and H lags and leads are included and the first lag is omitted as the baseline case, k = 1.

4.2. Robustness checks

A number of robustness checks were conducted. Firstly, to mitigate the risk of self-selection bias, we ran the same DID specification as in the baseline regression but considering only country-indication pairs where a PO is introduced at some point in time (ever treated) (Model 3.1).

Secondly, we considered only those indications that are *at risk* of R&D activity (Model 3.2). Indications were considered *at risk* after the first R&D event took place globally. This analysis restricted the sample only to those diseases that had the capacity and scientific knowledge to experience innovation. In fact, due to research hurdles and different understanding of diseases pathogenesis, innovation in one disease area might be more challenging in one disease are than in another.

In the baseline regression, we deployed a Poisson regression models with multiple high-dimensional fixed effects to better deal with zero values in the dependent variable. However, to assess the sensitivity of the analysis to different model selection, in Model 3.3 and 3.4 we use standard fixed-effect Poisson and linear regression, respectively. Specifications for the above-mentioned models are reported below.

Model 1.3:

$$E(Y_{cit}) = \exp\left(\beta_1 PO^b_{cit} + COUNTRY_{dummy} * YEAR_{cont} + size_{ci} + \delta_{ci} + \gamma_t\right) \tag{7}$$

Model 1.4:

$$E(Y_{cit}) = \exp\left(\beta_1 PO^b_{cit} + ATC_{dummy} * YEAR_{cont} + size_{ci} + \delta_{ci} + \gamma_t\right) \tag{8}$$

Model 1.5:

$$E(Y_{cit}) = \exp\left(\beta_1 PO^b_{cit} + COUNTRY_{dummy} * YEAR_{dummy} + size_{ci} + \delta_{ci} + \gamma_t\right) \tag{9}$$

To account for the potential influence of highly endowed POs, we conducted a regression analysis (Model 3.5) excluding organisations with a total budget exceeding 1 million euros.

Additionally, as only full Eurordis members pay fees depending on their budget (see Supplementary Material for further details), we ran our baseline regression (Model 1.1) excluding associate members. In our baseline regression we bundled associate members with the full members of small size to avoid sample selection bias. This is plausible considering that most members enrol as associate before becoming a full member and that the 50€ flat fee paid by associate members corresponds to a low budget (please see the Supplementary Material for further details). However, this is not a perfect indicator of POs' budget as we ultimately do not observe the actual size of the POs and cannot rule out these having higher budgets. Therefore, we ran a robustness check by omitting these observations from the regression (Model 3.6).

Finally, in our analysis we aggregated R&D activities across different phases due to limited data availability during the early stages of drug development. This was done as pharmaceutical companies often keep basic discovery and pre-clinical activities confidential, resulting in left-censored data. While it is challenging to pinpoint the exact timing of in-vivo experiments, we conducted a stratified analysis by development stage (preclinical/discovery, phase I, phase II, and phase III) to better understand the differential effects of POs across R&D phases (Models 4.1–4.4).

5. Results

Overall, 1504 patient organisations were included in the analysis. Across the study period and regardless of their geographic location, most rare diseases included in the database (89%) benefitted from the support of at least one patient organisation. Most POs had a budget lower than €100,000 (79%). While 19% and 2% of patient organisations had a budget between €100,000 and €1,000,000 or above €1,000,000, respectively. In the analysis period, the overall number of patient organisations increased over time. With respect to ATC classes, most POs focused on diseases affecting the nervous system (24%; ATC class: N), followed by anti-infective for systemic use (20%; ATC class: J), anti-neoplastic and immunomodulating agents (ATC class: L) and alimentary tract and metabolism (15%; ATC class: A) (Fig. 2 in the Supplementary Materials).

Estimates from the baseline regression (Model 1.1), reported in rate ratios, suggested that country-indication pairs with at least a PO are expected to have a rate of R&D activity 4·608 (95% CI 4.348–4.883; $p < 0.001$) higher than country-indication pairs with no POs (Table 2). Model 1.2 showed that a higher number of POs in a country-indication pair was associated with an increasing, though non-linear, number of R&D activities (95% CI 5.109–6.445; $p < 0.001$) compared to country-indication pairs that did not have POs. This seems to suggest that not only having at least a PO advocating for a rare condition in a certain country impacts on the R&D activity in the disease area, but that there is an incremental impact for each additional PO created. Results remain robust to the addition of country and ATC class specific year effects to the baseline regression albeit with smaller effect sizes (Models 1.3, 1.4, and 1.5).

While POs are found to impact R&D activity for both ultra and non-

Table 2
Effect of POs on R&D activity.

Variables	(1.1) Baseline regression	(1.2)	(1.3)	(1.4)	(1.5)
	Binary PO variable	Cumulative PO variable	Year (cont.)/country interaction	Year (cont.)/ATC interaction	Year (dummy) country interaction
PO binary (=1 if at least one PO)	4.608***		1.550***	1.576***	1.325***
	(0.136)		(0.026)	(0.025)	(0.000)
PO cumulative (=2 if at least one PO)		4.558***			
		(0.135)			
PO cumulative (=3 if more than one PO)		5.738***			
		(0.340)			
Constant	0.156***	0.156***	0.013***	0.005***	−0.007***
	(0.001)	(0.001)	(0.001)	(0.000)	(0.001)
Observations	1,646,910	1,646,910	1,646,910	1,631,250	1,646,910
Pseudo R-squared	0.346	0.346	0.385	0.392	0.442
Size	YES	YES	YES	YES	YES
Country-indication FE	YES	YES	NO	NO	YES
Year FE	YES	YES	NO	NO	YES
Country trends	NO	NO	YES	NO	YES
Year trends	NO	NO	YES	YES	YES
ATC trends	NO	NO	NO	YES	NO

Notes: Poisson pseudo maximum likelihood regression model estimates. Model 1.1 investigates the effect of the presence of at least a PO in a country-indication pair while Model 1.2 disentangle the effect depending on whether there are more than one PO. Additional control variables included are size, country-indication fixed effects (FE) to control for state and indication time invariant unobservables, and year FE to control for common shock. Models 1.3 and 1.4 control for country and ATC class-specific trends, by interacting the abovementioned variables with the year variable treated as continuous, while Model 1.5 includes country-specific year fixed-effects. Results are presented in incidence rate ratios (IRR). Robust standard errors are presented in parentheses; ***p < 0.01, **p < 0.05, *p < 0.1.

ultra-rare disease, their presence appeared to have stronger effects in more common rare diseases (Model 2.1). This might indicate that the role of POs in fostering innovation in ultra-rare conditions is weakened by the existing significant scientific barriers vis-à-vis more common rare diseases or that by affecting smaller number of people the scope for POs in this space to exert their countervailing power is limited (Table 3). When looking at the effects by POs size, they were not linear, with effects on R&D activity decreasing from the 1st to the 2nd and 3rd quartiles, for then increasing for POs with a budget higher than €500,000.

Table 3
Effects by rarity and size.

Variables	(2.1)[a]	(2.2)
	Rarity	POs' size
PO binary (=1 if at least one PO)	5.409***	4.608***
	(0.200)	(0.136)
PO binary # ultra-rare	0.746 ***	
	(0.034)	
PO binary # 2nd quartile (100,000 €)		0.904***
		(0.034)
PO binary # 3rd quartile (200,000–250,000 €)		0.459***
		(0.023)
PO binary # 4th quartile (500,000–20,000,000 €)		1.569***
		(0.103)
Constant	0.155***	0.156***
	(0.001)	(0.001)
Observations	1,646,910	1,646,910
Pseudo R-squared	0.345	0.346
Size	YES	YES
Country-indication FE	YES	YES
Year FE	YES	YES

Notes: Poisson pseudo maximum likelihood regression model estimates. Model 2.1 shows effects of POs for ultra-rare indications (interaction term). A disease is ultra-rare if it affects less than 1:50,000 people. Similarly, Models 2.2 presents results by POs' size quartile (proxied by budget). The reference category includes POs whose budget is in the 1st quartile (5000–10,000 €; N = 80,199) and includes associate members, which are assumed to have a budget of 5000€ per annum. Additional control variables included are size, country-indication fixed effects (FE) to control for state and indication time invariant unobservables, and year FE to control for common shock. Results are presented in incidence rate ratios (IRR). Robust standard errors are presented in parentheses; ***p < 0.01, **p < 0.05, *p < 0.1.

[a] In Model 2.1, the main effect of the (time invariant) ultra-rare dummy variable is absorbed by the indication FE.

In terms of robustness checks (Table 4), when considering only country-indication pairs that were ever treated (Model 3.1) or years after the first indication-specific global R&D event (Model 3.2), coefficients are similar in magnitude and significance to those presented in Table 1. Different model specifications – namely fixed-effects Poisson and linear regression – confirmed the size and direction of effects of the baseline regression (Model 3.3 and 3.4). Results from the regression where POs with a budget above 1 million euros and where Eurordis' associate members were omitted (Models 3.5–3.6) were in accordance with those from the baseline regression.

Results of the analysis stratified by R&D phase of development (Table 5, Models 4.1–4.4) show that the effect is stronger in the pre-clinical activities versus later stages of development, suggesting that POs have relatively less impact in directing R&D efforts in more expensive development programmes versus initial stages of development. When including separate indication-specific fixed effects, which help control for time-invariant cofounders specific to each disease, the results maintain the same direction of effects, albeit with smaller magnitudes. Finally, results from the event study were similar to the main findings and showed that coefficients on the pre-treatment effects in the event study design are not statistically different from zero, thus providing additional confidence on the identified causal impact of the treatment (PO introduction in a country-indication pair). Post-treatment coefficients became significant after approximately five years from PO creation, indicating a lag in effects (Fig. 2). This is expected, as POs might require time to build their internal capabilities to advocate, educate and reach patients.

6. Discussion

This is the first analysis to empirically assess the effect of POs on R&D activity in the rare disease context. Our results showed that disease areas where POs operate have a more intense R&D activity compared to areas that have no POs. Results from the event study indicated a lag in effects from PO introduction, suggesting that it takes approximately five years from their creation for POs to affect R&D activity. We found that the

Table 4
Robustness checks.

Variables	(3.1)	(3.2)	(3.3)	(3.4)	(3.5)	(3.6)
	Ever-treated country-ind only	Years after first global R&D event	Poisson	Linear regression	Binary PO variable (excluding POs with budget >1 mln€)	POs' size (excluding associate members)
PO binary (=1 if at least one PO)	4.553***	2.039***	4.608***	0.091***	4.432 ***	5.317***
	(0.136)	(0.064)	(0.119)	(0.001)	(0.097)	(0.183)
Size quartiles (1st quartile base category)						
2nd quartile (100,000 €)						0.787***
						(0.032)
3rd quartile (200,000–250,000 €)						0.414***
						(0.023)
4th quartile (500,000–20,000,000 €)						1.166***
						(0.085)
Constant	0.101***	0.278***	–	0.041 ***	0.157 ***	0.159***
	(0.002)	(0.002)	–	(0.000)	(0.001)	(0.001)
Observations	174,360	512,908	853,380	1,646,910	1,638,348	1,623,646
Pseudo R-squared	0.288	0.222	5441.35[a]	0.004[a]	0.346	0.346
Size	YES	YES	YES	YES	YES	YES
Country-indication FE	YES	YES	YES	YES	YES	YES
Year FE	YES	YES	YES	YES	YES	YES

Notes: Model 3.1 and 3.2 restricts the analysis to country-indication pairs where a PO is created at some point in time (ever treated) and to years after when the first global R&D event for each indication took place, respectively. In Models 3.3 and 3.4 we deploy fixed-effects Poisson (xtpoisson STATA command) and linear regression (xtreg command). Model 3.5 and 3.6 exclude POs with a high budget (above 1 million euros) and associate members from the analysis, respectively. All models deploy Poisson pseudo maximum likelihood regression unless differently specified. Additional control variables included are size, country-indication fixed effects (FE) to control for state and indication time invariant unobservables, and year FE to control for common shock. Results are presented in incidence rate ratios (IRR) but in Model 3.4, where they are reported as linear regression coefficients. Robust standard errors are presented in parentheses; ***p < 0.01, **p < 0.05, *p < 0.1.

[a] Please note that values refer to Chi-Square and R-squared for Poisson and linear regression, respectively..

Table 5
Effects broken down by R&D phases.

Variables	(4.1)	(4.2)	(4.3)	(4.4)
	Preclinical[a]	Phase I[a]	Phase II[a]	Phase III[a]
PO binary (=1 if at least one PO)	7.765***	4.862***	5.844***	4.432***
	(0.662)	(0.367)	(0.248)	(0.166)
Constant	0.039***	0.054***	0.071***	0.095***
	(0.001)	(0.001)	(0.001)	(0.001)
Observations	1,646,910	1,646,910	1,646,910	1,646,910
Pseudo R-squared	0.383	0.418	0.350	0.320
Size	YES	YES	YES	YES
Country-indication FE	YES	YES	YES	YES
Year FE	YES	YES	YES	YES

Notes: Poisson pseudo maximum likelihood regression model estimates. Model 4.1 to 4.4 shows effects of POs on specific phases of R&D activity, from pre-clinical to phase III. Additional control variables included are size, country-indication fixed effects (FE) to control for state and indication time invariant unobservables, and year FE to control for common shock. Robust standard errors are presented in parentheses; ***p < 0.01, **p < 0.05, *p < 0.1.

[a] In the IQVIA dataset, R&D activities are not uniformly coded according to a specific phase (e.g., preclinical, phase I, II, and III). Instead, some activities may be categorised as phase I/II or phase II/III, among others. Consequently, when disaggregating these activities into phases, we must inevitably double-count certain observations to avoid making assumptions such as trials labelled as phase I/II being exclusively phase II.

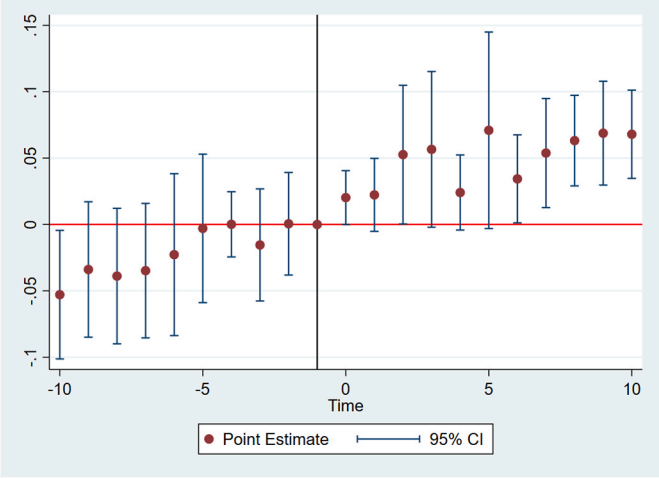

Fig. 2. Effects of POs on clinical trial activity (10 years pre/post PO introduction). This figure plots the estimates from an event-study regression of R&D activity with years to and years since the introduction of at least a PO in a country-indication pair.

effect of POs is cumulative, meaning that support from multiple POs leads to a higher increase in R&D activity. However, such effect appears to be non-linear, which implies that changes in R&D activity are not proportional to the number of POs operating in a certain country-indication pair. Furthermore, POs appeared to have a more prominent effect in non-ultra-rare diseases versus ultra-rare conditions. While almost the entirety of rare diseases are ultra-rare (Nguengang Wakap et al., 2020) – meaning that they affect fewer than 1 in 50,000 patients – these are also the conditions where little basic research has been conducted and limited understanding exists. Our results suggest that POs' advocacy has limited impact in increasing R&D activities for ultra-rare diseases. This could be due to the existing scientific barriers but can also be attributed to the fact that the bargaining power of POs focusing on ultra-rare diseases is insufficient to have any impact on industry R&D decisions, as the market for such conditions is too small. This might indicate that in such diseases, advocacy is not sufficient to promote innovations and needs to be complemented with other policies, such as public investments earmarked to key areas of need or aimed at stimulating translational research.

Our analysis confirms findings from qualitative studies, which highlights the important role of patient advocacy in advancing research in rare diseases (Crossnohere et al., 2020; Dunkle et al., 2010; Mavris and Le Cam, 2012; Polich, 2012; Roennow et al., 2020). Unlike more prevalent conditions, POs focusing on rare diseases are usually made up of patients, their families and carers (Halley, 2021). Because of this, they are uniquely placed to support research by helping in identifying patient-relevant outcomes and endpoints, drafting trial designs, and

supporting patients' enrolment and retention in clinical trials. Overall, the role of POs in influencing R&D outcomes is multifaceted. While POs have the potential to counteract the market power of the pharmaceutical industry and promote more equitable and user-centric research, it is important to recognise the complex dynamics between POs and industry funding (Hoffman et al., 2011). While our study did not directly investigate this, if POs rely on industry funding for a significant portion of their income, their interests might be aligned with those of pharmaceutical companies and hence influenced by profit-driven motives. This, however, does not necessarily prevent POs from addressing public health concerns and patients' needs. Nonetheless, it remains unclear whether their efforts are directed towards disease areas with the highest need or if they contribute to existing innovation inequalities (Barrenho et al., 2019). Evidence suggests that advocacy tends to cluster around already established disease areas and that it reinforces existing inequities rather than rectifying them (Halley, 2021). For example, in the UK, cystic fibrosis, a rare genetic pulmonary disorder associated with poor survival that affects around 11 in 100,000 people experienced a high level of innovation even before the creation of its first disease-specific PO in 2001, which further increased the level of innovation in the disease area. Conversely, Lennox-Gastaut syndrome, a severe childhood-onset developmental epileptic encephalopathy characterized by a higher prevalence point and similar health outcomes had very little research ongoing over the years and did not benefit from the support of any PO. In this instance, despite the high unmet in Lennox-Gastaut syndrome, there is more innovation in cystic fibrosis and POs presence widens that inequality.

A 2012 study found that diseases benefitting from more organised POs secured more research funding from the National Institutes of Health, compared to those supported by fewer organisations (Best, 2012). However, the paper also showed that less stigmatised conditions tend to have higher levels of advocacy, hence securing more funding. Furthermore, Ozieranski and colleagues found that industry funding to POs was concentrated among commercially attractive diseases, with multiple myeloma and breast cancer securing jointly almost 50% of all cancer funding (Ozieranski et al., 2019). This might pose risk of inadequate representations across rare diseases – and diseases in general – where POs target conditions where the unmet need is relatively low. Therefore, further investigation is needed to better understand the relationships between POs, the pharmaceutical industry, and their potential impact on research priorities and outcomes. Additionally, the observed increase in R&D activity in countries with POs does not necessarily imply more global trial activity. Instead, it may indicate a strategic change in the sequencing of clinical trials, where initial trials are prioritised in countries with established POs, or full displacement of the country where the trials are conducted. However, given that we do not have global data, we are unable to directly test these hypotheses.

The analysis here presented should be viewed in light of its limitation. First, our analysis is geographically limited as it focused on European countries only. This is due to data on patient organisations in the US not being publicly available. While this might be problematic as innovation is a global process, it is important to note that POs have a local outreach, hence it would be unlikely for them to influence research activities outside of the region where they operate. Therefore, while it could be the case that POs' advocacy impact R&D activities conducted in other regions with similar standard for clinical trials, this is deemed improbable. Second, we excluded from our analysis POs that focus on all rare diseases indistinctly (e.g., Genetic Alliance UK). This was done as including such organisations would likely result in an overestimation of the number of conditions receiving attention from POs in the sample, as virtually all rare diseases in the database would be *treated* (i.e., would benefit from the support of at least one PO). Furthermore, such organisations are more likely to engage with policymakers via advocacy and lobbying to ensure rare diseases are part of the national and international political agenda, rather than focusing on steering research activities of specific rare diseases. While this might bias our results, we expect this to have a negligible effect as such POs are likely to affect all conditions equally. Third, we considered Eurordis' members to be representative of most European POs. While we expect that most POs active in Europe become Eurordis' member at some point of their existence, we are aware that there might be POs that decided not to join or to withdraw their membership. However, Eurordis is the leading rare-disease POs alliance in Europe and one of the key stakeholders in shaping the rare disease policy and political environment. Therefore, we believe that most organisations actively involved in advocacy, support and research became either full or associate members over time. Fourth, the budget are estimated based on the average fees paid by the POs between 2012 and 2020. This approach was considered more appropriate than relying on a single cross-sectional point in time due to the unavailability of panel data for all years in the analysis from Eurordis. However, it is important to note that this approach may reduce the size effect across years within each company while retaining such effect between companies. Fifth, the data leveraged did not allow us to measure the value of medical innovation. This means that breakthrough medical innovations were given equal weight to incremental ones in our sample. This is an important area of investigation that should be further researched when more granular data is available. Sixth, our data does not enable identifying potential mechanisms for the observed effects. POs can foster innovation through a variety of mechanisms that can be more or less aligned with public health interests *vis a vis* pharmaceutical profit interests. One of the concerns that may arise with our analyses is possible endogeneity arising from pharmaceutical firms supporting POs in disease areas in which they commercialize new drugs. This would be particularly a concern if pharmaceutical firms would be engaged in the establishment of a PO in key strategic disease areas. However, no evidence could be found in the literature that POs were established by pharmaceutical industry, indicating that the creation of POs is exogenous to the outcomes assessed. This is further confirmed by the event study results that indicate parallel trends prior to the establishment of POs. On the other hand, numerous studies have indicated that industry provides financial support for the activities of already established POs across Europe (Gentilini and Parvanova, 2023; Ozieranski et al., 2019). Although the literature suggests dependency of POs on industry to be low in the UK (IQR, 0.1%–6.0%) (Ozieranski et al., 2022), we do account for the financial support aspect by controlling for the size of POs. By controlling for PO size, we capture the potential role of financial support from industry in shaping the activities of these organisations. In fact, the size of POs is an important factor that can affect their ability to advocate for specific research priorities and engage in collaborations that drive R&D efforts. Nevertheless, future research might explore the dependency of POs' budget from industry in the context of rare diseases and different geographic settings, especially in light of new evidence suggesting that rare-focused POs rely on industry payments from fewer companies (Gentilini and Parvanova, 2023). There could also be other sources of endogeneity not addressed in our analyses. For example, general concern about a particular disease might lead to more POs in that area and at the same time increased R&D in the very same area. While we have attempted to control for these through deploying an event study and controlling for a wide range of cofounders and fixed effects, we cannot exclude other factors may be driving both variables.

Finally, our classification of diseases as rare and ultra-rare is based on prevalence at the European level, without considering variations in prevalence among European countries. For instance, Wilson disease exhibits a higher prevalence in insular locations, exceeding mainland Europe by over 300% (Lo and Bandmann, 2017). While we anticipate that this limitation would have a negligible overall impact, it is important to acknowledge this constraint. In future studies, it would be valuable to explore this further using country-specific epidemiological data, which is currently unavailable.

Despite these caveats, the findings from our study provide important empirical evidence that POs increase R&D activity in rare diseases, which is robust across numerous checks. Policymakers should consider

these results when setting research priorities in the rare disease context, especially how higher levels of POs' advocacy can advance innovation in the disease areas they operate in. However, attention should be paid to how this might widen issues of inequitable representation of diseases. Our study open avenues for further research. For example, to explore POs' effect on R&D in different settings, the analysis could be expanded to include data on R&D activity and POs from other geographical regions, such as the United States. Furthermore, while medicines development is a necessary condition for improving patients' health outcomes, this is not sufficient, as drugs are of no value if people in need cannot access them. Further research on the role POs play in accessibility and affordability of medicines is warranted. Finally, to investigate whether POs widen existing health inequities across diseases, the concentration of funding directed to such organisations might be explored.

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Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.socscimed.2023.116332.

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