IP policies in early-phase research in public-private partnerships: an overview and assessment of current practices

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ABSTRACT

An Intellectual Property (IP) policy analysis reveals the use of a variety of IP frameworks within early-phase biomedical Public-Private Partnerships (PPPs). Dependent on the nature of the research objectives, enacted IP frameworks or 'knowledge sharing strategies' differ, ranging from 'partnership oriented' models towards 'open' models. While this variation seems instrumental to accommodate the variety in terms of objectives and (funding) partners present within PPPs, we also frequently observe vagueness and implicitness in terms of IP policies deployed. This latter feature seems to be less instrumental as coordination costs (within and outside the PPPS) are likely to increase.

INTRODUCTION

Since more than a decade, big pharma has evolved from the traditional model, wherein IP (i.e. formally protected knowledge such as know-how, data and materials) is used to appropriate returns internally, towards a more collaborative model wherein IP becomes shared and pooled. Within this paper we focus on how sharing of IP is organized through specific 'IP frameworks' or 'knowledge sharing strategies' in early-phase PPPs. In such PPPs, several partners combine expertise, materials and sometimes IP (therefore called 'background IP') in a consortium, in an attempt to answer basic, fundamental research questions; to create technology platforms, research tools, shared databases and/or predictive models. These activities might result in IP (called 'Foreground IP') instrumental to the development of safer and more effective drugs [1, 2]. A number of those PPPs also perform

downstream development of therapies whereby the importance of (access to) IP increases. Given the nature of intellectual property rights (IPRs), providing the owner the right to exclude others from using protected inventions, establishing agreements on sharing of IP within early-phase research PPPs becomes complex [3].

As PPPs focus on sharing and pooling of complementary skills, IP ownership and access to IP is a key factor and an incentive for the pharma industry to engage and invest in PPPs. IP policies and IP related issues in PPPs have been debated extensively. Several strategies and models to contractually agree on pooling and transferring knowledge have been suggested [4]. Some articles elaborate on the different innovation models applicable in collaborations, whereas others discuss a specific model applied in a well-defined PPP [5, 6]. However, what currently lacks, is empirical evidence and detailed information on the different IP frameworks and policies applied within early-phase PPPs, more in particular the characteristics of the knowledge sharing models and the extent to which partners negotiate the sharing conditions [7, 8].

The present study aims to unravel the IP policies developed by (bio)pharmaceutical research and development (R&D) PPPs operating in the precompetitive phase.

METHODOLOGY

This paper constitutes an analysis of the IP framework applied by early-phase biomedical research PPPs by means of exploring 1) the nature of the enacted IP policies in terms of transparency and clarity and 2) the content of the IP policies in terms of ownership rights, access and use or the potential to negotiate the rules and

clauses and to customize the rules and clauses proposed according to the partners' needs and desires. In addition, we assess the relationship between the research results and i) the PPPs' project focus, ii) envisioned project deliverables and iii) PPP funding sources. The empirical study focuses on 5 IP elements used in life sciences PPPs: 1) ownership of background IP, 2) ownership of foreground IP, 3) access rights to background IP, 4) access rights to foreground IP and 5) IP management.

The choice of the selected PPPs results from a literature study (Sources: Pubmed, SSRN, ScienceDirect, Google, and references cited in this study) complemented with experts consultations, leading to a non-exhaustive list of 30 biomedical PPPs worldwide. We included 20 PPPs thereof in the analysis (availability sampling). We typified the PPPs geographically and we categorized them according to the research stages covered on the discovery-development-delivery continuum (i.e. early-phase research ('Precompetitive'), and if applicable also proof-of-concept ('POC') research, product development ('PD') and product access ('PA')) [3]. We included only PPPs starting research projects in the early stage of drug discovery, meaning that we omitted PPPs who focus on product development or product access (purposive sampling). We categorized the PPPs according to their project focus as follows: 1) poverty-related and neglected diseases ('PRNDs') (e.g. neglected tropical diseases, malaria, tuberculosis and HIV/AIDS), 2) diseases of affluence ('Affluence') or 3) combinations of PRNDs and diseases of affluence ('Mixed'). Further, we mapped the envisioned project deliverables of the PPP, i.e. 1) drug development tools, such as technology platforms, (software) models, databases, research tools or materials ('Tools'), 2) drugs, diagnostic and therapeutic materials, or therapies ('Drugs'), or 3) a combination of research tools, tests and drugs ('Mix'). Also, we identified the

funding sources/partners of the PPPs (non-profit, for-profit and mixed funding (Mixed), i.e. combined non-profit and for-profit funding). Categorization of the different IP strategies applied in PPPs (Partnership-focused strategy, Open Collaboration strategy and Hybrid strategy) was based on the dominant framework described in the IP policy and applied within the majority of the projects.

The study intends to provide empirical evidence on precompetitive PPPs' use of IP policies and to provide an insight in the relationship between the IP elements used and the nature of the PPP.

RESULTS

Mapping of early-phase PPPs

Geographic scope – The 20 PPPs included in the study were geographically typified; 5 EU national PPPs (EU Nat), 2 regional PPPs (EU), 6 US PPPs (US) and 7 international PPPs (Internat) covering worldwide collaborations (Table 1).

Research phase – Eight (40%) out of 20 precompetitive PPPs conducted projects with a POC character, thereof 6 (30%) PPPs continued with projects up to the PD phase, and 3 (15%) of them conducted projects from the precompetitive phase up till the PA phase (Supplementary Fig. 1-2).

Project focus – The 20 PPPs under study focus their research projects either on PRNDs (4 or 20%) (4 Internat), diseases of affluence (11 (2 Internat, 4 US, 1 EU, 4 EU Nat) or both, i.e. a mixed focus (5) (1 Internat, 2 US, 1 EU, 1 EU Nat) (Table 1). In the 5 PPPs with a mixed focus, only a minority of the total amount of projects are focused on PRNDs. PPPs focused on PRNDs conduct projects in the different phases

of the drug development cycle, in contrast with PPPs focused on diseases of affluence that are mainly operating in the early research phase (Supplementary Fig. 1).

Project deliverables – The short-term outputs and the long-term outcomes envisioned in the mission and objectives of the 20 precompetitive PPPs were mapped. The PPPs focused in this study will not actually deliver drugs or therapies ready to market, as they are precompetitive; some PPPs mention such deliverables in the long term. Nine (45%) out of 20 PPPs envisioned drug development tools, such as technology platforms and databases, 3 (15%) target diagnostic tests, drugs or therapies in the long term, and 8 (40%) envisioned a mix of these outputs and outcomes (Table 1).

PPP Funding - Nine out of the 20 (45%) selected PPPs operating in the precompetitive phase are funded by non-profit organizations, such as governments, intergovernmental institutions or non-profit organizations (whether or not funded with private or public money) (Table 1). Eleven out of those 20 (55%) PPPs are funded by a mixed group of funders, being a combination of non-profit organizations and private industry funders. None of the PPPs focusing on PRNDs are funded solely by private industry, and only 3 out of 11 PPPs co-funded by the private industry focus (a minority of) their projects on PRNDs (Supplementary Fig. 3).

Transparency of IP information

Twenty of the 30 (67%) precompetitive PPPs contacted offered information regarding IP via an IP policy or guidance document. Actually, only 14 (47%) of such PPPs made this information publicly available. For 6 (20%) of the 30 PPPs, the

information was received through personal contact. Of the latter, 3 (10%) PPPs requested confidentiality regarding the documents obtained. With respect to the last 10 (33%) PPPs, no IP policy could be retrieved (2 (7%) PPPs stopped their activities and 8 (27%) PPPs did not respond to emails). Nineteen of the 20 (95%) PPPs provided information regarding the of IP elements under investigation (ownership of background IP, ownership of foreground IP, access rights to background IP, access rights to foreground IP and IP management) in the documentation offered. One of the 20 (5%) PPPs only provide minimal information regarding publication guidelines or the use of clinical data (Table 2).

Clarity of IP information

Remarkably, the majority of the PPPs does not provide clear definitions on the concepts used in their IP policy. Only 7 (35%) IP policies provide a clear definition for background IP, and 6 (30%) do so for foreground IP. Further, IP policies do not always provide clear definitions for access (rights) and use and do not make a distinction between the right to use background IP or foreground IP and the concept of 'freedom-to-operate'.

Ownership of IP

Background IP - Thirteen of 20 (65%) PPPs (6 non-profit funded (2 Internat, 2 US, 1 EU, 1 EU Nat) and 7 mixed funded PPPs (1 Internat, 1 US, 1 EU, 4 EU Nat)) provide information on ownership of background IP. Twelve of 20 (60%) PPPs claimed that ownership of background IP remains with the original owner (Table 2).

Foreground IP – Not every IP policy clearly specifies the possibility to file for patents on research results. Via information regarding foreground IP (Table 2), and

especially regarding the access rights to foreground IP, this information can be deducted. Half of the selected PPPs (50%, 3 US, 2 EU, 5 EU Nat) allow for IP protection via patenting of research results. Six (30%, 5 Internat, 1 US) PPPs state that patenting is possible, but that research results are preferable put within the public domain. Three (15%, 2 Internat, 1 US) PPPs state that research results in the project scope are not to be patented , or limit the potential to file for patents on specific research results, and in 1 PPP IP policy (5%, US), the possibilities with regards to patent protection of foreground IP are not specified.

Compared to information related to ownership of background IP, more information is provided about the ownership of results generated during the course of the project, commonly referred to as foreground IP (Table 2). Eighteen (90%) PPPs provide information about foreground IP ownership, namely 8 out of 9 non-profit funded PPPs (5 Internat, 1 US, 1 EU, 1 EU Nat) and 10 out of 11 mixed funded PPPs (2 Internat, 3 US, 1 EU, 4 EU Nat) (Table 2). There are differences to be noticed between non-profit funded and mixed funded PPPs (Table 2). For 3 (15%) PPPs, collaborative research resulting from the project is owned by the PPP itself. It concerns 2 out of 8 non-profit funded PPPs (1 Internat, 1 US) and 1 out of the 9 mixed funded PPPs (1 EU Nat) that provided foreground IP information. Four (20%) non-profit funded PPPs (2 Internat, 1 EU, 1 EU Nat) allow the idea generator to be owner of the IP to the invention. In case of mixed funded PPPs, 6 out of 9 (1 Internat, 2 US, 1 EU, 2 EU Nat) allow the idea generator to own the foreground IP. One (5%, Internat) mixed funded PPP does not allow the institution to own research results. Eight (40%) PPPs (1 US, 2 EU, 5 EU Nat) allow joint ownership of the foreground IP, 3 (15%) of them are funded by non-profit institutes, 5 (25%) are

mixed funded. One (5%) PPP (1 EU Nat) is joint owner for all research results of the PPP. A non-profit funded National PPP allowing joint ownership, explicitly states that *'joint ownership is only possible in exceptional circumstances, ownership by the industrial partner is favored'*. Joint ownership is thus more common within mixed funded PPPs.

Access Rights to IP

In the majority of the cases, IP policies refer to 'access rights' where it would be more correct to refer to 'use rights' or 'user rights'. The possibility to use IP linked to the project depends on the moment of generation of IP (background IP/foreground IP), the party using the IPRs (the PPP, project participants and/or affiliates, third parties), and the purpose of the research activity (research use/commercial use). Many of the PPPs make a distinction in access to (and thus 'use of') IPRs i) for completion of the project, ii) for research use outside the project scope, iii) to practice foreground IP outside the project scope and iv) for direct exploitation. Further, the way these rights are granted can vary: the majority of the PPPs state that these rights will be granted by means of a contractual agreement, signed between the licensor and the licensee, but there are also PPPs that grant those use rights by means of a (virtual) license, which might be agreed upon by the licensor (the respective PPP) and the licensee (members of the PPP community, or the research community in general) via ticking a box on the website (Box 1).

Access rights to background IP - Ten of the 20 (50%) investigated PPP policies provide information on access rights to background IP. Five of the 9 non-profit funded PPPs provide information regarding access rights to background IP. In case

of mixed funded PPPs, information is provided by 5 out of 11 PPPs (Table 2). The terms and conditions serving as a base for access rights to background IP range from 'royalty-free access rights' to 'royalty-free access OR access on fair and reasonable conditions'.

Seven PPPs (35%) provide a framework for partners' access rights to background IP *for completion of the project*. Five (25%) PPPs provide access to background IP for free (1 Internat, 1 EU, 3 EU Nat), 2 out of 7 (1 EU, 1 EU Nat) provide flexibility by stating that the access is for free, unless otherwise agreed. Three out of 5 (2 Internat, 1 US) provide royalty-free access rights *for research use*, 1 out of those 3 geographically limits the access rights for research directed to the needs of the least developed countries (LDC). Two out of 5 (2 EU) provide this access on a royalty-free or on fair and reasonable conditions base. The *practice of foreground IP* by means of background IP is on free or fair and reasonable conditions in 3 (15%) PPPs (2 EU, 1 EU Nat). *Direct exploitation of beneficiary's IP* is to be negotiated in 1 (5%) PPP (EU) and explicitly not obliged in 2 (10%) PPPs (2 EU Nat). A free license is provided in 1 (5%) PPP (Internat) for use of the IP in the LDC. An International non-profit funded PPP, states that '*One may retain the rights over the patents except to the extent to be used in the open source drug discovery process and for selling any product or process arising out of the use of your invention in that process',* suggesting that you may bring in background IP in the projects, but when this background IP is used by other partners for Open Source drug discovery, that you provide the licensing rights to the requesting party.

Access rights to foreground IP – Thirteen of the 20 (65%) investigated PPP policies provide information on access rights to foreground IP, whereof 6 out of 9 non-profit funded PPPs and 7 out of 11 mixed funded PPPs (Table 2). The terms and conditions on which access rights to foreground IP are granted range from 'royalty-free access rights' to 'royalty-free access OR access on fair and reasonable conditions' with some specifications. Often, there is a further specification that the license is worldwide, non-exclusive and non-sub-licensable.

Seven of those 13 PPPs provide a framework for partners' access rights to foreground IP *for completion of the project*. Six (2 Internat, 2 EU, 2 EU Nat) out of 7 PPPs explicitly provide access to foreground IP on a royalty-free base, 1 PPP thereof specifies that the partners have such access rights, but that the coordinating PPP has no access rights to the foreground IP. One (5%) (EU Nat) states that the access to non-tangible foreground know-how is for free, meaning that the know-how built in the consortium can be freely used by the partners. Five (2 Internat, 3 EU Nat) out of 10 (5 non-profit funded and 5 mixed funded) PPPs provide (conditional) royalty-free access rights *for research use*; access rights in 1 (Internat) PPP out of those 5 are geographically limited to the LDC, 1 (5%) (EU Nat) PPP specifies that free access for research use is guaranteed to academia and another PPP (5%) (EU Nat) specifies that royalty-free access is provided to 'the Licensee Group' to which project partners can commit. Two (2 EU) PPPs out of 10 provide this access on a royalty-free or on fair and reasonable conditions base. One (US) PPP out of 10 provides this access on fair and reasonable conditions. One (EU Nat) PPP out of 10 states that the access to non-tangible foreground know-how for research use is for free, 1 (EU Nat) PPP out of 10 states that foreground IP can be freely used by partners up to clinical phase IIA.

The *practice of foreground IP* is for free in 1 (5%) (Internat) PPP in the LDC, and on fair and reasonable or on royalty-free conditions in another PPP (5%) (EU). One (5%) (US) PPP does not provide financial conditions, and only states that the license should be non-exclusive and that it should not be sublicensed, except to affiliates and Third Party contractors. Two (EU Nat) out of 5 PPPs state that the access to non-tangible foreground know-how is for free. *Direct exploitation of beneficiary's IP* is to be negotiated in 5 (25%) (1 EU, 4 EU Nat) PPPs, whereby 1 (5%) grants free access to (non-)tangible foreground IP to partners. One (5%) (EU Nat) PPP obliges the academic partner to grant rights to the enterprises to exploit the results in predefined fields. One (5%) (US) PPP states that free exploitation of the foreground IP is possible for diagnostic testing methods and for consortium technology. A free license is requested by 2 (10%) (Internat) PPPs for use of the foreground IP in the LDC.

IP Management

IP expertise – Eight out of 20 (40%) PPPs specifically appoint an IP responsible or IP committee to manage specific co-ordination tasks related to the creation, maintenance and prosecution of IP within the consortium. Five (25%) of them are non-profit funded PPPs (3 Internat, 2 US), 3 (15%) are mixed funded (EU Nat). In case of the international PPPs, decisions regarding IP are taken by the IP expert or a body of experts representing the PPP. For the US PPPs, a Coordinating Committee (representative of each partner and a PPP representative), resp. the sponsoring foundation reviews decisions on IP prosecution and licensing. In case of the 3 (15%) European national PPPs, a dedicated person is appointed as Project IP Manager and coordinates tasks related to the creation, maintenance and prosecution of IP. This

person is an employee of one of the partners or, in 1 (5%) PPP, it can be a third party (Table 1).

Customization/room for negotiation - Three out of 20 (15%) PPPs (1 Internat, 2 EU Nat) explicitly state their IP policy to be binding. To become a partner in the PPP, you agree upon the IP policy by signing the terms and conditions in the agreement. In these 3 cases, the IP policy does not provide room for negotiations (e.g. whether access rights to background IP for use of foreground IP are on free or fair and reasonable conditions). Two of these 3 PPPs are mixed funded; the third is a non-profit (Open Source) PPP.

Two (10%) other mixed funded PPPs (EU Nat) state that only minor amendments to the clauses proposed can be considered. Three (15%) non-profit funded PPPs (Internat) explicitly state that each project is negotiated on a case-by-case base, whereby the minimal standard is accessibility of the foreground IP for use and commercialization in the LDC. In 2 (10%) PPPs, private industry is a partner only in specific predefined phases of the drug development. In those 2 PPPs, a stage-gate approach to negotiating IP is applied: new contracts are negotiated based on milestones reached in the product development phase. For each new phase, new rules and clauses are agreed between those 2 PPPs and their respective partners. The minimal standard of the negotiations is a royalty-free, exclusive license for geographically defined endemic areas or the LDC. It is the goal of both PPPs to enforce public dissemination of the research results to the widest possible extent, but they consider acquiring or otherwise enforcing IPRs when needed to ensure market access of the drug in the envisioned countries. In 3 (15%) PPPs (2 EU, 1 EU Nat),

the IP policy provides the possibility to negotiate within a given framework, 2 of them are non-profit funded, 1 is a mixed funded PPP. Only in 4 out of 20 (20%) PPP policies, support from an expert is advised in case of unsuccessful negotiations or disputes, those 4 PPPs respectively allowed or i) no room for negotiation (1 EU Nat) or ii) little room for negotiation (1 EU Nat), or iii) stated that the proposed IP rules need to be agreed upon case by case (2 Internat). Several PPPs, explicitly or less explicit, provide the role of an honest broker in the different consortia (Table 1).

Variation of IP frameworks

The current study provides a snapshot of the IP framework applied by PPPs operating in the earliest phase of the drug development cycle (Table 1). We found that there is quite some variation in the type of IP framework or knowledge sharing strategy adopted to structure the ownership, the use and the transfer of knowledge. The study allows distinguishing 3 different types of knowledge sharing strategies or IP frameworks: 1) a Partnership-focused strategy, 2) an Open Collaboration strategy and 3) a Hybrid strategy (Box 1). Nine of the 20 (45%) PPPs (2 US, 2 EU, 5 EU Nat), 6 (30%) mixed funded and 3 (15%) non-profit funded PPPs, apply a Partnership-focused strategy, wherein patenting is a possibility for safeguarding exclusive rights and the access to background IP and foreground IP is preferably preserved to the project partners. Seven (35%) PPPs (4 Internat, 3 US) apply an Open Collaboration strategy, wherein patenting is only possible in specific cases and research results are shared with the public under specific licensing conditions. Four (20%) PPPs (3 Internat, 1 US) explicitly state that a mix of strategies is possible and adopt a Hybrid Model; they allow patenting of research results, but request to preferably put the research results in the public domain (Box 1, Table 1).

Certain PPPs combine these strategies for different projects situated within one and the same PPP (i.e. a combination of different knowledge sharing strategies, depending on the specific project and the needs of the partners therein). Further, it sometimes occurs that particular projects apply a mix of strategies depending on the type of knowledge developed (e.g. the dominant IP framework within IMI is a Partnership-focused strategy, however, the U-BIOPRED consortium, a 1st Call project, applies an Open Collaboration strategy for the majority of its research results, and a Partnership-focused strategy for research tools that are being developed). In this study, we classified the PPPs based on the dominant PPP IP framework: i.e. the IP framework described in the IP policy and applied in the majority of the projects.

DISCUSSION

IPRs, in particular patents, help to structure, build and define innovation partnerships[9]. Literature suggests that the success of a PPP partly depends on the implementation and use of an IP framework [10, 11]. Negotiating clauses regarding the ownership of, access to and use of IP in precompetitive settings is not evident as technical outcomes and resulting economic values are to some extent uncertain and unclear. However, successful partnering in the early research phase depends on clear agreements on IP at the onset of the project as they introduce trust and coherence [3, 12].

The results from this study highlight the need for transparency and explicitness in IP policies. The level of information offered by the PPPs in their IP policy differs and a substantial amount of the IP policies under investigation lacks a basic level of clarity

and definitions, leaving room for ambiguity. Transparency is of utmost importance, not only for the partners in a consortium but for the public in general. Transparency reduces coordination costs, both within and outside consortia and might enable information sharing resulting in more effective partnerships [6].

The study further reveals that early-phase research PPPs apply a variety of IP frameworks or knowledge sharing strategies to structure the ownership of IP, the access to and the use of IP, to shape the partnership and to provide a frame for the different partners to make the collaboration successful. By linking different elements, such as the nature of the research (project focus), the objectives of the PPP (envisioned project deliverables) and the PPP business model and the feasibility thereof (PPP funding), we were able to distinguish 3 different types of IP frameworks: 1) a Partnership-focused strategy, 2) an Open Collaboration strategy and 3) a Hybrid strategy (Box 1).

The Partnership-focused strategy can be considered most in line with Chesbrough's 'Open Innovation' principles [13, 14] describing firm-centered innovation and the sharing of knowledge with other, specifically selected actors. This system is dominated by the for-profit sector, builds on the presence of IP, with subsequent license contracts creating restricted openness [15]. The term 'Partnership-focused' is preferred rather than 'Open Innovation' to distinguish from the firm-centered perspective, as these PPPs are partnerships wherein all partners are equal, while the 'firm-centered' connotation does not reflect the presence of a more balanced network. The Open Collaboration strategy, on the other hand, can be compared with the non-profit motivated user- and community-centered innovation, wherein universal access is

aimed for. The most extreme form of the Open Collaboration strategy is the dedication of foreground IP to the public domain.

Our study suggests that a Partnership-focused strategy is applied in almost half of the PPPs operating in early-phase research (9/20 or 45%). PPPs applying a Partnership-focused strategy tend to provide a moderate to substantial amount of IP information in IP Principles and Guidance Notes (Fig. 1-2). This facilitates information and knowledge exchange as the IP ownership, use and licensing structure are negotiated before the project initiation [4]. Nevertheless, the IP information provided by Partnership-focused PPPs is less frequently available to the larger public. This could be explained by PPPs preferring not to share the details of ownership and access rights with non-participants. Due to the substantial amount of IP information, clear definitions, templates and guidelines, the partners, who might become potential competitors in a later stage of drug development, are more supported and protected with respect to downstream development.

Patenting marketable research results is rather common, and if not patentable, alternative protection is considered. The Partnership-focused PPPs generally apply a private ownership structure (i.e. background IP remains with the owner, and the idea generator is owner of the foreground IP) and a private access structure (i.e. the consortium members acquire preferred and conditional access to the background and/or foreground IP) (Fig. 1). In this way, partners are able to build a unique IP portfolio, at reduced cost and in less time compared to working in isolation [11].

In the study, three PPPs applying a Partnership-focused licensing strategy deviate from this because ownership of the foreground IP is (partly) assigned to the PPP

(SC4SM and 2 PPPs that wished their IP policy to remain confidential). Becoming (co-)owner of the foreground IP allows the PPP to build a strong technological base instrumental for its sustainability [11].

In Partnership-focused PPPs there is a restricted openness; those PPPs apply an IP policy that clearly sets out certain permission constraints. During the project, only partners within the project are allowed to access the background IP and only if needed to complete certain tasks and to develop foreground IP. There is a restricted access policy on foreground knowledge developed in the PPP; for research use and exploitation of the research results, partners are advantaged compared to third parties. Contracts, i.e. the project agreement, will be the main legal agreement to define and limit the parameters for the activities performed by the various partners. The PPPs applying this particular IP framework focus (the majority of) their research projects on diseases of affluence (Fig. 1-2). These PPPs envision the development of drug development tools, as well as drugs, therapies and diagnostic tests or a mix of those deliverables (Fig. 2), and the majority of these PPPs (6/9) are funded by both for-profit as well as non-profit institutions (mixed funded) (Fig. 1).

The Partnership-focused PPP is an investment friendly collaboration model as the preferred access is a major incentive for the (industrial) partners [3]. Although precompetitive PPPs intend to conduct early-phase research projects wherein platform technologies are built and basic research questions are answered, rather than setting the development of drugs or therapies as the objective, the idea of gaining access to IP in a later stage of drug development is appealing [3].

On the other end of the contingency perspective, there are 'Open Collaboration PPPs' wherein the main target is to share the foreground IP resulting from the PPP project with a broad research community, sometimes even with the public in general (Fig. 1-1). The foundations for 'open' sharing of research results were laid as a response to the proprietary approach to DNA sequencing [16, 17]. Different forms of Open Collaboration, such as Open Source, Open Access and Open Transfer were a reaction to mitigate the effect of patent thickets [6, 18, 19]. Several collaborative projects are aimed at solving the problem of patent thickets over key technologies, guaranteeing that biotechnology tools are openly available for scientists and solving the problems in underserved communities [20].

The study shows that sharing with a broader community entails a specific license signed by a user, whereas dedicating research results to the public domain entails that nobody can be excluded from having access to or being able to use the public information. This type of IP framework includes different forms of 'Open' models, such as Open Source PPPs (e.g. OSDD), Open Access PPPs (e.g. SGC) and PPPs applying the Commons Principles (e.g. Sage). The Open Collaboration IP framework applies a private ownership-public access logic. Although the PPPs provide open access to the research results to its users, the use is limited by predefined boundaries. In the majority of the PPPs, this open way of sharing information within the consortium and with a broader community is organized by means of an 'open entry' license model, which then specifies the level of access to the community and their freedom-to-operate. The 'open-entry' license can be provided by, for example, ticking an 'I agree to the PPP license' box before accessing the research results or by creating a user account whereby you clarify your identity as researcher. Often,

research results can be improved, modified and used for (non-)commercial purposes, but the modified and improved results need to be provided to the PPP, or, when patent applications are filed, no blocking of the PPP's activities are allowed. 'Open' does not necessarily mean that there are no patents (or other forms of legally protected IP). Patenting research results is accepted in specific cases.

None of the PPPs analyzed applies the most extreme form of Open Collaboration, i.e. the Public Domain Strategy, whereby research results are put systematically in the public domain and no formal agreements are needed to gain access to the research results. The most extreme case of an Open Collaboration IP framework in this study is the International HapMap Project coordinated by The SNP Consortium (TSC) wherein it is claimed that no patent applications will be filed related to the HapMap project core, no blocking of HapMap data is allowed and only patent applications on SNPs or haplotypes outside the project core can be filed. Another example of this openness in sharing research data and materials is the Structural Genomics Consortium (SGC), an Open Access PPP claiming that 'SGC will not perform projects where patent applications are a deliverable'.

Investment in such Open Collaboration Strategy forms of PPPs by commercial entities seems less likely as foreground IP resulting from any PPP's information needs to be provided to the PPP, or if modified results are patented, no strategic blocking of the PPP's activities is allowed. The study reveals that the majority of the PPPs applying an Open Collaboration model are focusing on diseases of affluence (6/7) (Table 1, Fig. 1-2). However, we notice that this IP framework is applied when the envisaged project deliverables are research tools, platform technologies, shared databases and

predictive models; upstream research results leading to precompetitive biotechnology tools aimed at speeding up drug development. The deliverables of these PPPs have one common characteristic; commercialization of drugs (at this stage) is not (yet) the primary objective. When it concerns research in the field of diseases of affluence, the competition to develop research tools such as specific models, probes, assays developed for specific tests is high, and the cost implications of patenting can be a hurdle for filing such patents as it is not clear yet which tool might trigger the 'winning pathway' leading to a solution for the disease.

Research in the field of PRNDs is inextricably characterized by unpredictability, uncertainty and risks. There is an unknown distribution of probability and a horizon for return on investment which is considerable. Due to the lack of predictability in terms of business strategy, private ownership might not work. The result is a market failure, wherein PPPs, a collaborative effort of both private and public partners, can offer a potential solution. However, PPPs need to provide enough incentives for the pharmaceutical industry to invest in PRNDs. Variation in terms of IP frameworks whereby IP policies enable further investments seems hence not only appropriate, they can be even considered as preferred/desired.

Between the Partnership-focused strategy and the Open Collaboration strategy, one can situate PPPs applying a Hybrid strategy. Those PPPs state in their IP policy that the IP framework applied is negotiated on a case-by-case base. The PPPs applying a Hybrid strategy provide a rather limited IP policy with respect to ownership, use and transfer of knowledge and materials (Fig. 1-2). The PPPs explicitly state that it is preferred to put research results in the public domain, however, when it is needed to

obtain the project objectives, patenting is possible, private ownership will be assigned and a conditional licensing structure will be negotiated (Table 2). Access to the research results outside the consortium, however, is strongly preferred and freedom-to-operate is nevertheless restricted through licensing. This Hybrid strategy is an interesting IP framework for development of downstream diagnostic tests and drugs for PRNDs, as the project agreement including the IP clauses can be negotiated with the (industrial) partners whereby more (commercially interesting) incentives can be provided to convince pharmaceutical companies to invest in projects addressing the PRNDs compared to an Open Collaboration strategy. Hybrid PPPs are all non-profit funded PPPs.

The variation between a more restricted IP framework (Partnership-focused strategy) and an open IP framework (Open Collaboration strategy) seems justified given the heterogeneity of the partners, each with their own objectives and needs. This variation in IP ownership and use models is necessary to serve the PPP's mission and to obtain its objectives. PPPs wherein downstream development results (drugs and diagnostic tests) are targeted tend to apply an IP sharing strategy wherein access to foreground IPRs and freedom-to-operate (FTO) are permission-constrained and preferably negotiated with the consortium partners (Partnership-focused strategy). PPPs wherein upstream research results (research tools and platform technologies) or PRND-specific downstream products are developed are more likely to adopt an IP framework that allows sharing IPRs with a broader (Open Collaboration strategy). Both models imply benefits and drawbacks, strengths and weaknesses. Hybrid strategies, with preferred public release of research results unless patenting is necessary to secure market access or to engage the commercial partner, become

deployed when either model is appropriate to proceed the project. As such, we argue for a contingency perspective. Dependent on the research focus, the business strategy and the feasibility thereof, different scenarios for sharing knowledge are and should be applied.

A second level of variation observed within this study, relates to the transparency and explicitness of the IP policies. A review of existing IP frameworks of PPPs reveals that transparency is often missing in terms of IP policies of early research phase PPPs. Further, the majority of the IP policies lack basic information on IP concepts such as definitions of background IP and foreground IP, and rules on ownership thereof, access thereto and use thereof. Even when knowledge is shared in the broadest possible way, IP ownership rules, access and user rights need to be addressed explicitly in order to proceed effectively. Moreover, standardization of the definitions for the different elements discussed could ease the potential to exchange data and materials between different PPPs and avoid legal interoperability issues resulting in less coordination costs. While the different stakeholders in the partnership agree that transparent and broadly defined IP frameworks are indispensable for successful project negotiations and to build trust [3, 7, 21], few PPPs apply such a clear and defined framework. Transparency and clear guidelines for IP management are crucial for trust creation amongst the partners in the consortium. A complete publicly available set of policies and procedures allows potential partners to assess their roles and responsibilities, and to get insight into the rewards and expectations they might expect from participation [21].

Hence, it is recommended for biomedical PPPs to include in their IP policies a basic level of information regarding IP concepts such as background IP and foreground IP, the ownership and use thereof and access thereto. There is not a single perfect IP framework applicable to the different PPPs operating in early phase research. Depending on the focus and the objectives of the PPP, variation in the customization to negotiate key IP elements exists and seems appropriate: customization of the IP policy is relevant to incentivize participation in the PPP.

Figure Legend

Figure-1 The IP framework as defined in the IP policies of the PPPs analyzed.

Figure-2 Link between the IP framework as defined in the IP policies of the PPPs analyzed, the information provided in the IP policies, the project focus and envisioned project deliverables.

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DISCLOSURE STATEMENT

The authors declare that they have no competing financial interests.

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Table 1: Non-exhaustive list of PPPs performing activities in the early research phase in the life science R&D sector[2].

Public-Private Partnership	Abbreviation	Start Date	Geographic scope	Research phase				IP Policy publicly available	available upon request	IP framework	Project focus	Project deliverables**	PPP Funding
				PreC	POC	PD	PA						
Alzheimer's Disease Neuroimaging Initiative	ADNI	2004	US	x					x*	Open Collaboration Strategy	Affluence	Tools	Mixed
Biotechnologies Wallonie Innovation	BioWin	2006	National	x					x	Partnership-focused Strategy	Affluence	Mix	Non-Profit
Center for Translational Molecular Medicine	CTMM	2007	National	x	x	x		x		Partnership-focused Strategy	Affluence	Mix	Mixed
Drugs for Neglected Diseases Initiative	DNDi	2003	International	(x)	x	x	(x)	x		Hybrid Strategy	PRNDs	Drugs	Non-Profit
European Framework Programmes	FP7	2007	EU	x				x		Partnership-focused Strategy	Mixed	Mix	Non-Profit
Innovative Medicines Initiative	IMI	2008	EU	x	(x)			x		Partnership-focused Strategy	Affluence	Mix	Mixed
Medicines for Malaria Venture	MMV	1999	International	(x)	x	x	x	x		Hybrid Strategy	PRNDs	Drugs	Non-Profit
Osteoarthritis Initiative	OAI	2001	US	x				x		Open Collaboration Strategy	Affluence	Tools	Mixed
Observational Medical Outcomes Partnership	OMOP	2007	US	x				x		Hybrid Strategy	Affluence	Tools	Non-Profit
Open Source Drug Discovery	OSDD	2008	International	x	x	x		x		Open Collaboration Strategy	PRNDs	Mix	Non-Profit
Stem Cells for Safer Medicines	SC4SM	2007	National	x				x		Partnership-focused Strategy	Affluence	Tools	Mixed
Sage Bionetworks Commons	Sage Bionetworks	2009	International	x				x		Open Collaboration Strategy	Affluence	Tools	Mixed
The SNP consortium	TSC	1999	International	x				x		Open Collaboration Strategy	Affluence	Tools	Non-Profit
The Biomarkers Consortium	The Biomarkers Consortium	2006	US	x				x		Partnership-focused Strategy	Affluence	Tools	Mixed
The RNAi Consortium	TRC												
Diabetes Genetics Initiative		2003	US	x	x			x		Open Collaboration Strategy	Mixed	Tools	Mixed
Structural Genomics Consortium	SGC	2004	International	x					x	Open Collaboration Strategy	Mixed	Mix	Mixed
WIPO Re:Search	WIPO Re:Search	2001	International	x	x	x	(x)	x		Hybrid Strategy	PRNDs	Mix	Non-Profit
XXX	XXX	2006	National	x	x	x			x	Partnership-focused Strategy	Mixed	Mix	Mixed
XXX	XXX	2007	National	x					x	Partnership-focused Strategy	Affluence	Drugs	Mixed
XXX	XXX	2005	US	x					x	Partnership-focused Strategy	Mixed	Tools	Non-Profit

[2] XXX: PPPs that requested their name and IP policies to remain confidential

X*: answer via email: "In terms of discovery, any findings with IP would need to be patented by the investigators prior to publication. And 1) we have no formal policy and 2) in the absence of any policy, the policies of the individual universities or companies would hold."

Project deliverables**: Tools = drug development tools, such as technology platforms, (software) models, databases, research tools or materials; Drugs = drugs, diagnostic and therapeutic materials, and therapies; Mix = envisioned project deliverables is a mix of research tools and drugs

Table 2: Information regarding terms and conditions for IP as specified in IP documents of 20 PPPs operating in the early research phase[3]

Research focus of PPP	Neglected (4)				Affluence (3)			Neglected + Affluence (5)					Affluence (8)							
Funding source of PPP	Non-Profit funding (9)									Mixed funding (Non-Profit + For-Profit) (11)										
PPP acronym	OSDD	MMV	DNDi	WIPO Re:Search	BioWin	OMOP	TSC	FP7	XXX	XXX	SGC	TRC	IMI	CTMM	XXX	Sage	OAI	SC4SM	Biomarker	ADNI
IP framework	Open collaboration strategy	Hybrid strategy	Hybrid strategy	Hybrid strategy	Partnership-focused strategy	Hybrid strategy	Open collaboration strategy	Partnership-focused strategy	Partnership-focused strategy	Partnership-focused strategy	Open collaboration strategy	Open collaboration strategy	Partnership-focused strategy	Partnership-focused strategy	Partnership-focused strategy	Open collaboration strategy	Open collaboration strategy	Partnership-focused strategy	Partnership-focused strategy	Open collaboration strategy
No information related to ownership/access rights																	x			
Background ownership info	x			x	x	x		x	x	x			x	x	x	x		x	x	
remains with owner				x	x	x		x	x	x			x	x	x	x		x	x	
Sideground ownership info									x				x		x					
Foreground ownership info	x	x	x	x	x		x	x	x	x	x	x	x	x	x	x		x	x	x
for PPP	x								x									x		
idea generator				x	x		x	x					x	x	x	x			x	x
joint					(x)*			x	x	x			x	x	x				x	
no researcher/institution's ownership allowed											x									
Background access rights info	x			x	x	x		x		x			x	x				x	x	
for completion project				x	x			x		x			x	x					x	
for research use	x			x		x		x					x						x	
to practice foreground IP				x				x										x		
for direct exploitation				x						x			x	x						
Foreground access rights info	x	x		x	x			x	x	x		x	x	x	x			x	x	
for completion project	x			x				x					x	x	x			x		
for research use	x			x	x			x	x	x			x	x	x			x		
to practice foreground IP	x			x				x	x					x	x					
for direct exploitation	x			x					x	x			x	x	x			x		
IP Management in PPP project	x	x	x	x		x		x	x	x				x	x					
Room for negotiation	No	Case-by-case	Case-by-case	Case-by-case	x			x		Little			x	No	No			Little		
Expert support			x	x						x				x						
IP Mgmt	CSIR		Executive Director or Assignee	DB hosted by WIPO		FNIH			Coordating Committee	Patent Coordinator				Project IP Manager	Project IP Manager					

[3] (x)*: joint ownership is only possible in exceptional circumstances, ownership by the individual partner is favored.

Box 1: Different IP frameworks in PPPs

Knowledge sharing strategies applied in biomedical PPPs				
Conditions		Partnership-focused strategy	Hybrid strategy	Open Collaboration strategy
Possibility to patent		Yes	Yes, but results preferably in public domain	Yes, but with limitations specified
Access	Access mechanisms / legal basis	Contractual framework based upon IP rights: Contracts (e.g. Project Agreement) including different clauses regarding patents and other industrial rights	Contracts & IP in case of Partnership-focused strategy, licenses in case of Open Collaboration strategy	Contractual framework based upon IP rights: (viral) licenses (e.g. Open Access Protocol, Creative Commons or Copyleft Licenses), to help continue the virtuous cycle of research
	Target group	During project: project participants After project termination: project participants, affiliates and/or defined third parties	During project: project participants, consortium members or public After project termination: PPP participants, affiliates and/or defined third parties	All
	Duration	Limited/defined	Limited to undefined	Undefined
Project focus		Profit- or non-profit-driven research, mainly focusing on diseases of affluence	Non-profit driven research, focusing on PRNDs	Profit- or non-profit-driven research, focusing on diseases of affluence and/or PRNDs
Envisioned project deliverables		-Biotechnology tools (upstream research results) -Drugs, therapies and diagnostic tests for diseases of affluence (downstream research results) -A mix of tools and drugs for PRNDs and diseases of affluence (downstream research results)	-Biotechnology tools (upstream research results) -Tools and drugs for PRNDs (upstream and downstream research results)	-Biotechnology tools (upstream research results) -Diagnostic tests and drugs for PRNDs (downstream research results)
PPPs wherein the strategy prevails		IMI, BioWin, The Biomarkers Consortium, FP7, SC4SM, CTMM, 3 PPPs that expressed for their IP policy to remain confidential	MMV, DNDi, OMOP, WIPO Re:Search	SGC, SAGE, TSC (HapMap), OSDD, OAI, TRC, ADNI