

# **Practical Considerations for Collaborative Research Between the Pharmaceutical Industry and External Investigators**

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# 1 ABSTRACT (290 words)

2 Traditionally, clinical research has been conducted via either industry sponsored studies or non-  
3 industry investigator sponsored studies. Collaborative Research provides a relatively new  
4 mechanism for industry and non-industry partners to work together in the pursuit of effective  
5 and safe treatments for the patient. The aims of this article are to provide both industry and  
6 non-industry investigators with a greater insight into the complex processes that are currently  
7 employed by industry when entering into Collaborative Research agreements, and to  
8 encourage consistency and transparency in approach across companies.

9 In Collaborative Research, instead of being limited to providing funding and/or product, the  
10 industry partner contributes expertise complementary to that of the non-industry partner, who  
11 is the sponsor of the study. Collaborative Research may be conducted before, during or after  
12 regulatory approval of a drug or medical device, and may be interventional, observational or  
13 preclinical.

14 A collaboration requires appropriate process and governance frameworks to be established in  
15 order to be successful. Important considerations include the routes for submitting a request,  
16 the review and approval process, due diligence criteria, budgeting and contracting processes,  
17 permissible interactions during the execution of the research, the closing out of the research,  
18 and dispute resolution. It is also necessary to have in place an agreed communication strategy  
19 and a risk control framework. Clear and specific contract language around roles and  
20 responsibilities, intellectual property, rights to data, registration and disclosure of publications,

- 1 and an understanding of adverse event reporting procedures are other critical facets of
- 2 Collaborative Research that are essential to avoid delays and disputes.
- 3 With no global standards for Collaborative Research, it is important that partners establish
- 4 practical procedures, good ongoing communication, alignment of goals, and transparent
- 5 interactions and disclosure to jointly advance the science of new, safe and effective therapies.

# 1. INTRODUCTION

Increasingly demanding research and regulatory environments, the extensive resource requirements required for research and development, and the drive to seek more novel therapies<sup>1</sup> have led the health care industry to turn to collaborations with external investigators to support research in innovative and cost-effective ways.<sup>2,3</sup> Large-scale collaborations between industry and academia, such as the Center for Biomedical Innovation (between Sanofi and MIT) and the Novo Nordisk Research Centre Oxford (between Novo Nordisk and the University of Oxford), have broad remits of advancing knowledge of human health, developing therapeutic applications and conducting translational research.<sup>4-6</sup> However, most collaborations are on a smaller-scale, involving an individual academic institute or Health Care Organization (“HCO”) with a lead investigator, and relating to a specific study.

Both partners in a research collaboration share the goals of improving patient health and safety, increasing understanding of the therapeutic area, and disseminating findings via timely disclosure of results and publications. These shared goals must be balanced with partner-specific objectives, which may be different or even competing.

For example, non-industry investigators are typically focused on finding reliable sources of funding and obtaining interesting and novel pharmacological compounds with which to conduct their research.<sup>7</sup> On the other hand, the incentive for industry collaborators may be to access skills and resources that are unavailable within their own organization and can facilitate research complementary to internally-driven research at bringing new drug candidates or medical devices to the market, and enhancing their safe, effective and appropriate use.<sup>8</sup>

Research practices may also differ between partners not least the milestone-driven research model employed by industry is anathema to many non-industry investigators.<sup>8</sup> Collaborative Research contracts and processes can be daunting to develop and difficult to navigate for investigators. In the UK, the National Institute for Health Research developed the model Industry Collaborative Research Agreement (“mICRA”) to facilitate and standardize collaborations between private and public organisations.<sup>9</sup> Therefore, for a collaboration between an investigator and industry to be successful, it requires appropriate communication and governance frameworks to be established and agreed to at the beginning. A crucial feature of Collaborative Research is that while either of the collaborating parties can initiate the research, the Collaborative Research is led by the non-industry sponsor of the research. Other key responsibilities, such as the registration of study protocols, reporting of results, timelines, and ownership of data should be clearly defined and documented.<sup>8,9</sup> Furthermore, appropriate contractual safeguards are essential to protect the credibility of both partners against potential accusations that the collaboration and financial support of the research is simply a means of influencing doctors’ prescribing practices.<sup>10</sup> In most collaboration situations, however, it falls to the industry partner to ensure that appropriate processes and contractual arrangements are in place, although differences in approaches between companies can add to the challenges faced by non-industry investigators. The aim of this article, therefore, is to provide the research community, including both industry and non-industry investigators, with greater insight and alignment into the complex, but necessary Collaborative Research processes employed by industry, to encourage greater

consistency and transparency in approach by different companies. To aid in this shared understanding, we will provide practical guidance for both partners considering Collaborative Research.

## 2. DEFINING COLLABORATIVE RESEARCH

It is important for all partnering organizations to define from the outset what qualifies as Collaborative Research. Unlike Investigator Initiated Research (IIR, also known as Investigator Sponsored Studies or Investigator Sponsored Trials), in which the involvement of the industry partner is limited to providing funding and/or study product, in Collaborative Research, the industry partner contributes expertise complementary to that of the non-industry partner organisation. This can take the form of providing input to the study design, protocol, statistical analysis plan, clinical study report and publication. As noted earlier, it is also critical that the decision-making process is clearly understood early on. For example, will all parties be involved to the same degree in developing the research program? Who will be the lead collaborator and act as the sponsor of the research, responsible for ensuring that the study is conducted in accordance with the protocol, all applicable laws and regulations, and good practice quality guidelines such as, Good Clinical Practices and Good Laboratory Practices (collectively, GxPs)? Table 1 provides a comparison of the key responsibilities of the industry and non-industry partners in Company Sponsored Research, Collaborative Research and Investigator Initiated Research.

**Table 1.** Comparing key responsibilities in Company Sponsored Research, Collaborative Research and Investigator Initiated Research

Key responsibilities	Company Sponsored Research	Collaborative Research	Investigator Initiated Research
Initiator of study proposal	Industry/Company	Industry or Non-industry partner/ investigator	Non-industry investigator <i>must not be solicited by the Industry partner</i>
Regulatory responsibility/ sponsor	Industry/Company	Non-industry investigator	Non-industry investigator
Study objectives	Industry/Company	Both parties	Non-industry investigator, but may be aligned with Industry Objectives
Study design	Industry/Company	Non-industry partner driving the design and input from both parties	Non-industry investigator
Protocol design/ development	Industry/Company	Non-industry partner driving the development and input from both parties	Non-industry investigator
Study Execution	Industry/Company	Non-industry partner driving the execution but potential input from industry partner	Non-industry investigator
Data ownership/sharing (including alignment with General Data Protection Regulation)	Industry/Company	As per agreement	Non-industry investigator
Data reporting (including registration and clinical study report disclosure and publications)	Industry/Company	As per agreement	Non-industry investigator
Ownership of intellectual property	Industry/Company	As per agreement	Non-industry investigator

1 When developing a Collaborative Research agreement, it is imperative for the participating  
2 organizations to understand why the proposed research objectives may not be achievable without  
3 the partnership agreement. Collaborative Research provides a basis for industry partnerships  
4 with academic research organizations, government agencies, networks, cooperative groups and  
5 other appropriate HCOs. Having a Collaborative Research operational framework allows a well-  
6 defined approach to research within appropriate regulatory and health care compliance  
7 boundaries, while also providing flexibility to contract to each party's strengths and execute  
8 accordingly. Each partner can bring to the table a different contribution, whether it be specific  
9 expertise, patient access, scientific leadership and excellence, or access to equipment and  
10 analytical techniques. Thus, a collaboration provides the opportunity for all contributing  
11 partners to access areas of research of mutual interest that would otherwise be impossible,  
12 whilst appropriately shaping the design of the research for faster access to the results,  
13 interpretations, and sharing these more rapidly with the broader medical and clinical  
14 communities.

15 Collaborative Research arrangements do not, however, come without risks. If either partner  
16 fails to fulfil their obligations, this could have a profound impact on outcomes, and poor data  
17 could even impact future regulatory submissions. Since most regulatory agencies do not, to  
18 date, officially recognize collaborations in terms of sponsorship responsibilities and obligations,  
19 industry partners risk being considered a single *de facto* sponsor of a given trial and being  
20 forced to assume all regulatory responsibilities. Furthermore, there is a risk that Collaborative  
21 Research may be perceived as pre-approval or off-label promotion, especially when it involves  
22 a product in the early stages of its lifecycle. Clear and specific contract language around roles



and responsibilities, intellectual property, rights to (particularly patient-level) data, registration and disclosure of publications, adverse event reporting, and other critical facets of Collaborative Research are essential if delays and disputes are to be avoided, particularly when there are more than two partners involved. Ultimately, it is up to each partnering organization to conduct their own internal benefit/risk assessments before agreeing to participate.

### 3. COLLABORATIVE RESEARCH DIFFERS BY STUDY TYPE AND REGION

Collaborative Research may be conducted before, during or after regulatory approval of a drug or medical device, and the study design may be interventional, observational or preclinical. The type of research and its intent introduces different considerations for how to negotiate and execute the collaboration, and each type of study has their own benefits and challenges. For example, pre-clinical studies may be undertaken during early stages of drug development, while interventional studies may be used to support a regulatory submission. Non-interventional or observational Collaborative Research is often pursued to fulfil post-approval commitments or to support the utilization of a product for a recommending body or advisory committee (e.g., The Advisory Committee on Immunization Practices (“ACIP”)).

#### *Interventional studies*

Collaborative Research has been most readily adopted in oncology and HIV therapy areas, both pre- and post-regulatory approval, and has supported regulatory submissions. In many cases, the non-industry sponsor was a government agency or a cooperative group, such as the NIAID (National Institute of Allergy and Infectious Diseases), the NCCN (National Comprehensive Cancer Network), the American College of Radiology Imaging Network (“ACRIN”) and the

European Organisation for Research and Treatment of Cancer (“EORTC”). In such cases, the collaborative approach brings together scientific and technical expertise, facilities and infrastructure necessary to conduct the research which is not entirely available within the individual organizations.

Importantly, it is the non-industry partner that will be the regulatory sponsor and will initiate and take responsibility for the clinical trial.<sup>11</sup> The sponsor holds the appropriate regulatory authorisation to conduct the research, such as obtaining an Investigational New Drug (“IND”) application or European Clinical Trial Application (“CTA”) and will be responsible for all regulatory aspects of the study, as well as for its implementation. Industry can contribute by providing regulatory support, such as allowing the regulatory agencies the ability to cross-reference the industry filing. Industry can also provide the sponsor with various types of support including, but not limited to, funding, equipment and drug and/or device to support the interventional research. Drug supply can be an important budgetary element of the study. It is also important for industry to provide the sponsor with regular updates to the list of Suspected Unexpected Serious Adverse Reactions (“SUSARs”) for each product. In some instances, the non-industry sponsor may need to utilize a Clinical Research Organization (“CRO”) or other qualified third party. The CRO will be selected and managed by the non-industry sponsor but should also be aligned with standards of the industry partner.

# 1 *Observational studies*

2 Observational studies are often run to assess burden of disease, or the safety or effectiveness of  
3 marketed products in routine clinical practice. Although the investigator is required to obtain  
4 ethics approval for an observational study, there are fewer regulatory obligations than for  
5 interventional research, which can make the lead collaborator more difficult to differentiate.  
6 Therefore, when an observational study is conducted using a Collaborative Research model, it is  
7 especially important that the respective roles and responsibilities of the industry and non-  
8 industry partners are clearly defined upfront and outlined in the contract.

9 It is important for the non-industry sponsor to maintain responsibility for all aspects of the  
10 collaboration, or to document clearly the justification for the industry collaborator taking on  
11 specific responsibilities (e.g., preclinical expertise in sample analysis). Observational study  
12 scenarios where Collaborative Research may be appropriate include industry working with  
13 universities to access electronic medical records for regional/local registries, and cooperative  
14 groups for prospective collection of routine clinical practice data. In future, Collaborative  
15 Research agreements may be one of the few compliant approaches for collecting and analysing  
16 digital data from third-party custodians.

# 17 *Preclinical research*

18 In most cases, preclinical studies conducted outside a company's own research laboratories are  
19 conducted on a fees-for-service basis or result from unsolicited proposals from external  
20 investigators for IIR. However, there may be situations where Collaborative Research may be  
21 appropriate, such as where specific materials (e.g., a pharmacological compound) or industry

expertise is required to conduct the research. These responsibilities, along with intellectual property rights, must be clearly outlined in the agreement.

### *Regional differences*

Ideally, contractual requirements for Collaborative Research should not vary across regions. However, divergences between countries and regulatory authorities are emerging. For example, the provision for co-sponsorship of clinical trials on medicinal products for human use within the European Union (specifically, the European Medicines Administration of 536/2014 Article 72<sup>12</sup>), is not reflected by other regulatory authorities, such as the U.S. Food and Drug Administration (“FDA”). Until there is more global acceptance and clearer understanding of the implications and risks of co-sponsorship, industry partners will generally continue to avoid entering into co-sponsorship partnerships. Also to be considered are differences between countries in restrictions on industry access to patient data (e.g., Sweden and Taiwan), and 2018 changes to the US regulations concerning International Review Board obligations to protect human subjects.<sup>13</sup> Finally, in some less developed regions, funds can be provided for leasing equipment or proration costs for the duration of the study when the availability of standard equipment, such as refrigerators, is limited.

More general issues to be considered when engaging in collaborations outside of the USA, Western Europe and other regions with established research bodies, include research capabilities and infrastructure of the organization, determining sponsorship and coordinating center responsibilities (multi-country studies), tax implications and quality control for import/export of drug supplies, data requirements and consenting (i.e., General Data Protection Regulation (GDPR) requirements) and adverse event reporting. When engaging in regional or

local collaborations, translations of key collaboration documentation, such as the protocol, informed consent document and research agreement, will promote understanding and transparency, as well as assisting in the event of an internal or external audit.

#### 4. COLLABORATING PARTNERS SHOULD AGREE AIMS AND RESPONSIBILITIES

Before engaging in research collaborations, it is critical that both parties should be aligned with the intent and purpose of conducting the research. Expectations in terms of study conduct and the quality of data generated can be very different depending on its intended use. For example, whether the data will be used to support a regulatory submission, for generation of medical evidence, or for publication purposes only. It is important for collaborative parties to be completely transparent about their expectations, capabilities, infrastructure and ability to carry out the intended research. Collaborations allow the parties to contribute to the success of the proposed research. Developing a task ownership matrix or RACI matrix (Responsible, Accountable, Consulted, Informed) can be a useful tool in defining the roles and responsibilities of each party, especially in complex clinical trials which may involve multiple sites in multiple countries and involve the use of third-party vendors.

If the purpose of the research is to support a regulatory submission, the industry partner is required to guarantee the quality of the data, even though the non-industry partner may own it. The company may, therefore, need to conduct due diligence activities in advance, such as reviewing and evaluating the partner's governing processes and systems for study conduct and data management. The verification that the partner will follow International Conference on Harmonisation Good Clinical Practice, including following proper documentation practices, is

especially important because they may be audited by the sponsor country's regulatory agency. Other factors to consider include monitoring plans, consenting practices and ensuring that the use of the data is disclosed to study subjects in the informed consent documents. It is important for the non-industry sponsor to understand that their industry partner may need to conduct periodic audits and assess quality plans, especially for studies being utilized in regulatory submissions. If quality issues are found, remediation by the non-industry sponsor is expected. However, this may result in increased costs and resources. The non-industry sponsor should also be prepared to respond to the industry collaborator in case of regulatory authority queries once the data are submitted.

As explained above, once aligned on the intent and purpose of the research, it is important to understand and establish the expected roles and responsibilities of each party. Will any responsibilities be delegated to a third party and, if so, is the third party qualified to do the work? What oversight will be put in place and how frequently will it occur? Who will be responsible for data analysis and the development of the study report? For example, in the case of a regulatory submission, the industry partner may be best placed to draft the clinical study report, in order to ensure that the requirements set forth by the agencies are met.<sup>14,15</sup>

## 5. PRACTICAL GUIDANCE

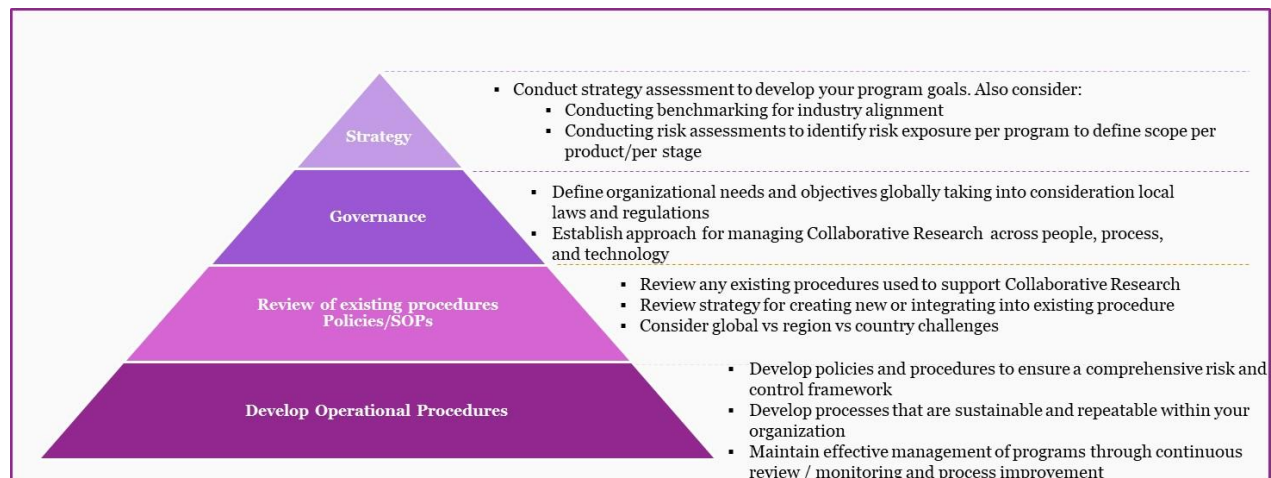
The challenges, risks and concerns outlined above highlight the need to bring structure and standards to the management of Collaborative Research in the form of formal procedures. Collaborative research is complex and, when considering the most appropriate way to support research, the industry partner should consider the rational for pursuing Collaborative Research

rather than a company sponsored study, which may be the more practical option. This is especially true for observational studies, where establishment of the sponsor of the research may be difficult to establish. It is also critical to ensure that both industry and non-industry partners have sufficient resources to support the Collaborative Research.

### *Establish standards and procedures*

When experience of managing Collaborative Research is limited, the industry partner may utilize existing policies and procedures (e.g., Standard Operating Procedures [“SOPs”] such as those employed for managing IIRs). While the non-industry investigator is the sponsor for both IIR and Collaborative Research, the existing IIR SOP would need to be enhanced to address the collaborative nature of the research. Alternatively, the industry partner may develop new policies and/or SOPs tailored specifically for Collaborative Research.

Key consideration for developing SOPs in support of managing and executing Collaborative Research are summarized in Figure 1. Other considerations include whether the SOP will have global or regional reach, and whether a single SOP will cover all Collaborative Research study types and all areas the industry partner’s organisation.



**Figure 1.** Summary of potential steps for setting up the framework, governance and SOPs to support collaborative research

### *Establish a comprehensive approach*

A comprehensive high level strategy, to be shared internally and externally, will define the industry partner's position on considering Collaborative Research proposals, including the route for submitting a request, who will be involved in the review and approval process and how will it be conducted, what are the due diligence criteria, what is the budgeting and contracting process, and what are the level of permissible collaborations and interactions during the execution of the research and closing out of the research. Possible tools that may facilitate a standardized and consistent approach include a checklist for confirming that the research is collaborative, as opposed to company-sponsored research or IIR, and contract templates for defining and documenting roles and responsibilities of each party.



1 *Ensure appropriate governance and oversight strategy*

2 Complaint practices and clarity may be aided by the creation of a dedicated Collaborative  
3 Research management group within the industry partner organization which will be responsible  
4 for transition oversight (if applicable), review and approval of proposals/protocols, strategy,  
5 management and execution, contracting, funding decisions, and budget ownership. Such a  
6 group would ensure that that Collaborative Research aligns with the annual strategic medical  
7 plan. Importantly, a firewall must be established between the commercial arms of the  
8 organisation (Marketing and Sales) and the Collaborative Research management group.

9 *Monitor and review procedures to support Collaborative Research*

10 All stakeholders should contribute to the development of overall procedural strategy and  
11 governance, and the initial strategy and the procedures should be reviewed after 6-to-12  
12 months to monitor whether early decisions and objectives are delivering the expected  
13 outcomes. When reviewing existing procedures, it is important to consider potential issues  
14 specifically related to Collaborative Research that become more apparent as the procedures are  
15 applied to multiple grants, including the type of research (interventional, observational and pre-  
16 clinical) and to consider the regional or global perspective.

17 *Develop a communications strategy*

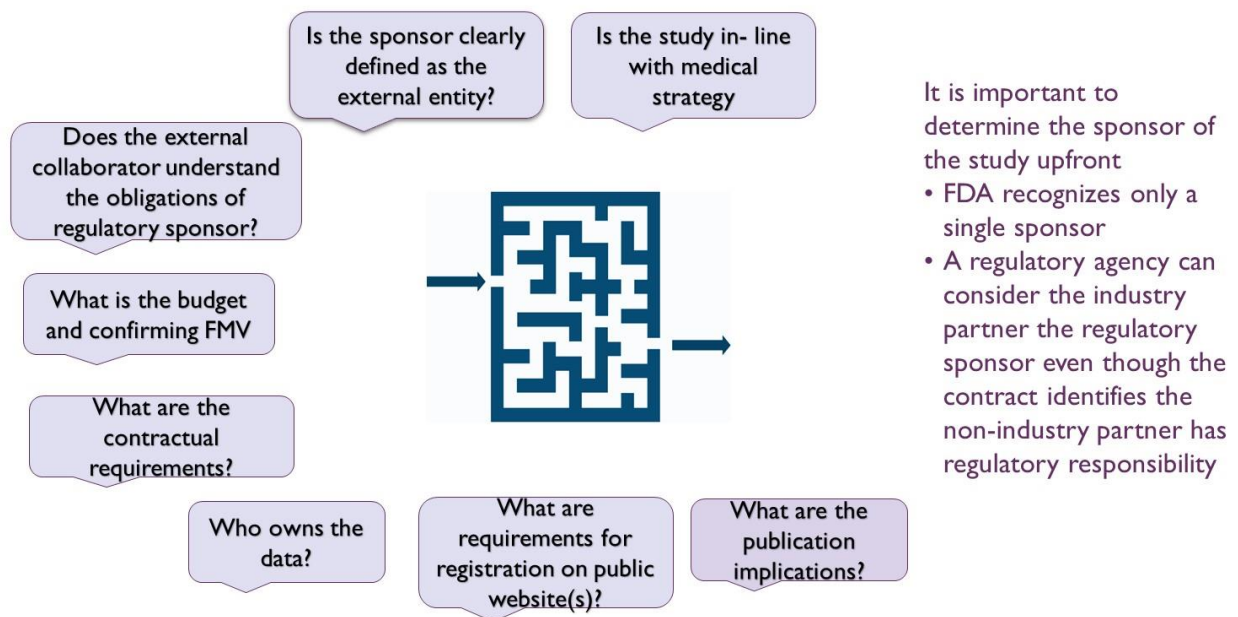
18 A key element of a Collaborative Research agreement is that communication and information  
19 sharing are clearly defined in order to minimise the risk of confusion and potential discord  
20 between the partners. Approaches to sharing information within the collaborating  
21 organisations should also be considered, particularly within the various departments of the  
22 industry partner.

1 Finally, if information is to be shared via a website or portal, the non-industry collaborator  
2 should receive appropriate training. If such a website or portal also supports IIR or sponsored  
3 studies, the Collaborative Research area must be clearly demarcated.

#### 4 *Control risks*

5 Collaborative Research procedures should include an integrated risk and control framework. A  
6 Collaborative Research proposal should be reviewed from a risk comprehensive perspective  
7 (Figure 2). There should be clear guidelines and process for appropriate interactions between  
8 collaborators, criteria for selection, debarment and due diligence checks should be established,  
9 fair market value should be applied, and the recording and archiving of decisions should be  
10 described. As discussed in the earlier sections, the industry partner should include in the  
11 contract rights to conduct audits to ensure that the Collaborative Research remains compliant  
12 with all laws, ethical considerations, existing legislation and regulations, including compliance  
13 with all Pharmacovigilance requirements and data privacy regulations.

# Collaborative Research, like all research, requires Health Care Compliance controls



**Figure 2.** Consider potential risks to the industry partner associated with participation in Collaborative Research.

## 6. SUMMARY

Collaborative Research is evolving and, while it brings a new avenue for industry and non-industry partners to work together, it brings its own challenges and risks. With no global standard on what is “Collaborative Research” in industry, non-industry or regulatory authorities, partners need to recognize that they each face different challenges, but with practical procedures, good ongoing communication, alignment of goals and transparent interactions and disclosure, Collaborative Research can enhance and advance the science of new, safe and effective therapies.

# DISCLOSURES

Cynthia Barbitsch, Mary Voehl Hirsch, Antonia Panayi and Eric Southam are employees of Pfizer, Sanofi, Shire (part of Takeda) and Oxford PharmaGenesis, respectively. Maureen Lloyd is an independent consultant providing consultancy services to the pharmaceutical industry. This work was initiated and conducted by the authors, and the views represented are their own. All authors contributed equally to the development of this article.

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