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REVIEW

Past, Current, and Future Cancer Clinical Research Collaborations: The Case of the European Organisation for Research and Treatment of Cancer

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Although collaborations between academic institutions and industry have led to important scientific breakthroughs in the discovery stage of the pharmaceutical research and development process, the role of multistakeholder partnerships in the clinical development of anticancer medicines necessitates further clarification. The benefits associated with such cooperation could be undercut by the conflicting goals and motivations of the actors included. The aim of this review was to identify and characterize past, present, and future stakeholder partnership models in cancer clinical research through the lens of the European Organisation for Research and Treatment of Cancer (EORTC). Based on the analysis of several landmark EORTC trials performed across the span of three decades, four existing models of stakeholder cooperation were delineated and characterized. Additionally, a hypothetical fifth model representing a potential future collaborative framework for cancer clinical research was formulated. These models mainly differ in terms of the nature and responsibilities of the partners included and show that clinical research partnerships in oncology have evolved over time from small-scale academia-industry collaborations to complex interdisciplinary cooperation involving many different stakeholders.

Academia-industry collaborations in the discovery stage of the pharmaceutical research and development process have led to major scientific advances that have benefited patients significantly.[1–3] Their rationale and challenges are well-documented,[2,4–8] and models for such partnerships have been extensively described in the literature.[1,3,7–10] However, downstream cooperation in the area of cancer clinical research remains poorly characterized. Furthermore, the complexity of translating evolutions in the field of oncology into concrete and meaningful results for patients necessitates new forms of collaboration between all relevant stakeholders.[11–15] Although industry and independent academia can both be considered key actors in the anticancer drug development process, their objectives and underlying motivations may differ substantially. For example, whereas the former mainly performs pivotal trials for the purpose of achieving regulatory approval for their products, the latter strives to tackle research questions that clinicians are facing in real-world clinical practice.[16,17] These diverging goals and motives give rise to tensions,[18,19] which could undermine the advantages associated with setting up academia-industry partnerships in the clinical development of cancer treatments. There is a lack of information available on models of cooperation that are able to overcome these tensions[13,14] and address the issues accompanying the rise of precision oncology.[14,20] In this review, we set out to identify and outline both existing and novel models for collaboration in cancer clinical research among industry, academia, and, if applicable, other stakeholders from the perspective of an academic research organization (ARO), namely the European Organisation for Research and Treatment of Cancer (EORTC). We also aimed to highlight key factors that have shaped the continuous transformation of the relationship between these actors in this field based on a detailed analysis of a number of EORTC-led clinical trials.

ROLE OF THE EORTC IN CANCER CLINICAL RESEARCH

The EORTC is a not-for-profit ARO headquartered in Brussels, Belgium. Since its founding in 1962, it has conducted over 1,400 clinical trials through its network of > 5,300 investigators and 390 institutions across 37 countries, with the explicit aim of improving survival and quality of life of patients with cancer.[21] These include many studies that have changed clinical practice and influenced treatment guidelines in the field of oncology. Although the EORTC maintains a strict policy of operational and financial independence, it has been involved in a multitude of research partnerships with pharmaceutical companies and other stakeholders over the years. This review presents an overview of how EORTC clinical research collaborations have evolved since the 1980s.

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REVIEW SCOPE AND METHODOLOGY

The premise of this review was to select and analyze clinical trials that were performed by the EORTC and which have had a major impact on the organization's interactions and partnerships with external stakeholders. The studies examined herein were chosen in consultation with clinical research experts who were employed at the EORTC in a senior management position and who had been working there for at least 20 years. This was done in order to maximize the scope and time frame of the review. The experts were individually asked to name key EORTC trials in which external stakeholders were, or conversely, were not involved as a partner. The research team then discussed the provided answers and reached a consensus on the list of studies to be scrutinized further. In total, 10 trials, all of which took place in the last 30 years, were selected (**Table 1**). Unstructured interviews were subsequently conducted between September 2017 and January 2018 with EORTC employees who had managed the organizational aspects of the relevant studies. Although certain themes of interest were identified in advance and some questions were, therefore, formulated beforehand, the unstructured nature of the interviews allowed the interviewer to explore in depth any additional topics that were brought up by the interviewees. In addition to the interviews, internal EORTC trial documents (e.g., protocols) and journal articles that were published for each included study were reviewed in detail. The selected trials were analyzed in terms of (i) the stakeholders involved, (ii) the objective(s) of the trial, (iii) the challenges experienced, and (iv) any accompanying issues that in hindsight could have been prevented or dealt with in a more efficient way. Through the synthesis of information from a variety of different sources, this approach enabled an extensive and multifaceted analysis to be undertaken of the included studies.

MODELS OF COLLABORATION

Based on the analysis of the 10 chosen trials, four existing models of collaboration between the various stakeholders involved in cancer clinical research were identified and outlined. Moreover, a hypothetical fifth model was drawn from insights obtained from the interviews. These models are visually represented in **Figure 1** and described below. Note that the years between brackets indicate the decade(s) in which each model first emerged. All models continue to exist beyond their inception. They reflect the past, present, and future of collaborative cancer clinical research in Europe from the viewpoint of the EORTC and mirror legal, technological, and scientific advances in the field. A growing convergence among the activities of AROs, manufacturers, and other stakeholders in the domain of oncology drug development can be observed over time.

Model 1: Fully academic trials (1980s)

Prior to the 1990s, the EORTC conducted cancer clinical trials in a fully independent manner, without any involvement of the industry. The studies performed in this period can be characterized as purely academic in nature and mainly investigated multimodal therapies (e.g., surgery in addition to chemotherapy and/or radiotherapy) and combinations of multiple treatments, or compared different therapeutic options in a head-to-head fashion. They also focused on the generation of scientific knowledge and often incorporated translational research. Examples include the larynx preservation trials EORTC 24891[22] and EORTC 24954,[23] in which it was shown that induction chemotherapy with cisplatin and 5-fluorouracil followed by radiotherapy leads to similar overall survival rates and disease control as the conventional treatment of total laryngectomy and postoperative radiotherapy in patients with locally advanced hypopharyngeal cancer. Although these studies changed clinical practice and improved patients' quality of life, no company was interested in sponsoring them at the time because they did not involve a potential commercial benefit.

Model 2: Fully industry-supported trials (1990s)

In 1993, the EORTC set up a partnership with Schering AG for the conduct of the EORTC 20921 study.[24] This was the first time such a collaboration was organized in the EORTC's history. The two parties negotiated an agreement in which the EORTC would be responsible for performing the trial within a certain time frame, whereas the company covered the costs associated with its conduct. The objective of this fully industry-supported study was to compare fludarabine (Fludara) with conventional combination chemotherapy in patients with advanced non-Hodgkin's lymphoma and to subsequently achieve regulatory approval for the drug within this indication. The expertise and network of the EORTC's lymphoma group were key factors in Schering AG's decision to approach the EORTC as a potential partner. Such types of cooperation between academic institutions and commercial organizations aim to confirm and safeguard scientific value, while at the same time having clear registrational purposes. By outsourcing study management and oversight to academia, trial outcomes cannot easily be controlled or influenced by the industry, but submission of a marketing authorization application to the regulatory authorities remains possible if positive results are obtained. As such, these kinds of partnerships can represent a win-win situation for the actors involved and synergistically leverage the interests of all relevant stakeholders to develop more effective treatments and improve patient outcomes. Nevertheless, these settings may give rise to conflicts of interest, which need to be managed in a transparent way. To do so, the EORTC has composed a set of principles of independence, which allow parties to work together while maintaining scientific integrity (**Figure 2**).

Model 3: Partially industry-supported trials (2000s)

Some EORTC studies address research questions with a scientific and/or practice-changing focus and generate results that can indirectly be of commercial interest because they make use of compounds owned by specific pharmaceutical companies. Therefore, they are often partially supported by the industry through educational grants and free supplies of the investigational drug. Although these kinds of trials are not a priority for manufacturers, their

Table 1 Overview of the 10 selected EORTC trials

EORTC number	NCT number	Sponsor	Partner(s)	Phase	Trial type	Objectives	Reference
24891	N/A	EORTC	N/A	III	FA	To determine if laryngeal preservation with induction chemotherapy followed by radiotherapy is safe in the treatment of hypopharyngeal squamous cell carcinoma	22
24954	NCT00002839	EORTC	N/A	III	FA	To compare the efficacy of two regimens of cisplatin and 5-fluorouracil combined with radiation therapy in preserving the larynx in patients who have resectable hypopharynx or larynx cancers	23
20921	N/A	EORTC	Schering AG	III	FIS	To compare fludarabine with conventional combination chemotherapy in patients with advanced non-Hodgkin's lymphoma and to achieve regulatory approval for the drug within this indication	24
08971	NCT00003279	EORTC	Merck KGaA ImClone	III	PIS	To compare the efficacy of vaccination with monoclonal antibody BEC2 and BCG with that of no further therapy in patients with limited-stage small cell lung cancer	25
18991	NCT00006249	EORTC	Schering-Plough	III	PIS	To determine the effectiveness of pegylated interferon alfa-2b in patients who have undergone surgery for stage III melanoma	26
20981	NCT00004179	EORTC	Hoffmann-La Roche	III	PIS	To compare combination chemotherapy and rituximab with combination chemotherapy alone in patients with relapsed non-Hodgkin's lymphoma	27
26981	NCT00006353	EORTC	Schering-Plough	III	PIS	To compare the efficacy of radiation therapy with or without temozolomide in treating patients who have newly diagnosed glioblastoma multiforme	28
10041	NCT00433589	EORTC	Agendia Breast International Group Hoffmann-La Roche Novartis Sanofi-Aventis Patient groups	III	MBD	To compare genetic testing with clinical assessment in determining the need for chemotherapy in women with breast cancer that is either node-negative or involves no > 3 lymph nodes	29
90101	NCT01524926	EORTC	Pfizer	II	MBD	To assess the antitumor activity of crizotinib in a variety of tumors with alterations in ALK and/or MET pathways	30
1559	NCT03088059	EORTC	Boehringer Ingelheim Pfizer Innate Pharma AstraZeneca TESARO Bayer	II	MBD	To investigate the use of a personalized biomarker-based treatment strategy or immunotherapy in patients with recurrent or metastatic squamous cell carcinoma of the head and neck	31

ALK, anaplastic lymphoma kinase; EORTC, European Organisation for Research and Treatment of Cancer; FA, fully academic trial; FIS, fully industry-supported trial; MBD, multi-partner biomarker-driven trial; N/A, not applicable; NCT, National Clinical Trial; PIS, partially industry-supported trial.

Figure 1 Evolution of different models of stakeholder collaboration used in landmark EORTC trials. The decade of emergence is indicated for each model. All models are additive and exist in parallel. The pawn represents (assumed) sponsorship (in the 1980s and 1990s this notion was not yet demanded by law). P (pink) = patients; A (blue) = academic organization; I (green) = industry; R (orange) = regulator; P (dark blue) = payer; H (yellow) = HTA body; R (purple) = registries. ARO, academic research organization; EORTC, European Organisation for Research and Treatment of Cancer.

trust in the EORTC's network of expertise, the potential commercial benefits connected with such research collaborations, and the low degree of risk involved can spur their participation in such activities. The EORTC initiated its first partially industry-supported (PIS) trial in 1998, when the EORTC 08971 study[25] was launched with logistical support from Merck KGaA and ImClone, which provided the treatment under investigation (BEC2, a monoclonal antibody designed to mediate an immune response against GD3-expressing tumor cells). Other notable PIS trials conducted by the EORTC include the EORTC 18991, 20981, and 26981 studies,[26–28] which further professionalized the conditions and procedures under which the EORTC performed clinical research as they were the first EORTC-led trials that were carried out in full compliance with the legal requirements imposed by the newly adopted EU Clinical Trials Directive 2001/20/EC. Furthermore, whereas the EORTC normally retains ownership of all data it collects as part of its PIS-related research activities, the databases associated with these particular studies were ultimately retro-acquired for the first time by the participating industry partners for registrational purposes due to the positive results observed. Three additional such retro-acquisitions have since occurred.

Model 4: Multi-partner biomarker-driven trials (2010s)

In recent years, advances in the understanding of cancer biology at the molecular level have greatly facilitated and improved tumor cell characterization for individual patients. The emergence of precision medicine has enabled the identification of responders and nonresponders to existing therapeutic interventions in advance. The clinical research landscape in oncology has evolved along with these developments, as demonstrated by the launch of the MINDACT study (EORTC 10041)[29] under the umbrella of the Breast International Group. In this practice-changing international stratification trial, which was initiated in 2007, the EORTC collaborated with a diverse group of actors and/

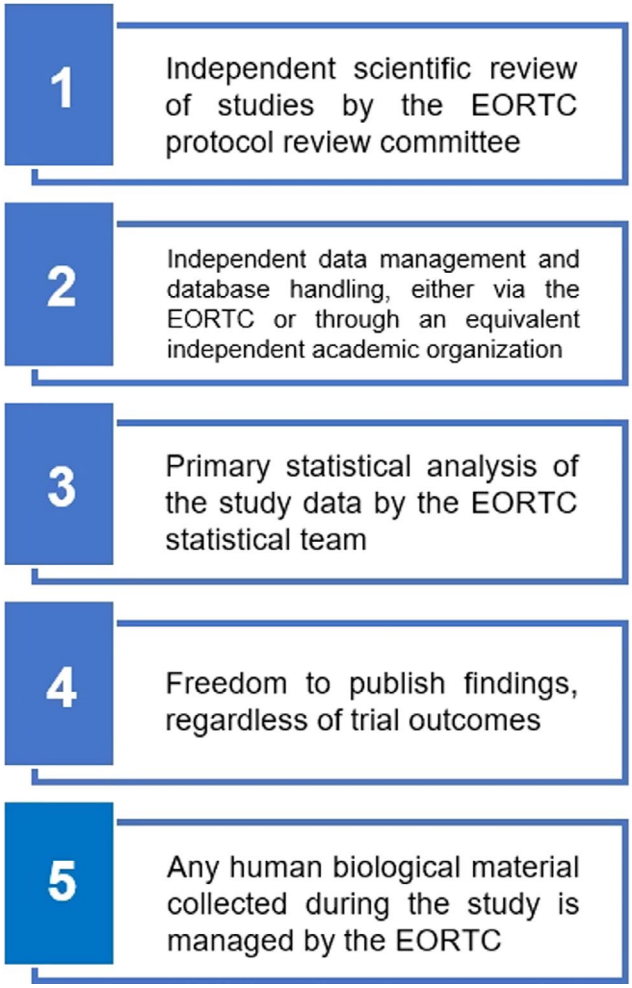

Figure 2 The EORTC principles of independence for research projects in which it collaborates with external partners, including pharmaceutical companies. EORTC, European Organisation for Research and Treatment of Cancer.

or funders, including other academic organizations (e.g., Breast International Group), manufacturers of pharmaceuticals, and *in vitro* diagnostics (Agendia, Hoffmann-La Roche, Novartis, and Sanofi-Aventis), patient advocacy groups (e.g., Europa Donna), policymakers (the European Commission), and nonprofit organizations (e.g., the Breast Cancer Research Foundation (BCRF)). The investigators involved in this study achieved major economic and health benefits by establishing that many patients with early-stage breast cancer who are considered at high clinical risk of recurrence can be spared from aggressive types of adjuvant chemotherapy without significantly impacting their risk of distant metastasis at 5 years.[29] The extensive cross-company involvement in its conduct can be explained by the lack of commercial interest in its results on the part of most of the participating industry partners (Agendia being a notable exception). The MINDACT trial illustrates the growing interest in the molecular characterization of tumor cells to improve health outcomes, which has led to an increased incorporation of translational research in cancer clinical studies.

Other landmark biomarker-driven trials carried out by the EORTC include the CREATE (EORTC 90101)[30] and UPSTREAM (EORTC 1559)[31] studies. The former started in 2012 and is an example of a basket trial (**Figure 3a**). It examines the activity and safety of crizotinib (Xalkori), a tyrosine kinase inhibitor, in six different very rare tumor types (anaplastic large cell lymphoma, inflammatory myofibroblastoma, papillary renal cell carcinoma type 1, alveolar soft part sarcoma, clear cell sarcoma, and alveolar rhabdomyosarcoma).[30] The challenge posed by the extremely low prevalence of these cancers was overcome by cooperating with specific institutions belonging to a network of sites with experienced investigators. Patients were preselected on the basis of their tumors harboring mutations in the *ALK* and/or *MET* genes. The UPSTREAM study on the other hand is an umbrella trial (**Figure 3b**) that began in 2017 and investigates the use of six different drugs (some of which have not yet been approved by the regulatory authorities) for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck.[31] Although this study serves exploratory purposes (i.e., signal detection), it partly operates in the competitive space because potential label adaptations and regulatory approval of the investigational therapies are not excluded. Given the large number of products and, therefore, companies involved, measures to mitigate commercial conflicts of interest were introduced in the form of formal agreements between the partners to not cross-compare any trial results.

Model 5: Integrated patient-centric trials (2020s)

Note that this model was derived entirely from the interviews and that it therefore represents a preview of future cancer clinical research collaborations according to the EORTC.

In light of the continuously evolving landscape in oncology drug development, novel models of stakeholder cooperation will be required to generate the evidence underpinning the uptake of future anticancer therapies into real-life practice. Cancer clinical research is in need of new made-to-measure types of partnerships that can be customized depending on the nature of the project, for example, in the areas of dose de-escalation, biomarker, outcomes, long-term follow-up, and comparative effectiveness studies. Such additional collaborative frameworks will have to address common technological challenges with regard to the collection of real-world data, the setup of screening platforms, the introduction of data standards and curation, and the exchange and use of electronic health records. This will necessitate not only the involvement of industry and academia, but of nontraditional partners as well, including (but not limited to) regulators, payers, health technology assessment bodies, patient organizations, and philanthropic groups. However, any form of cooperation among these actors should always start from the patient rather than the investigational medicine. Within such a multistakeholder environment, there is a clear potential for conflicts of interest to arise. The EORTC principles of independence and similar standards will, therefore, remain highly relevant in the future.

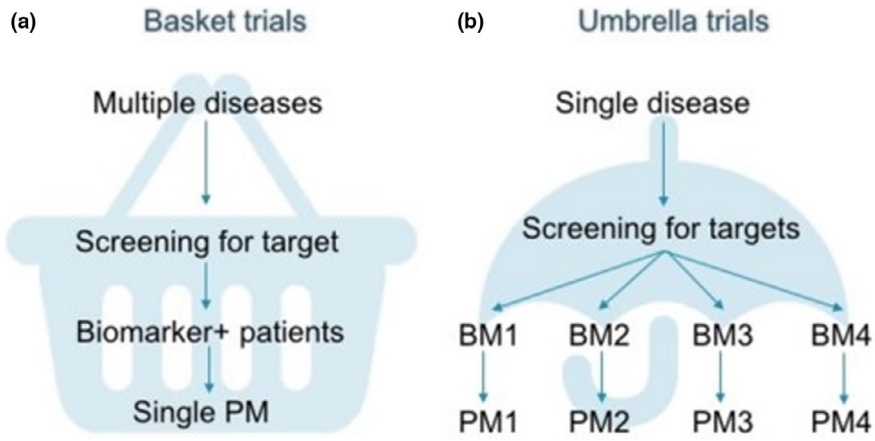

Figure 3 Overview of emerging trial methodologies enabling the testing of one or multiple hypotheses in one or multiple diseases. (**a**) Basket trials aim to evaluate the effects of a treatment against a specific molecular target while agnostic of the histological context. (**b**) Alternatively, umbrella trials evaluate a variety of targeted agents matched to a particular molecular profile. BM, biomarker; PM, precision medicine.

HISTORICAL CONTEXT

Before the 1980s, the role of the pharmaceutical industry in the conduct of oncology trials was more limited than it is today because cancer clinical research at the time focused on less frequently occurring cancers (e.g., childhood leukemia), and thus was of little commercial interest to manufacturers.[32,33] Consequently, the vast majority of studies were undertaken by academic institutions (model 1). As research targets started to shift more toward common cancers, larger markets began to emerge, and companies started to invest more in the development of anticancer medicines.[32,33] Gradually, fully industry-backed trials (model 2) became the norm in oncology, supplemented by academic studies receiving some degree of support from manufacturers (model 3).[34]

However, as a result of, among other reasons, the increased regulatory burden imposed on sponsors by the introduction of EU Clinical Trials Directive 2001/20/EC and the subsequent rise in costs associated with carrying out clinical research, the conduct of fully academic trials and PIS studies in Europe has become more challenging over time, leading to a substantial decrease in the sponsorship of oncology trials by academia.[35,36] Nevertheless, larger AROs, such as the EORTC, managed to adapt to the changing legal environment and continued to perform independent clinical research,[37] while the industry further solidified its dominant position in the cancer drug development space.[35,38,39]

PRESENT SITUATION AND FUTURE EVOLUTIONS

The rise of precision medicine in oncology has led to the arrival of new trial designs, including biomarker-driven basket and umbrella studies (model 4).[40,41] These novel approaches have underscored the pivotal role of academic research in generating health technologies that are of benefit to patients with cancer.[36] Most trials performed by the industry are aimed at obtaining regulatory approval for a particular product and do not address clinically relevant questions that fall outside of a commercial scope.[16,17] Nevertheless, non-commercial entities in Europe are facing significant hurdles that could jeopardize their involvement in cancer clinical research.[36,42] There is an urgent need for rethinking today's drug-driven medicines development paradigm and implementing a more patient-centered framework (model 5).[17,43–48] Although independent partners, such as academic organizations, may be uniquely positioned to effectuate such a transformation,[16,17,44] this will require novel models of collaboration between all stakeholders involved in the process of developing new anticancer therapies.[12,13,16,17,36,44,47,49] Academia, industry, and all other actors in the field must therefore cooperate to bridge the translational research gap.

CONCLUSIONS

From the viewpoint of the EORTC, clinical research partnerships in oncology have evolved from small-scale bilateral cooperations between academia and industry to more complex multistakeholder and interdisciplinary collaborations, paralleling scientific and technological advances in the field. To overcome the challenges facing cancer drug development, new and tailor-made collaborative models that integrate and align the interests of all partners involved in a patient-centric fashion will be needed in the near future.

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