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SPECIAL COMMUNICATION

Promoting large multinational academic clinical trials for gastrointestinal cancers in Europe: the ENGIC (European Network for GI Cancers) initiative

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This paper outlines proposals for the setup of a European Network for Gastro-Intestinal Cancers (ENGIC) initiative, aiming at promoting and fostering strategic academic clinical trials for gastrointestinal cancers in Europe. We discuss the presentation of the network, its main objectives, organization, internal/external processes, operational activities, governance and, finally, priority actions for the future. We propose that this provides a model that could be adopted by researchers working in other disease areas.

Key words: European research network, gastrointestinal tumours, precision medicine, molecular oncology, clinical trials

BACKGROUND: RELEVANCE AND CHALLENGES OF ACADEMIC RESEARCH IN EUROPE

Academic research has contributed significantly to developing therapeutic options and improving existing treatment strategies in gastrointestinal (GI) malignancy. Recently, results of academic trials sponsored by cooperative groups, mainly at national levels, led to the introduction of meaningful changes to clinical guidelines and modified the standard of care for patients with GI malignancy worldwide. Notable successes include shortening the duration of the adjuvant therapy in a proportion of International Union Against Cancer (Union Internationale Contre le Cancer) stage III colon cancer patients; avoiding chemoradiation and surgery in mismatch repair-deficient (dMMR) rectal cancer patients with locally advanced disease; adopting perioperative strategies in locally advanced gastric cancer; intensifying the upfront treatment of advanced pancreatic cancer and metastatic colorectal cancer with three-drug regimens; refining the target population of epidermal growth factor receptor (EGFR)-targeted drugs in metastatic colorectal cancer; and offering liver transplantation to patients with persistently unresectable liver-limited metastatic colorectal cancer.

However, conducting such research is becoming increasingly challenging, evidenced by both a decline in the absolute number of interventional trials led by academic groups in Europe, and a reduction of the relative percentage of these academic efforts out of the overall number of newly launched studies. Potential reasons for this include the necessary subdivision of many GI cancers into molecular subgroups, with targeted and specific therapeutic approaches that are impossible to evaluate on a national scale due to the low frequency of these molecular alterations; the high number of patients needed to carry out de-escalation trials with noninferiority statistical design, which only academic groups can undertake; and, finally, the growing complexity of the administrative and regulatory procedures involved in starting up and running clinical trials, which requires more advanced training for research professionals and has significant financial implications.

Moving cohesively from national to multinational research efforts could help these current challenges that academic research groups face. Furthermore, multinational research will create and deepen collaboration, deliver more generalizable research and hasten recruitment, which will ensure the most pertinent questions are asked and are answered efficiently.

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Firstly, the ability to align national efforts focused on small patient subgroups (i.e. for rare cancers, or those with uncommon but often druggable molecular alterations) might allow quicker answers to clinically relevant questions. Evidence originating from a prospectively generated unique international trial is clearly preferrable to the pooling of data of smaller studies in a retrospective evaluation.

Secondly, the validation of technologies that are not (yet) universally available may give earlier access to useful tests to patients in different countries while accelerating the development of academic assays in well-conceived and adequately powered trials.

Thirdly, the joint effort of researchers with a leadership role in different countries may increase the feasibility of ambitious projects that might be more appealing and competitive to receive public funding in the frame of multinational calls, or to be partially supported by companies focusing on the development of drugs or diagnostics. Additionally, having larger and joint trials funded at a multinational level would also reduce the competition among academic researchers to receive grants in their own countries for similar smaller projects.

Fourthly, sharing experiences and competencies regarding shared and different administrative and regulatory procedures would be helpful both to increase efficiency for future collaborative research but also to support the personal growth of research professionals (e.g. trial managers and methodologists) involved in the setup, approval and conduction of studies.

Lastly, intergroup trials with varying responsibilities may also support the collaborative effort of individual academic groups and provide a favourable basis for younger researchers to successfully apply for public grants that are dedicated to support fellowships in foreign universities and study groups.

THE REGULATORY FRAMEWORK: OPPORTUNITIES FROM THE EU 536/2014 EU REGULATION

The harmonization of the processes for the assessment and supervision of clinical trials throughout the European Union (EU) is one of the main objectives of the EU 536/2014 regulation, which aims at fostering innovation and research in the EU, facilitating the conduct of larger clinical trials in multiple EU member states/European Economic Area (EEA) countries. From a practical and technical point of view, the regulation enables sponsors to submit one online application via a single platform—the Clinical Trials Information System (CTIS)—to obtain the authorization to conduct a clinical trial that may involve centres in several European countries. Despite the challenges associated with the introduction of this new system, a clear advantage of this regulation might be the improved feasibility of conducting multinational trials.

Therefore, the EU 536/2014 regulation could be seen as great opportunity to promote collaborative international efforts in academic research. Between January 2022, when the CTIS platform was launched, and December 2024, 8277 trials were authorized, with neoplasms the focus of 35% of them. Of 8277 authorized trials, 3703 (45%) were sponsored by noncommercial entities, but only 548 of these were multinational, which corresponds to 7% of all authorized trials. Notably, the median time from initial submission to final decision did not significantly differ according to sponsor type (commercial versus noncommercial) or number of involved member states.

The UK is no longer an EU member state and is therefore unable to utilize the CTIS platform with its associated advantages and access to certain academic funding streams. However, the UK has a track record of conducting academic research in GI cancer and has a research community motivated to participate in collaborative international research. Currently, studies originating in the UK require an EU sponsor, then CTIS applications can be made. Conversely, EU studies require separate application to UK regulators. In addition, working models of successful collaboration, mainly based on the co-sponsorship of studies, were elaborated, moving from an initial effort of document harmonization to be compliant with both EU and UK regulatory requirements.

THE LAUNCH OF THE ENGIC INITIATIVE: GENERAL PRINCIPLES

Addressing the above-described challenges and with the aim of sharing experiences and perspectives, on 8 September 2022, following an invitation of the Fédération Francophone de Cancérologie Digestive (FFCD), a meeting with the representatives of several European GI groups was organized in Paris. The objective was to preliminarily discuss scientific, regulatory and administrative challenges in GI research, underlining national peculiarities and differences, to find pragmatic approaches to strengthen and intensify collaboration between national groups at European level with the ultimate goal of advancing research and treatments for GI cancers patients. The representatives of European GI groups agreed on the proposal to establish a new collaborative academic network called the European Network for GI Cancers (ENGIC) to propose a new European model of clinical research in GI oncology. Building upon individual experiences at country level, ENGIC aims at overcoming national borders to increase the effectiveness of European research.

Researchers from 10 countries (Belgium, Denmark, Finland, France, Germany, Italy, Netherlands, Spain, Switzerland and UK), actively contributing or not to 11 national academic groups [Arbeitsgemeinschaft Internistische Onkologie (AIO), British Colorectal Oncology Group (BCOG), Belgian Group of Digestive Oncology (BGDO), Dutch Colorectal Cancer Group (DCCTG), FFCD, Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR), Fondazione Gruppo Oncologico del Nord Ovest (GONO), Nordic Gastrointestinal Tumour Adjuvant Therapy Group (NORDIC), Swiss Cancer Group (SAKK), Grupo Español para el Tratamiento de los Tumores Digestivos (TTD) and Unicancer Gastrointestinal Group (UCGI)] were involved in ENGIC

activities from the beginning and agreed on the general principles and mechanisms of functioning of the network.

It was clearly opted to develop a governance-streamlining, low-cost-strategy model without administrative structure, to minimize the administrative work, avoid staff costs, and rely on the administrative and human resources of each national group that already existed. Therefore, it was agreed that the ENGIC network will not be managed through any legal entity of any country involved in the network, but will be recognized through a non-official agreement, crucially rotating responsibilities to organize network meetings.

ENGIC provides infrastructure for the research collaborations. At ENGIC meetings, researchers present trials (already open nationally or in conception) to be adopted. Representatives from national collaborative groups then judge whether the proposed trial can be delivered in their country and consider potential funding routes. At each meeting, updates on each study are provided.

Importantly, ENGIC is not responsible for the promotion, funding or delivery of ENGIC trials. Instead, this task is the responsibility of the cooperative group/public institution associated with the coordinating investigator of each research project, with the aim of choosing the most appropriate structure to run the trial efficiently. It is sponsors' responsibility to coordinate all the activities related to the study setup, including part 1 of the CTIS application, to coordinate country-specific submissions (part 2 of the CTIS application) and to oversee the conduct of the study. However, the responsibilities related to the study start-up and conduction at national levels are devolved to each national cooperative group through specific agreements, which may contain the rules of data property and data sharing. The expertise of national groups in launching clinical trials in their countries will likely help to overcome the heterogeneity of some ethical and start-up procedures still evident at national levels, notwithstanding the common EU regulations. In the case of studies including non-EU countries such as the UK, Norway or Switzerland as participating countries, models of co-sponsorship can be adopted. Therefore, initial efforts of harmonization concerning operating procedures are needed, including discussion about the specific financial needs that should be taken into account when building budget proposals through a shared multinational budget model. Similarly, general rules defining the policy for the authorship of the output of ENGIC trials have been established.

Based on these principles, no competition is foreseen with already existing institutions aiming at sponsoring international trials in Europe and offering headquarters not only for scientific exchange but also for the administrative management of academic research efforts (i.e. European Organization for Research and Treatment of Cancer—EORTC).

The ENGIC networking meetings are linked to two face-to-face meetings held during the annual European Society of Medical Oncology (ESMO) meeting and the ESMO GI cancer conference, and one intermediate virtual meeting. Each meeting is organized by a cooperative group/institution that takes care of setting the agenda and managing logistical details. The ENGIC network is dedicated to involving representatives of all participating study groups, including all researchers who are needed to cover the respective disease entities.

ENGIC MECHANISM OF FUNCTIONING: THE CURRENT FLOW OF ACTION

As a general rule, new study proposals are presented during ENGIC meetings. Researchers presenting a study idea may receive feedback from other groups on the relevance, design and methodology of their project, and a request for potential participation, depending on the interest of each national group and the potential presence of competing trials or other barriers to participation. Although the primary objective of the ENGIC network is to conceive joint research efforts, additional potential collaborative methods are foreseen:

- The preplanned pooled analysis of national studies answering the same question, through a properly designed and shared statistical analyses plan (SAP);
- To expand clinical trials initially launched at a national level to multiple countries, to ensure the earlier achievement of the target accrual and increase the power of the study, to investigate more ambitious endpoints by increasing the trial sample size.

In terms of seeking funding and overall trial setup, two main distinct structures can be envisioned, consisting of a centralized and a decentralized model (Figure 1). In addition, some examples of successful international collaborative trials for colorectal cancer, carried out in the past 20 years, with their main characteristics are summarized in Table 1 to show the reader the various possibilities of efficient collaboration. ENGIC researchers agree that the preferred mode of action should be the search for only one funding source for each project from the beginning, either through public calls for multinational trials or from private institutions (pharmaceutical companies, charities, biotechnology companies). However, addressing the funding realities in many European countries, ENGIC studies can also be funded by different national grants to support study procedures in each participating country.

Given the evolving landscape of molecular selection and based on the need of a not yet marked molecular assay as a selection tool for patient eligibility in precision oncology trials, the EU *In Vitro* Diagnostic Regulation (IVDR) will be followed, both for assays developed at an academic level and for industry-level tests, which will require collaboration with diagnostic companies.

This general workflow has been followed for the setup of the first European trials endorsed by the ENGIC network in colorectal (COLOSOTO EUDRACT: 2024-514030-20-00, ARIEL EUDRACT: 2025-521209-42-00, CHIMERA), gastric (FRUQUITAS) and intestinal (FOLFIRINOX SBA EUDRACT: 2023-505486-92-00) cancers.

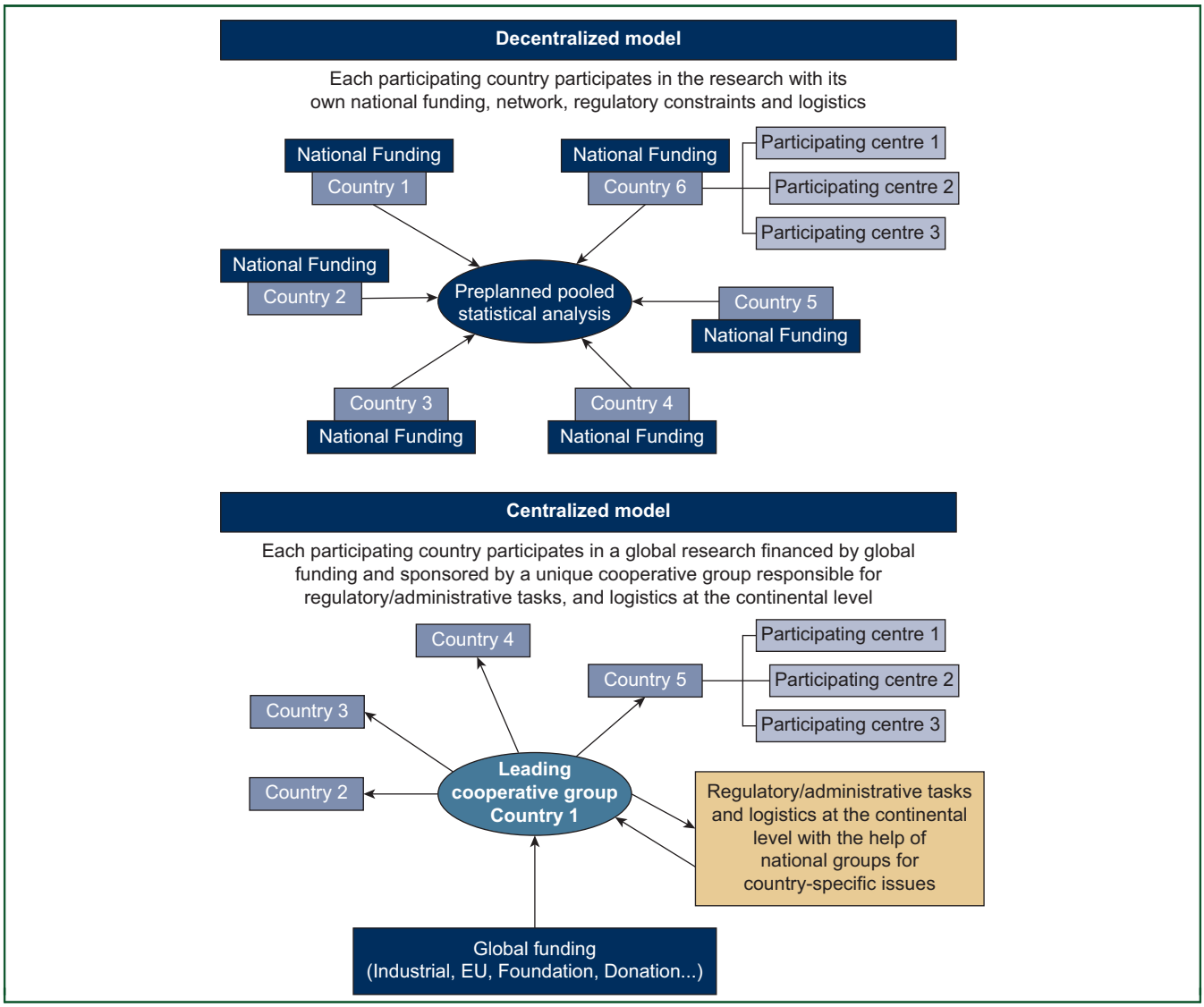

Figure 1. Centralized and decentralized research models.
EU, European Union.

FUTURE PERSPECTIVES

While the substantial increase of productive, frequent, independent scientific exchanges among European researchers in the field of GI cancers is the first clear success of the newly launched ENGIC initiative, many other long-term and large-scale objectives can be pursued.

If the delivery of pragmatic academic trials with the aim of answering clinically relevant questions is the first objective of the ENGIC network, co-sponsored trials including ENGIC members who provide their expertise to study design and setup in the frame of drug development driven by pharmaceutical companies might be envisioned. To this end, the interaction with pharmaceutical companies could be a fruitful opportunity to orientate the steps of new drug development towards clinical practice, and to identify the best clinical settings for their use. Moreover, building a common experience in the conduction of multinational trials might make the ENGIC network a reliable spokesperson to advise regulatory authorities about the strong and weak points of trial conduction in the EU and European partner countries, to improve future research processes by removing potential dysfunctions and bureaucratic obstacles that impair the feasibility of academic trials.

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Table 1. Characteristics of past successful international colorectal cancer trials

Model	PETACC8	IDEA	IROCAS	FIRE4.5
Design	Phase III—randomized trial (RT)	Phase III—RT	Phase III—RT	Phase II—RT
Patient population	Allcomers	Allcomers	High-risk stage III	*BRAF*-mutated metastatic colorectal cancer
Patient number	3000+	2000+/country	800	99
Participating countries	11 European Union (EU) countries	12 EU and non-EU	France /Italy/Canada	Germany/Austria/France
New drug registration	Yes	No	No	No
Sponsor	One for all	Multiple	One for all	One for all
Contract research organization	Yes	No	No	Yes
Funding	Industry	National grants	National grants	Industry

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