Clinical Trial Perspective

CLINICAL INVESTIGATION

International investigator-driven clinical trials: challenges and opportunities for US–Europe cooperation through the US cooperative group networks

Clin. Invest. (2011) 1(4), 493–500

Denis Lacombe[1], Anastassia Negrouk[1] & John Bean[†1]

[1]European Organisation for Research & Treatment of Cancer, Avenue E. Mounierlaan, 83/11, Bruxelles 1200, Brussels, Belgium
[†]Author for correspondence:
Tel.: +32 2774 1671
Fax: +32 2772 3545
E-mail: john.bean@eortc.be

International investigator-driven clinical trials (IDCTs) satisfy international standards for quality, achieve maximum efficiency, avoid duplication of effort, and realize effective and widespread implementation of research results into medical practice. This article focuses on specific intercontinental issues involving the development and conduct of IDCTs and reviews what is necessary for a successful international partnership, specifically, intergroup trials involving the European Organisation for Research and Treatment of Cancer (EORTC) and the US-based National Cancer Institute intergroup system. Through examples, it is shown that the lead group of an international intergroup IDCT must have the expertise and capabilities to work effectively in the international setting, establish working procedures, consider the regulatory environment and QA/QC in the trial setting, and secure the principles of academic independence.

Keywords: clinical trial • EORTC • investigator-driven trials • US cooperative groups

Casting cancer patients center stage in the development of more effective therapeutic strategies is a critical aspect of investigator-driven clinical trials (IDCTs). IDCTs complement the scientific agenda of drug development performed by industry by optimizing therapeutic strategies. This includes promoting innovative research, enabling the translation of laboratory research into medical practice, defining state of the art treatment, and also identifying ineffective or redundant treatments.

Advantages & objectives of international IDCTs

International IDCTs offer considerable benefits. These large-scale trials can address common and devastating malignancies where even a small improvement in survival would have a major impact on public health. In the current environment where science and knowledge develops quickly, performing clinical trials rapidly and efficiently is an absolute requirement so that generated data do not become outdated by the time of their maturity. In addition, tumors frequently tend to be divided into subgroups that are characterized by specific molecular entities, and these subgroups would then be subject to specific clinical trials, and international trials allow studies concerning these subgroups to be conducted rapidly. Similarly, due to their ability to reach required sample sizes, international IDCTs are the ideal platform for studies involving rare tumors. Furthermore, and in keeping with this premise, unpowered small-scale trials with intention to conclude or aimed at changing practice should be discouraged insofar as they are inconclusive, unethical and conducted concurrently in several countries. Exploratory small-scale trials should on the other hand not be discouraged when aimed at hypothesis-generating or proof-of-principle testing.

FUTURE SCIENCE part of fsg

Another major advantage of international collaborations is that they allow cross-fertilization and standardization of reference treatments. They also enable global progression in standards of care in a parallel manner, and thereby facilitate the practicality of addressing subsequent research questions. In a similar fashion, they allow quality control measures to be harmonized such as, but not limited to, quality standards in the administration of radiotherapy (RT).

As opposed to other approaches, such as merging of databases, large clinical trials are of higher data integrity. In addition to the objective of reaching high recruitment in a single and well-powered trial (as opposed to possible several trials that may not be adequately powered), single trials have the advantage of streamlining approaches, fostering similar quality assurance procedures and setting up better grounds for the next questions to be addressed.

Direct possible advantages of such trials is to reach a certain level of harmonization for clinical research, such as the agreement of relevant study end points and related methodology, and consensual approach of population definition and reference treatment, as well as standardizing common multidisciplinary quality assurance measures. This may impact on better selection of needed trials of true relevant importance.

Principals & challenges of international intergroup IDCTs

The main objectives of international intergroup IDCTs are to satisfy international standards for quality, achieve maximum efficiency, avoid duplication and realize effective implementation of research results into medical practice. These objectives lead directly to the principles of intergroup policies. These principles maintain that for a given intergroup trial there should be only one protocol, one set of case report forms, one database, one coordinating data center, and a single trial steering committee. Furthermore, the lead group and the joining group(s) should be designated.

A major challenge currently being addressed by the US cooperative groups is the time required to activate these trials. The median time to have academic trials up and running is due to multifold issues that do not necessarily overlap, but can add up for intercontinental trials.

The US cooperative group system identified a median activation time of 830 days for Phase III trials, mostly as a result of long and cumbersome processes inherent to the group systems itself. For international trials in Europe, although some optimization of clinical research organization may still improve efficiency, the main reasons for delays in starting trials remain the disparities across the EU Member States and the variety of national requirements, processes and approval systems. The median activation time in Europe for international academic trials is around 650 days for all steps to be performed from study concept to first patient recruited.

Principles of cooperation

The lead group for the intergroup trial must have the procedures in place and the capacities to handle international trials, and, preferably, an established track record in conducting international trials. In addition, the lead group should have full knowledge of quality control/quality assurance (QC/QA) procedures to handle data from the International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) standards. Finally, established membership criteria and defined lines of authority should also be in place.

There remain numerous strategic challenges for intergroup trials. The feasibility of the study needs to be considered carefully, and much consideration needs to be given to the clinical questions that will be posed. In such an international setting, the reference treatments need to be well chosen, and issues related to the handling of biological materials and patient access require input from persons familiar with the international setting for the trial. It is critical that international clinical trials are as pragmatic as possible in order to meet the requirements of all concerned environments where the trials will be conducted. This includes, notably, reference treatment and supportive care measures. Common approaches should always be preferred to avoid nonhomogeneity. If those do arise, prospective conventions need to be established.

Setting up such trials should not be underestimated; this requires know-how and expert resources. Financially, assessment of direct and indirect costs must be considered.

Framework for cooperation

Administratively, a set of working procedures must be established and the regulatory environment and QA/QC setting in the trial must be considered. In addition, contracts and agreements between groups that are valid in the trial setting must be drawn up and signed. Throughout the collaboration, flexibility in interpretation and implementation of trial processes must be maintained (Figure 1).

Inevitably, addressing these challenges entails frequent working meetings. In order to ensure uniformity, master documents such as protocols and contracts need to be developed, and the use of common data elements should be prescribed. It is critical that terminologies are harmonized in order to achieve clarity, and

methodological approaches should be simplified so as to assure reproducibility. Protocols need to be pragmatic and implementable in all medical systems, and inclusion criteria should reflect the targeted populations so that research results can be readily implemented in multiple countries. In these tasks, there are clearly mutual benefits of peer review processes.

Along the same lines, intergroup partners should adopt common procedures for cooperation with industry as well as common approaches to regulatory bodies.

Organization of EORTC Intergroup studies

For nearly 50 years, the European Organisation for Research and Treatment of Cancer (EORTC) has developed, conducted, coordinated and stimulated translational and clinical research in Europe aiming to improve the standard of cancer treatment by testing more effective therapeutic strategies. Headquartered in Brussels, Belgium, the EORTC Network comprises over 300 hospitals or cancer centers in over 30 countries. It has long-standing expertise in conducting and coordinating international trials at both the European and intercontinental level; currently the EORTC collaborates with more than 25 national and regional groups.

The EORTC participates in intercontinental intergroup trials that cover several territories. It has a common scientific agenda with the US-based Cooperative group supported by the NCI, but also with the NCI – Canada Clinical Trials Group (NCIC) as well as with Australian cooperative groups; for example, the Tasmanian Radiation Oncology Group (TROG) and Cooperative Clinical Trials Group for Neuro–Oncology (COGNO). Currently, 20 intergroup trials are open, and the EORTC leads 11 of these. Annually, up to 1500 patients are recruited via the intergroup model.

At present, the EORTC is cooperating with US groups on several Phase III trials. These include two brain tumor studies, one of which is lead by EORTC, and a pancreatic cancer study with the Radiation Therapy Oncology Group (RTOG), a brain tumor study with the North Central Cancer Treatment Group (NCCTG), a leukemia study with the Cancer and Leukemia Group B (CALGB), and a closed genito-urinary tract cancer study with the Southwest Oncology Group (SWOG).

The glioma platform as a model: EORTC intergroup cooperation

The EORTC 22981/26981 trial, conducted in collaboration with the NCIC (Figure 2) led to a global platform of four large Phase III trials with cooperation between the EORTC, US groups and NCIC [1].

This global platform includes a two-arm trial led by the RTOG addressing temozolomide (TMZ) schedules in glioblastoma multiforme (1300 patients), a four-arm trial led by the EORTC addressing anaplastic gliomas without 1p/19q loss for the role of the concurrent and adjuvant treatment (830 patients), a three-arm trial led by the NCCTG addressing radiotherapy and TMZ for 1p/19q co-deleted good prognosis glioma (500 patients), and a two-arm trial led by NCIC addressing radiotherapy and TMZ in elderly patients (560 patients).

In the EORTC 26052–22053/RTOG 0525 trial, a Phase III trial comparing conventional adjuvant TMZ with dose-intensive TMZ in patients with newly diagnosed glioblastoma, all patients received surgery followed by concommitant radiotherapy and TMZ treatment. Patients were randomized to receive either adjuvant TMZ on days 1–5, for 28 days, 200 mg/m²/day or adjuvant TMZ on days 1–21 for 28 days, 100 mg/m²/day. The challenges for the EORTC in setting up this trial were manifold: it was the first transatlantic trial to be set up (in 2006) after the implementation of the European directive (in 2004), the first transatlantic 'clinico–genomic' trial, the first transatlantic trial to be set up in cooperation with a pharmaceutical partner,

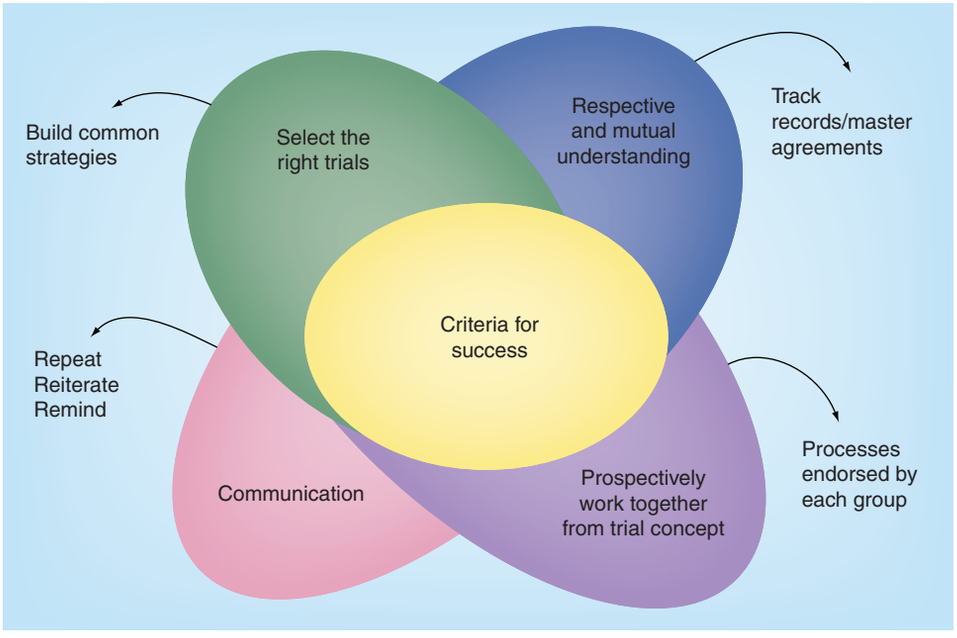

Figure 1. Criteria necessary for developing international clinical trial collaborations.

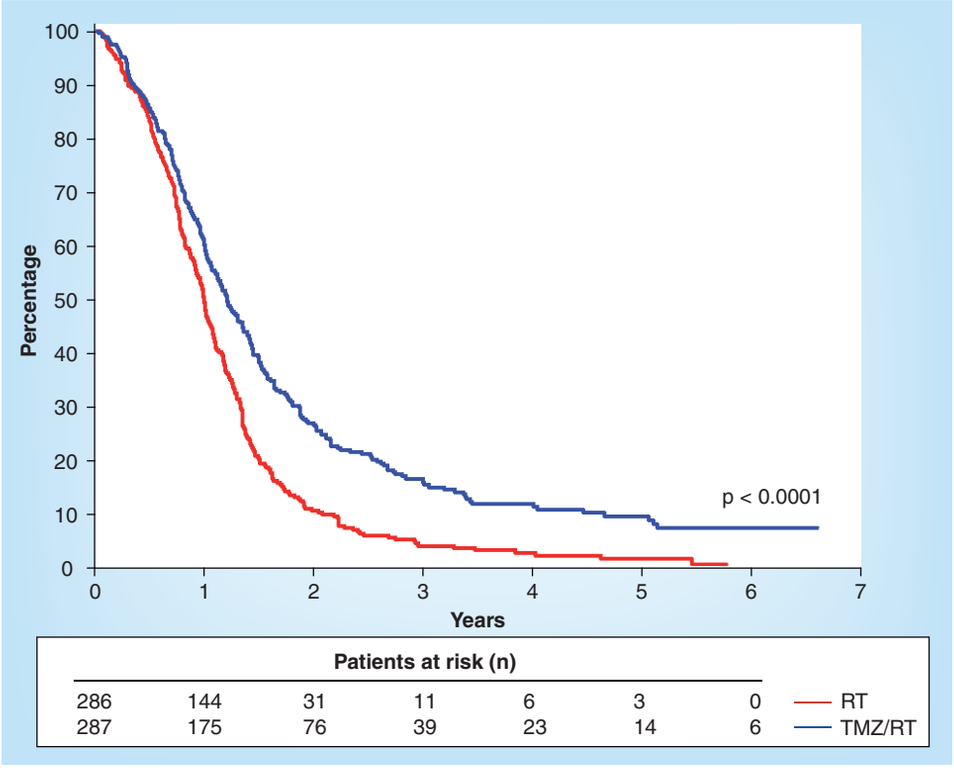

Figure 2. The European Organisation for Research and Treatment of Cancer 22981/26981 trial conducted in collaboration with NCIC. At a median follow-up of 61 months, median OS was 14.6 months with RT plus TMZ and 12.1 months with RT alone. Adding TMZ to RT for newly diagnosed glioblastoma resulted in a clinically meaningful and statistically significant survival benefit with minimal additional toxicity.
OS: Overall survival; RT: Radiotherapy; TMZ: Temozolomide.
Reproduced with permission from [1].

and the first transatlantic trial with a prospective QA RT program. This was truly a learning experience for everyone involved, and we also recognized much that we still need to learn.

Types of challenges

■ Optimize interactions between clinicians

There are many challenges that need to be addressed when organizing an intergroup study (Table 1). To begin with, for the EORTC 26052–22053/RTOG 0525 trial, we needed to optimize interaction between the USA and EORTC clinicians with respect to protocol development and scientific input. In the protocol development process, the processes and timing for the NCIs Cancer Therapy Evaluation Program (CTEP) and Central Institutional Review Board (CIRB) approvals and the schedule of the EORTC approval processes needed to be integrated in order to mitigate difficulties and mishaps. Naturally, there was a learning curve involved in optimizing these processes for the involved organizations.

The EORTC re-evaluated the QA requirements for RT, identified differences in RT approaches (volumes), and installed a QA RT program.

■ Registration/randomization procedures: case report forms

Despite a very strict clinical trial environment in Europe including the data protection directive, the US Office for Human Research Protection (OHRP) imposes that any clinical trial be reviewed annually by an appropriately accredited IRB. Such a system adds a significant burden on sites. Fortunately, the EORTC has a properly accredited IRB that can perform such a review, and this review would then be valid for all centers that are part of the EORTC network. The EORTC headquarters holds a Federalwide Assurance (FWA), an Office for Human Research Protection (OHRP) approved assurance, and has set up an IRB under this FWA that ensures that EORTC procedures follow Title 45 Code of Federal Regulations Part 46 requirements/Health and Human Services (HHS) regulations, as well as provides for an annual review of transatlantic trials.

Still, this system prevented the EORTC from using a remote capture system, a condition of centralized FWA, which imposes data to be circulated through the FWA holder. For future trials, the EORTC has convinced US structures that using a remote data capture system while giving EORTC 'read only' access to such a system, provided that this is technically feasible, would satisfy this condition. In general, the EORTC would welcome US recognition that the EU has clinical trial legislation that guarantees patient protection up to US levels even though continuous review is performed differently than in the USA.

■ EORTC-specific requirements for extensive verification of all the eligibility criteria

The accurate verification of eligibility criteria is critical for trial quality and patient protection. It is essential to avoid having non-eligible patients registered in a trial from the very beginning as opposed to a retrospective verification. Therefore, the EORTC has very strict requirements pertaining to the performance of

eligibility checks, and all criteria are usually checked one by one, preferably by asking for physical data as opposed to a general yes or no response. On the other hand, US groups are accustomed to a more limited eligibility check that favors a general overarching yes or no reply from the investigator with respect to whether a patient met all eligibility criteria. These divergent approaches necessitated the generation of intermediate steps in the patient registration process so that patient eligibility could be assessed in a more thorough and consistent manner.

■ Pharmacovigilance & serious adverse events

NCI collaborative groups are required to report all serious adverse events into the NCI's web-based Adverse Event Expedited Reporting System (AdEERS). US investigators are accustomed to using this system, and NCI collaborative groups can then configure the extraction they need for the clinical database. By contrast, the situation for the EORTC is more complicated. Training all of the EU investigators to use AdEERS for just one trial is unrealistic, not just because of the time required, but also because the reporting requirements in the EU and the US are different. If the EU investigators encode directly into AdEERS, then the EORTC is not be able to meet its legal obligations in the EU. Here, the only acceptable solution is to doubly encode the reported cases, once in the EU format and then again into AdEERS.

■ Contract & agreement development

Definitions are of major importance for contract and agreement development. Some key EU definitions, such as sponsor, are not interpreted the same way on the other side of the ocean. Outside of trials with an IND, our US colleagues frequently see the sponsor as the funder, whereas in the EU the role is seen more with respect to responsibility. The clinical Trial Directive of 2001 in Europe has now formalized in a very stringent format the role and responsibilities of the sponsor. Sharing intercontinental responsibilities now impose that duties are laid out in a binding document ready for auditing and inspections. The notion of a contract as such is abandoned in favor of a memorandum of understanding: a document that defines terms of collaboration without its liability aspects, the liability aspects being unacceptable for some US partners. These differing perspectives make

Table 1. Bottlenecks observed in a selection of European Organisation for Research and Treatment of Cancer intergroup trials.

	EORTC led		EORTC joins US groups	
Bottlenecks\trials	EORTC 26053–22054 NCIC CTG CEC.1 RTOG 0834 MRC BR14	RTOG 0525 EORTC 26052–22053	NCCTG N0577 EORTC 26081–22086	RTOG 0848 EORTC 40084–22084
Heterogeneity of groups and infrastructures[†]	x		x	x
Awareness of the legal environment (Form 1572)				x
Sponsorship, insurance and legal responsibilities		x	x	x
QA and QC procedures		x		x
Biobanking agenda				
Pharmacovigilance reporting (AdEERS)	x	x	x	x
Contractual aspects and financing		x	x	X

[†]Solutions found for trial 26052 could not be transposed easily to other trials.

EORTC 26053–22054, NCIC CTG CEC.1, RTOG 0834, MRC BR14 and HUB: Phase III trial on concurrent and adjuvant temozolomide chemotherapy in non-1p/19q deleted anaplastic glioma. The CATNON intergroup trial.

EORTC 26052–22053, RTOG 0525: Phase III trial comparing conventional adjuvant temozolomide with dose-intensive temozolomide in patients with newly diagnosed glioblastoma.

EORTC 26081–22086, NCCTG N0577: Phase III intergroup study of radiotherapy versus temozolomide alone versus radiotherapy with concomitant and adjuvant temozolomide for patients with newly diagnosed anaplastic oligodendroglioma or anaplastic mixed glioma with chromosomal co-deletions of 1p and 19q.

EORTC 40084–22084, RTOG 0848: a Phase III trial evaluating both erlotinib and chemoradiation as adjuvant treatment for patients with resected head of pancreas adenocarcinoma.

the negotiation quite complicated and underscore the mutual need to learn the other partner's contractual language and culture.

■ Handling of amendments

When the task concerns the handling of amendments, the US groups, which act within a single country, have a distinct and obvious advantage over their counterparts in the multimember European state. US groups do not experience any particular difficulties with amendment management, and therefore protocols are modified rather frequently. Each change is implemented after the appropriate approvals are obtained centrally. In Europe, on the contrary, many changes require submission as substantial amendments to each of the participating member states competent authorities and ethics committees. Aside from the huge workload that this generates, it is not possible to synchronize all these approvals, and as a consequence, amendments frequently languish in the approval process in Europe even while they are already being implemented in the USA. Moreover, as far as eligibility criteria and amendments are concerned, some systems do not allow for coexistence of several versions of the prescribed check that is to be performed.

■ Working with a pharmaceutical partner and a contract research organization for biological materials testing

Working with commercial partners in a transatlantic setting is not always easy. Budgets may be very different on both sides of the ocean due to different legal requirements. In the EORTC 26052–22053/RTOG 0525 trial, the EORTC had to negotiate a separate budget with the pharmaceutical partner. Similarly, cross-border transfer of biological materials is not trivial, so it was necessary to engage CROs on both continents to perform MGMT (O6-methylguanine-DNA methyltransferase) analyses.

Overall, the most frequently encountered operational bottlenecks were heterogeneity of groups and infrastructures, awareness of the legal environment (Form 1572), sponsorship, insurance and legal responsibilities, QA and QC procedures, biobanking agenda, pharmacovigilance reporting (AdEERS), contractual aspects and financing. We now have, in 2011, a better understanding of the respective procedures, standard approaches and systematic checklists. We have established a platform of cooperation for QA RT standards and have shared common initiatives such as the Imaging Program. There now exist well developed intercontinental platforms and models for rare tumors/molecular subentities, key public health questions, and partnership with industry and regulators.

Intergroup studies & cooperation with industry

Intergroup studies offer access to large networks with cross-expertise, a shortened time to recruitment completion, high credibility and acceptance by physicians, a multidisciplinary therapeutic approach, and special focus, say, on niche populations. These intergroup studies can be resource- and cost-effective if well built, and they can deliver readily and globally acceptable results. Intergroup trials optimize the expertise of the three main actors to the benefit of the scientific community and patient.

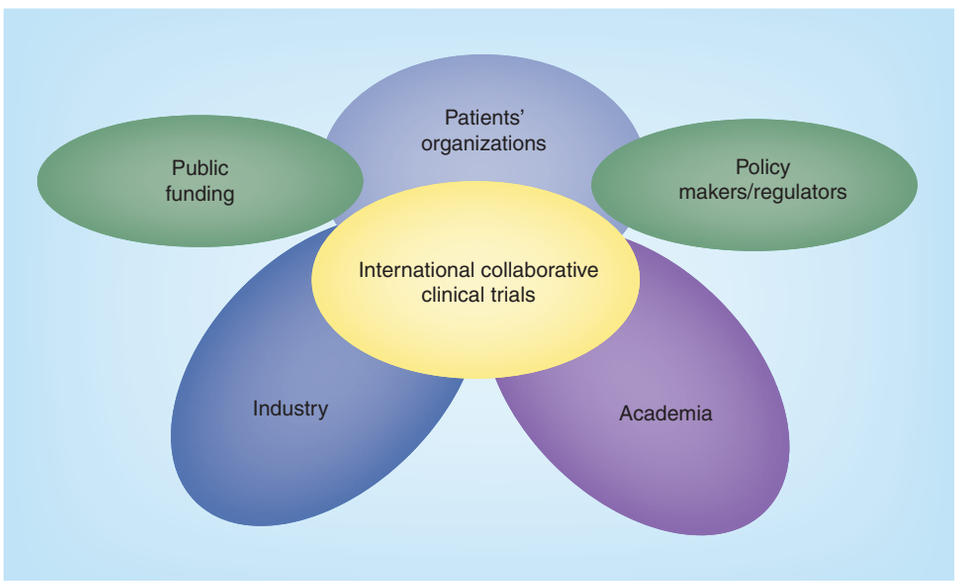

Figure 3. Cancer clinical trials in the 21st century. International investigator-driven clinical trials have multiple stakeholders.

In cancer clinical research, there is certainly a pressing need for new models of cooperation between academia and industry in the international clinical trial setting [2]. For example, there are ethical and scientific concerns related to the conduct of international clinical trials and in maintaining academic integrity in academic–commercial partnerships [3,4]. Independent review of the design, conduct and reporting of clinical trials should be seen as essential, and guaranteeing the independence of academic networks should be seen as an important corollary to this [5,6].

Several models of cooperation are possible, and these cooperative

agreements can address commercial needs that can be addressed by academic networks. These needs can be addressed by writing specific contracts between the academic and commercial partner, but the bottom line, the desired outcome concerning the drafting of these contracts, is the assurance that the principles of academic independence are secured.

The EORTC holds to a set of principles for collaboration with industry. These are:

- The protocol is designed by academia;
- The protocol concept be reviewed by an independent peer review committee;
- The integrity of the database be controlled by an independent group with a focus on the validity of the primary end point release;
- The statistical analysis and publication be independently processed;
- Charters for the use of biological material.

These principles ensure public and regulatory independence. In addition, even if financially compensated for incurred costs, research organizations do not have any benefit related to study outcomes, which also guarantees an additional level of independence. In this respect, maintaining study payers blinded to study end point is an important level of integrity. The above principles have actually been endorsed by several, but not all, academic groups.

Future perspective

Considerable progress has been made in conducting international IDCTs, but the processes still need to be optimized. Increased involvement of the many cancer clinical trial stakeholders (Figure 3), will help shape the future of international IDCTs. Within the international intergroup cancer clinical trials setting, these stakeholders can work together to enforce independence and guarantee public reliability of clinical trial results.

The cancer clinical trial stakeholders all play an important role in the conduct of international IDCTs, and cooperation among these stakeholders is necessary to effect further change. In particular, it is important to enlarge the discussion to include regulatory bodies, as they are also stakeholders in this effort.

The experiences gained here will be advanced to build a modern international clinical trial platform that incorporates imaging, translational research, biobanking and quality assurance in radiotherapy, as well as quality assurance in surgery. Such an integrated translational and clinical research platform will bring us closer to the realization of personalized medicine.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- International investigator-driven clinical trials (IDCTs) can address common and devastating malignancies where even a small improvement in survival would have a major impact on public health.
- Due to their ability to reach required sample sizes, international IDCTs are the ideal platform for studies involving rare tumors.
- International IDCTs enable global progression in standards of care.
- International intergroup IDCTs satisfy international standards for quality, achieve maximum efficiency, avoid duplication, and realize effective implementation of research results into medical practice.
- The lead group of an international intergroup IDCT must have the capabilities to work effectively in the international setting.
- Working procedures must be established and the regulatory environment and QA/QC in the trial setting must be considered.
- Challenges in setting up and conducting international IDCTs include, but are not limited to, optimizing interactions between clinicians, registration and randomization procedures, case report forms, verifying eligibility criteria, pharmacovigilance and serious adverse event reporting, contract and agreement development, handling of amendments, and working with a pharmaceutical partner or CRO.
- There is a need for new models of cooperation between academia and industry in cancer clinical research.
- Several models of cooperation between academia and industry are possible, so long as the principles of academic independence are secured.

Bibliography

Papers of special note have been highlighted as:

- ▪ of interest
- ▪▪ of considerable interest

1 Stupp R, Hegi M, Mason W *et al.* Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised Phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol.* 10(5), 459–466 (2009).

▪ **Results of the clinical trial referred to in the text.**

2 Meunier F. Challenges and opportunities of cancer clinical research at pan-european level. In: *Crosstalks. In Sickness and in Health. The Future of Medicine: Added Value & Global Access.* Wynants M (Ed.). VUB Press, Brussels, Belgium, 215–227 (2009).

▪▪ **Current challenges and future goals.**

3 Glickman S, McHutchinson J, Peterson E *et al.* Ethical and scientific implications of the globalization of clinical research. *N. Engl. J. Med.* 360, 816–823 (2009).

▪ **International perspective on clinical trial issues.**

4 DeAngelis C, Fontanarosa P. Impugning the integrity of medical science: the adverse effects of industry influence. *JAMA* 299, 1833–1835 (2008).

▪ **Addresses influence of industry on academic trials.**

5 Piccart M, Goldhirsch A. Keeping faith with trial volunteers. *Nature* 446, 137–138 (2007).

▪▪ **Deals with the importance of academic independence.**

6 Schilsky R, Bressler L. Collaboration between cooperative groups and industry. *J. Oncol. Pract.* 4, 140–141 (2008).

▪ **Addresses issues involved in establishing collaborations between academia and industry.**