Ref. Ares(2018)1917090 - 10/04/2018

Co-funded by
the Health Programme
of the European Union

JARC
JOINT ACTION ON RARE CANCERS

*"This Deliverable is a part of the joint action "724161/JARC" which has received funding from the European Union's Health Programme (2014-2020)".*

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# D7.1

# Proposals to improve collaborative international clinical trials in the EU, particularly inter-group clinical trials

## Objectives

Investigator-driven clinical research on rare cancers faces huge difficulties at the European level from the regulatory point of view, while waiting for the implementation of the new EU Clinical Trials Regulation. On the other hand, ERNs provide a framework which allow substantial opportunities for improvement. Thus, in the context of the JARC, our aims were:

- to make an inventory of regulatory constraints for international investigator-driven collaborative clinical trials on rare cancers in the European Union (EU),
- to provide recommendations to support international investigator-driven collaborative clinical trials on rare cancers in the context of the European Reference Networks (ERNs).

## Methods

The following steps were undertaken:

- review of literature to identify major regulatory and organisational challenges in conducting international investigator-driven collaborative clinical trials on rare cancers;
- development of a questionnaire, based on the results of the literature review;
- discussion of the questionnaire with WP7 partners (please refer to Annex 1 for details);
- circulation of the questionnaire to the coordinators of the 3 ERNs dealing with rare cancers: EURACAN (on rare solid cancers of the adults), PaedCan (on childhood cancer), EuroBloodNet (on rare haematological diseases).

## Results

We received answers from all 3 ERN representatives. EURACAN includes 10 different domains of rare cancer families and we got answers from representatives of each of the 10 domains.

### Characteristics of responders

Most of respondents work at academic or comprehensive cancer centres. They are experienced researchers in clinical studies. Half of respondents were coordinators in 1-10 studies, 25% in >10 and 25% in >20 clinical studies.

### Identified challenges

The tables below highlight major challenges identified by the respondents.

| Regulatory Challenges | Relevance on a scale from 1 to 5 (1=not a challenge at all; 5=major challenge) | | | |
|---|---|---|---|---|
| | 1-2 | 3 | 4-5 | missing |
| Competent authority procedures | 25% | 25% | 44% | 6% |
| Ethics committee procedures | 38% | 25% | 31% | 6% |
| Lack of communication between national authorities and ethics committees | 69% | 25% | 0 | 6% |
| Insurance/indemnification coverage | 44% | 6% | 38% | 12% |
| Identification of the sponsor | 50% | 25% | 13% | 13% |
| Monitoring procedures/ frequency | 56% | 25% | 6% | 13% |
| Adverse reaction reporting procedures/frequency | 50% | 25% | 13% | 13% |
| Increased scrutiny and restriction of bio-banking and repository research (Material transfer agreement) | 44% | 25% | 25% | 6% |
| Ownership of data and publication rights | 63% | 19% | 0 | 6% |
| Differing regulations between countries | 31% | 25% | 38% | 6% |

| Organisational Challenges | Relevance on a scale from 1 to 5 (1=not a challenge at all; 5=major challenge) | | | |
|---|---|---|---|---|
| | 1-2 | 3 | 4-5 | missing |
| Lack of institutional facilities | 38% | 38% | 6% | 18% |
| Different infrastructure for cancer clinical trials across countries | 31% | 31% | 32% | 6% |
| Differing licensing arrangements for specific drugs amongst countries | 25% | 31% | 38% | 6% |
| Drug delivery in different countries | 25% | 44% | 25% | 6% |
| Shipment of specimens across borders (need of approvals). | 50% | 19% | 25% | 6% |
| Lack of research materials | 44% | 19% | 31% | 6% |
| Lack of trained personnel | 44% | 19% | 25% | 6% |
| Lack of time of trained personnel | 25% | 19% | 44% | 13% |

| Other Challenges | Relevance on a scale from 1 to 5 (1=not a challenge at all; 5=major challenge) | | | |
|---|---|---|---|---|
| | 1-2 | 3 | 4-5 | missing |
| Lack of incentives | 44% | 19% | 6% | 31% |
| Pharma companies do not want to embark into an already commercialised drug to study rare cancers. | 6% | 0 | 75% | 19% |
| Limited scientific interest among researchers | 56% | 13% | 6% | 25% |
| Researchers are afraid to embark into a risky trial (early closure for low patient recruitment) | 31% | 13% | 31% | 25% |
| It is difficult to engage multidisciplinary expert teams in rare cancers | 31% | 38% | 6% | 25% |
| Lack of collaborative clinical research groups with strong operational facilities | 25% | 31% | 19% | 25% |

Among the regulatory challenges, the most relevant (relevance ≥3) were the cumbersome procedures requested by the Competent Authorities and by the Ethics Committees, the request to develop material transfer agreement vis-a-vis increased restrictions to bio-banking, and the heterogeneity of regulations across countries (e.g., a lack of harmonisation in insurance requirements, co-sponsorship agreements, designation of investigational medical products (IMP), GCP monitoring requirements, serious adverse event reporting, etc.)

Among the organisational challenges, the most relevant (relevance ≥3) were the lack of institutional support, limited infrastructures for clinical trials across countries and time constraints and/or lack of trained personnel.

Among other challenges, the following were identified:

- a lack of interest of pharma companies in supporting clinical studies on already marketed drugs to extend the label to rare cancers;
- a lack of funding for international academic collaborative trials (applications to national funding bodies are fragmented).

All agreed that the role played by the academia and independent groups in rare cancer research is higher compared to common cancers. Hurdles may be handled as a matter of fact, but at least there are delays.

How these challenges differ for rare compared to common cancers?

For rare cancers, regulatory issues may be more challenging as long as more countries can be involved in trials. Thus several competent authority (CA) and ethics committee (EC) procedures need to be dealt with, with a high variability among them, and insurance requirements are discrepant.

From the organisational point of view:

- institutional funding is lower for rare cancers compared to common cancers;

- more doctors are dedicated to common cancers compared to rare cancers;

- identifying centres with expertise on rare cancers is much more difficult than for common cancers and it is more time-consuming;

- on rare cancers, patient involvement in study definition and involvement may be more difficult;

- Clinical Trial facilities, including their personnel, have limited specific background and skills on rare cancers. National rare cancer networks may exist, but their funding is limited.

From the funding point of view:

- costs of a trial are the same, regardless of whether it is on a rare or a common cancer, with costs to be factored on trial design (statisticians) management (trial coordinators, data management, database costs), trial governance (sponsor oversight, CA/Ethics committee fees, monitoring), drug costs, drug dispensing costs, institutional fees. In rare cancers, even if a trial enrols a limited number of patients, costs per patient are high all the same, having to do with trial management and sponsor costs;

- in rare cancers, resources needed to enrol few patients are high.

## Possible solutions

### The new Clinical Trials Regulation (CTR)

The CTR is an opportunity to support harmonisation across countries because a EU regulation comes into force automatically in all EU countries and overtakes national rules. This is a factor of improvement, since any rule is easier to implement with international trials as long as it is harmonized.

Centralized submission should make it much easier for a collaborative group to sponsor a trial in the EU. However, it is left to learn how much the financial agreements with each institution will be harmonized, as well as how much centre-specific requirements dictated by institutional ethics committees will be in place, e.g., in regard to the informed consent, etc.

The provision in the CTR of a risk-based approach should greatly benefit investigator-driven trials. Several academic studies in rare cancers may be expected to be low-risk studies. However, it is left to learn how much benefits thereon will be discrepant across EU member states, e.g., how much insurance policies will be harmonized, how much costs of marketed drugs and diagnostic exams, etc., will be handled by each member state. National health care systems could actively promote and support research for rare cancers, at the very least with a view to trials which could decrease health costs (and which companies may not be interested to sponsor). In any case, possible extra-costs for health systems implied by such trials should be limited in trials implemented within ERNs, i.e. carried out by centres of expertise on rare cancers endorsed by national governments.

The possibility to split sponsorship among HCPs might be a way by which they can afford launching trials which otherwise would not be feasible. Some studies could be co-sponsored between the academia & pharma. However, it will be crucial to address the many issues in place with trials co-sponsored between the academia and the industry.

### The establishment of an ERN-specific research infrastructure

ERNs are a unique opportunity in the rare cancer field. In other words, clinical trials implemented over a ERN can exploit healthcare routines as well as the expertise of centres of excellence that are used to work together and that serve as reference institutions for specific rare cancers. For example, quality of care items, such as the appropriateness of pathologic diagnosis, may be relied upon much more than usual. In addition, HCPs' IT facilities can be set to be interoperable with standard electronic CRFs, etc. As a consequence, ERNs represent a framework in which investigator-driven international collaborative studies on rare cancers can be undertaken minimizing costs, thus allowing studies which otherwise would not be affordable for the academia. This said, a dedicated CRO for ERNs or a consortium of CROs sharing open infrastructures could serve collaborative trials set up within ERNs. Minimum requirements of any research infrastructure should:

- serve all the HCPs of a specific ERN;
- be interoperable with the electronic health records of the HCPs and available bio-banks;
- be flexible to accommodate the requirements pertaining to different rare cancers and possible study objectives;
- be compliant with privacy requirements, as foreseen by the CTR and the EU General Data Protection Regulation;
- be interoperable with administrative data bases in the EU countries and cancer registries.

All this should substantially decrease costs, thereby making it possible to undertake clinical trials which otherwise would not be affordable to the academia.

This would set up a research infrastructure. Then, an entity serving as the trial sponsor for this kind of studies would be needed. Possible solutions in principle may be:

1. establishing a consortium of all Health Care Providers (HCPs) of a ERN operating as a legal entity;
2. exploiting a scientific/professional society or any multi-stakeholder initiative being a legal entity.

Funding

Decreasing costs for investigator-driven clinical trials on rare cancers within the ERNs framework should make it more appealing and feasible for charities, and the like, to support them. It would be highly recommended that the EU research funding infrastructures could launch dedicated calls for clinical trials on rare cancers in this circuit.

Annex 1

Questionnaire to identify major problems faced in conducting international investigator-driven collaborative clinical trials on rare cancers

The aim of this questionnaire is to identify major problems faced in conducting international investigator-driven collaborative clinical trials on rare cancers:

1. Head and neck cancers (cancers of nasal cavity and sinuses, nasopharynx, hypopharynx, larynx, salivary glands, oropharynx, oral cavity and lip, eye, middle ear)
2. Thoracic rare cancers (tumours of trachea, thymus, malignant mesothelioma)
3. Male genital and urogenital rare cancers (tumours of testis, penis, renal pelvis, ureter, urethra, and extragonadal germ cell tumours)
4. Female genital rare cancers (tumours of vulva and vagina, non-epithelial tumours of ovary, trophoblastic tumours of the placenta)
5. Neuroendocrine tumours
6. Tumours of the endocrine organs (cancers of thyroid, parathyroid, adrenal cortex, pituitary gland)
7. Central Nervous System tumours (Glial tumours, medulloblastoma, malignant meningioma)
8. Sarcomas (soft tissue sarcomas, bone sarcomas, gastrointestinal stromal tumours)
9. Digestive rare cancers (Tumours of small intestine, anal canal, gallbladder and extrahepatic biliary duct)
10. Rare skin cancers and non-cutaneous melanoma (melanoma of mucosae and of the uvea, adnexal skin carcinomas, Kaposi sarcoma)
11. Haematological rare malignancies (acute myeloid leukemia, myeloproliferative neoplasms, myelodisplastic and myeloproliferative neoplasms, histiocytic and dendritic cell neoplasms)
12. Pediatric cancers (all)

Answering this questionnaire, we would appreciate if you could also think of whether and how these challenges differ between rare and common cancers.

Your contribution will be used to:

- provide proposals to improve national and European regulations and/or their interpretation,
- develop recommendations about the optimal ways to connect the new European Reference Networks (ERNs) to collaborative clinical research. In the field of rare cancers, research should never be split from healthcare, so the ERNs may be a formidable opportunity to promote collaborative clinical research.

Profiling

In which institution are you working?

- Comprehensive cancer centre
- Research Institute
- Academic hospital
- General hospital
- Other (please specify)

Which type of studies are you most involved in (on rare cancers and common cancers)? are allowed to choose more than 1 answer

- Phase I
- Phase II
- Phase III
- Post marketing
- Observational
- Real world
- Other (please specify)

How many collaborative, investigator-driven clinical trials on rare cancers have you joined in the last 5 years?

- None
- 1-10
- 10-20
- >20

Which was the role that you had in the previously listed investigator-driven clinical trials on rare cancers?

- Investigator
- Study sponsor
- Others, please clarify

Please select the main regulatory issues you faced in conducting international investigator-driven collaborative trials in the last 5 years. For each challenge, please select the relevance on a scale from 1 to 5 (1=not a challenge at all; 5=major challenge)

| Challenge | Select relevance from 1 to 5 | Does it differ from common cancers? If yes, how? |
|---|---|---|
| Competent authority procedures | | |
| Ethics committee procedures | | |
| Lack of communication between national authorities and ethics committees | | |
| Insurance/indemnification coverage | | |
| Identification of the sponsor | | |
| Monitoring procedures/ frequency | | |
| Adverse reaction reporting procedures/frequency | | |
| Increased scrutiny and restriction of biobanking and repository research<br>(Material transfer agreements) | | |
| Ownership of data and publication rights | | |
| Differing regulations between countries (lack of harmonisation in insurance requirements, in allowance of co-sponsorship agreement, in the designation of investigational medical products (IMP), in GCP monitoring requirements and adverse effects reporting, etc.) | | |
| Others (please clarify) | | |

Please select the main organisational problems you faced in conducting international investigator-driven collaborative trails in the last 10 years. For each challenge please select its relevance on a scale from 1 to 5 (1=not a challenge at all; 5=principal challenge)

| Challenge | Select relevance from 1 to 5 | Does it differ from common cancers? If yes, how? |
|---|---|---|
| Lack of institutional facilities | | |
| Different infrastructure for cancer clinical trials across countries | | |
| Differing licensing arrangements for specific drugs amongst countries | | |
| Drug delivery in different countries | | |
| Shipment of specimens across borders (need of approvals). | | |
| Lack of research materials | | |
| Lack of trained personnel | | |
| Lack of time of trained personnel | | |
| Others (please clarify) | | |

Considering these challenges, in your opinion how the new Clinical Trials Regulation will be of help?

Please identify additional major issues hindering collaborative investigator-driven trials on rare cancers. You are allowed to select more than one answer and to add personal considerations based on your experience. For each issue please select its relevance on a scale from 1 to 5 (1=not a challenge at all; 5=principal challenge)

| Issue | Select relevance from 1 to 5 | Does it differ from common cancers? If yes, how? |
|---|---|---|
| Lack of incentives | | |
| Pharma companies do not want to embark into an already commercialised drug to study rare cancers<br>If a drug is licensed, it is difficult to find funds to buy the drug within the study | | |
| Limited scientific interest among researchers | | |
| Researchers are afraid to embark into a risky trial (early closure for low patient recruitment) | | |
| It is difficult to engage multidisciplinary expert teams in rare cancers | | |
| Lack of collaborative clinical research groups with strong operational facilities | | |
| Others (please clarify) | | |

In which setting do you think the investigator-driven clinical trials will be most useful for rare cancers?

- Drug development
- Post licensing studies
    - Follow-up
    - Repurposing
- Others (please list and clarifies)

In your opinion, which is the main source of costs of collaborative investigator-driven trials in rare cancers?

In your opinion, who should/could fund of collaborative investigator-driven trials in rare cancers?

Can you please list major sources of funding for the international collaborative trials on rare cancers you benefited from? are allowed to choose more than 1 answer

- Government
- Charities

- Private foundations
- International source such the EU
- Others (please list and clarifies)

Which mechanisms do you envision to reduce cost of collaborative investigator-driven trials in rare cancers?

Do you see ways in which the national healthcare system could be involved to facilitate/reduce costs of collaborative investigator-driven trials in rare cancers