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JARC
JOINT ACTION ON RARE CANCERS

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Deliverable D7.4

"Roadmap on precision medicine in rare cancer care within ERNs"

Contents

1. DESCRIPTION

1.1 Joint Action on Rare Cancers

The Joint Action on Rare Cancers (JARC) is aimed to integrate and maximize efforts of the European Union (EU) Commission, EU Member States and all stakeholders to advance quality of care and research on rare cancers.

The public health challenges posed by rare cancers include the limited professional expertise in the community, the difficulties in clinical research, the need of a timely and appropriate diagnosis and optimal treatment from the very beginning of the patient's journey. An accurate clinical, pathologic and biological assessment of the disease of the individual patient is key to survival and cure, as well as an expert clinical decision provided by a multidisciplinary team. To this end, proper referral of patients and effective clinical networking are crucial in rare cancers. This is the main reason why JARC decided to shape its efforts around the new European Reference Networks (ERNs) with the following objectives:

1. Improving epidemiological surveillance of rare cancers in the EU
2. Identifying standards of care for all families of rare cancers to ensure sharing of best practices and equality of care for rare cancers across Europe, particularly through clinical networking
3. Improving the implementation at local level and within ERNs of clinical practice guidelines on rare cancers
4. Promoting integration of translational research innovations into rare cancer care
5. Improving education on rare cancers for medical and non-medical experts to ameliorate management of rare cancers and to improve rare cancer patients' empowerment in the EU
6. Identifying core strategies to incorporate in National cancer plans and Rare disease plans to address the specific needs of rare cancers across EU MSs

The JARC is structured in 10 work packages (WPs). Three cross cutting WPs (WP1 coordination, WP2 dissemination, WP3 evaluation) and 7 specific WPs based on the JARC objectives: WP4 epidemiology, WP5 quality of care, WP6 clinical practice guidelines, WP7 innovation and access to innovation, WP8 medical education, WP9 childhood cancers and, WP10 rare cancers policy. Patients work across all work packages, driving the JARC efforts along the needs of the only end users of all what we can do, in care and research as well

1.2 Work Package 7

The goal of WP7 is to establish optimal ways to bring the best treatment and care to patients by advancing translational and clinical research on rare cancers trough ERNs.
Objectives:

1. to stimulate translational research on RCs by exploiting networking, namely through the new ERNs, as a mean to promote banking
2. to promote exploitation of "big data", namely those generated through the new ERNs, as a mean to advance our knowledge on rare cancers to provide recommendations on how to optimize long-term surveillance of rare cancer patients in an effort to address the many survivorship's issues
3. to make proposals on how to exploit available regulations across the EU, and/or how to improve them, on collaborative prospective interventional clinical research, especially academic clinical research joining national collaborative groups (inter-group research, etc)

1.3 Aim and purpose of deliverable

This deliverable aims at resuming the conclusions gathered during the course of the Joint action within this work package. The deliverable will serve as the basis for the comprehensive document on the joint action : the 'JARC Book'.

1.4 The target group of the specific deliverable

The main target group of this deliverable are the members of the European Reference Networks, especially the responsibles/principle investigators for clinical trials within the context of rare cancers. In addition, policy makers involved in facilitating, controlling or authorizing clinical trials are a key target public.

1.5 Summary of the main conclusions of the deliverable

Six key areas of attention have been identified for future action:

Challenge 1: lack of clinical expertise
Challenge 2: rare cancers are not attractive for drug developers
Challenge 3: No priority for public sector due to low health impact
Challenge 4: Rareness vs statistically valid outcomes
Challenge 5: lack of evidence in choice of experimental treatments
Challenge 6: limited tissue/data repositories

2. INTRODUCTION

Clinical research for rare cancers faces many challenges:

1. lack of clinical **expertise**
2. less interesting for drug developers due to small **market potential**
3. public sector focuses on greatest **health impact**
4. need for large numbers of patients to obtain **statistically** valid outcomes
5. choice of experimental treatments is often based on inadequate or minimal **evidence**
6. limited tissue **repositories**

Randomized controlled trials (RCT) are today the 'golden' standard for assessing the therapeutic efficacy of an intervention as compared to a control group (i.e., no treatment or previously tested treatment). RCTs are challenging though in the case of rare cancers due to limitations in available cases.

In recent years, innovative clinical trial methods have been developed that offer promise for promoting more efficient (minimize the total number of patients) and effective research, maximizing the potential to answer research questions. All these alternative strategies require further consideration and assessment as potential clinical trial design options for rare cancer studies.

Rare tumors account for a considerable proportion of cancers. Overcoming (some of) the above-mentioned challenges inherent in the study of rare cancers is critical to achieve improvements in patient outcomes. Combining a redesign of clinical trial protocols with the new paradigm for the treatment of all cancers, may lead to improvements in survival benefits for rare cancers in line with those achieved in the treatment of more common types.

Purpose: In this deliverable, we have gathered on how to move forwared care for patients suffering a rare cancer by coordianted, integrative research within the ERN context. Below, we have outlined in somewhat more detail what exactly could/should be performed to facilitate running clinical trials for rare cancers.

3. MATERIAL AND METHOD

In this Workpackage we applied the following methods:

1 literature surveys
2 surveys with relevant partners in the member states
3 expert workshop
4 expert opinions

The Workpackage partners met on 3 WP meetings to discuss aims of the WP and share work progress. Bilateral meetings with the coordination team and amongst partners were organized in parallel.

4. RESULTS AND DISCUSSION: "CRITICAL ORGANIZATIONAL ASPECTS OF CLINICAL RESEARCH IN RARE CANCERS"

Challenge 1: lack of clinical expertise

The lack of expertise can be addressed and managed through three action paths:

- ✓ maximize the implication of the reference network on rare cancers in innovative research

The ERN involving centres of expertise along with other centres are established basically as a means to provide good quality of care to all patients suffering a rare cancer. Quality control programs should be in place in these networks assuring high-quality care across the whole network. Thus, ERN and national reference networks on rare cancers will support not only the improvement of care but provide moreover a unique advantage for accrual in trials, as well as guaranteeing hogh-quality within clinical trials

- ✓ Evolution of pathologic diagnosis

To improve diagnostic accuracy in clinical studies (based on trial and/or database), it will be essential to address the pitfalls of pathologic diagnosis in rare cancers. Possible tools to address these issues could be teleconferencing on pathology issues (e.g. integrated within so-called Molecular tumor boards), expert panels, dedicated training facilities within the ERN context.

- ✓ Optimization of biomarkers

Research on biomarkers should be an inherent part of research on new drugs, because it may help identify those patient populations in which the drug is able to provide remarkable benefits. Recommendations are needed to optimize the way biomarkers are developed and validated and can be incorporated into pathologic diagnosis.

As data formats of molecular/biochemical/imaging test results obtained from rare or common cancers are alike, we do not recommend to develop a register specific for rare cancers but support the possibility to integrate results obtained from rare cancers within data-registers produced for common cancers. It is important that such registers investigate the impact of the new GDPR as access to these type of data is essential for retrospective and prospective clinical trial assessment. Implicit informed consent by the patients is recommended especially when dealing with molecular information with hereditary/genetic impacts.

Challenge 2: rare cancers are not attractive for drug developers

Rare disease markets by nature are small and thus for the Industry only attractive if high priced market entry can be achieved.

In some cases, the lower commercialization costs in these less competitive and highly motivated markets with significant unmet needs, together with the advantages of an orphan drug status and the perceptive of premium pricing, were a true incentive for Pharma companies to focus on some rare diseases. In general, however, rare cancer therapies offer a different challenge to the Industry when compared to more familiar areas of care they are used to operate in.

Clinical trials often use less robust methodology (e.g. randomized clinical trials can be unethical given survival rates). Standard of care might be limited, or very complex, and off label use might be the only option, making the choice of a feasible comparative arm in a study difficult. Nevertheless, regulators are not comfortable when hard clinical comparisons are absent. The acceptance of alternatives to classical randomized clinical trial design, such as adaptive trials, cross-over trials, and early escape designs might be a way out. Once a product makes it to the market in a rare disease, there is limited room for a second product, but this lack of competitiveness provides no incentive for lowering prices and ensure availability and access for more patients. Even when initial results are promising there is always the risk of withdrawal of a regulatory submission for a rare cancer treatment, if the company realizes that revenues will not match projected expectations.

Luckily, valuable high quality independent academic research is currently conducted in Europe and has the potential to provide patients with sustainable access to additional effective treatment options. However, how to include rare cancer indication on label, based on published data, is another challenge where policy makers and regulators in Europe should focus on, in order to at least facilitate access to affordable solutions, even when the marketing authorization holder is not interested in fulfilling the necessary requirements.

Challenge 3: no priority for public sector due to low health impact

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.

It is important to create an integrated ERN IT infrastructure. IT facilities must be set to be interoperable with standard electronic CRFs, etc across ERN HCP. The support from dedicated independent research

infrastructure is needed for developing ambitious clinical research agenda. As an example, the EORTC is currently serving as research infrastructure for the ERN EURACAN. Similarly, a consortium of CROs or academic entities sharing open infrastructures could serve collaborative trials set up as an alternative model.

Entity serving as the trial sponsor:
1. using preferentially established trial sponsor such the EORTC with track records in rare cancers research.
2. establishing a consortium of all Health Care Providers (HCPs) of a ERN operating as a legal entity;
3. exploiting a scientific/professional society or any multi-stakeholder initiative being a legal entity.

Finally, one should maximally exploit the options provided in the clinical trial regulation: centralised submission, low-interventional trials, co-sponsorship

Challenge 4: Rareness vs statistically valid outcomes: Bayes shows the ways

Longitudinal studies of rare events often involve correlated binary data. Risk factor for these events cannot be reliably examined using conventional statistical methods. For example, logistic regression models that incorporate generalized estimating equations often fail to converge or provide inaccurate results when analyzing data of this type. Exact conditional logistic regression models have long been used to study binary events in cross-sectional and case-control studies (i.e. single endpoint) with sparse data (e.g. due to small sample size, multiple exposure strata, few events, etc.). However, there are few exact methods for correlated binary event data. Some methods are only applicable when each cluster contains exactly two individual observations, other simulation-based method for testing logistic regression coefficients with cluster samples rely on the fact that the logistic regression model converges. For rare or uncommon events, often nonconvergence of the logistic regression model is encountered.
Bayesian approaches have been proposed which provide a plausible solution to rare event clustered binary data. However, the Bayesian methods require extensive and complicated computations. Decision making in situations of high uncertainty (e.g. due to small sample size) should nevertheless follow strict rules. In principle, any piece of new evidence would need to be exploited in rare cancers. Methodologies to explicitly weigh and combine all the available evidence should be refined, and the Bayesian logic can be instrumental to this end. Likewise, Bayesian-design trials may help optimize the low number of patients liable to be enrolled in clinical studies on rare cancers, as well as adaptive trials in general, with their inherent potential of flexibility when properly applied.

Challenge 5: lack of evidence in choice of experimental treatments

To address these issues, alternative strategies for clinical trial designs crucial to studying small populations could benefit from:

- the development of smooth interoperable access facilities to rare cancer registries
- the development of simple mechanisms for patients to access information about ongoing trials
- increasing the length of treatment observation in order to observe more events
- factorial designs proposed in order to provide answers to multiple treatment questions within one study population
- low power randomized trials (internal control maintained with the trade-off of potentially missing a smaller treatment effect)
- adaptive trials that may include a series of stopping rules for futility or conversion from phase II to III trial
- Bayesian approaches to optimize the low number of patients to be enrolled in trials.

Patient communities should be involved as much as possible in the conception of new clinical trials, particularly in regard to study design and the selection of study end-points…. Patient accrual should be

actively supported through participation of patient advocacy groups and through full exploitation of media communication and information technology

Collaborative investigator groups should be stimulated to conduct platform trials where different treatments (new drugs from industry as well as repurposed ones) can be evaluated side by side with only one control group, thus limiting the number of patients needed in trials.

Regulators should think how to deal with these new study designs, but also on how to accept results from independent research when the pharmaceutical company that owns the marketing authorisation for the drug is poorly or not motivated to take the necessary steps to adapt the label in order to include the rare cancer indication. This could limit the off-label use that can cause liability issues for the prescribing physicians, uncertainties with regard to reimbursement, and patient safety concerns in the absence of formal benefit-risk assessments.

Challenge 6: limited tissue/data repositories

Three routes of action:

- ✓ Biobanks within the ERN/clinical networking
  It should be noticed that the major difference between common and rare cancers is the occurrence of the events within a population. For this, considering the high cost of prolonged high quality tissue preservation (e.g. through cryopreservation), it is proposed to prioritize such conservation of samples derived from rare cancers to those from common cancers. A biobanking effort can essentially be envisaged in two ways: a centralized conservation of all relevant specimens (e.g. the EORTC SPECTA configuration) or as a federated entity with common governance structure (e.g. the BBMRI initiative). Either approach has pro's en con's but both should have: 1°) a clearly expressed mission and vision of the entity consolidated in an expression of common understanding (such as a consortium agreement), 2°) common practices on storage of specimens and data, expressed in SOPs, FORMs and DOCs, which are applicable to all specimens in the biobank 3) as agreement by patients on sample storage and downstream use is key in the success of any research initiative on rare cancers, a common communication strategy on the importance of research in the field of rare cancers should be present or is to be developed. ERNs should play a central role in this communication.

- ✓ Exploitation of electronic clinical records, clinical registries
  How electronic clinical records could be improved to maximize their usefulness for research purposes? Feasibility considering the current investment (OECD report). Clinical registries/clinically annotated bio-bank vs. electronic clinical record. The implementation of structured clinical detailed information in the electronic clinical records is necessary to facilitate the data extraction and exchange. Theoretical and methodological issues posed by the use of these data and Artificial Intelligence to advance medical knowledge (in a framework, which is radically divergent from the one of clinical trials). Correct exploitation of expert systems trained by electronic clinical records to assist clinical decision-making, especially in the area of very rare cancers, where even single cases may be crucial. (In collaboration with education WP).

- ✓ Population-based cancer registries (CR) and other data sources as a source of knowledge
  Population-based cancer registries have, next to the well-known epidemiological descriptive role (serve public health by monitoring changes in cancer occurrence and prognosis) also an important role in the quality of care and cancer control. This is due to the growing interest in real-world data, i.e. population based data on diagnoses, treatment enriched with more relevant clinical data.

In many countries, there are efforts on going or in place to strengthen the links between population-based cancer registration systems, clinical care, research and routine healthcare data. The aim is to both increase the efficiency of data collection and to enhance the clinical content available to the cancer registries. Once these systems are mature, with robust, sustainable technologies in place for data linkage and compliant with GDPR/Privacy regulations, they should provide the platform for a prospective clinical epidemiology framework program for outcome research in rare cancers. Through the auspices of the ENCR and the content of its successive calls for data from the CRs, we envisage that the European Cancer Information System (ECIS) will reflect on and eventually provide such a function in medium-term.

CR should also register all off-label use in rare cancers. In combination with outcome research, this information could be an extremely valuable tool for selecting marketed drugs for "repurposing" and further development in well designed clinical trials finally leading to affordable treatment options.

Two projects have been undertaken within task 7.2 that shed light on these capabilities, the timescales and resources required:

Through a JARC pilot study coordinated between WP4 and WP7.2, we have established that most of the European population-based cancer registries with paediatric data do not have ready access to the detailed clinical information that is required to decide on individual treatment and prognosis. Whilst the pilot study to evaluate the implementation of the Toronto staging principles in CRs was successful, all registries had to use additional resources and data sources to obtain the necessary data for patients diagnosed in the era up to 2016. Nearly all registries will have better access to more complete clinical data, including treatment, tumour biology and relapse, for prospective cases, though privacy issues may limit available data in some countries.

Since several years, the prognostic impact of the HPV status for oropharyngeal cancer is well recognized with a clear distinction between HPV+ and HPV- oropharyngeal cancer. In the present JARC pilot study, several CRs of participating member states were contacted by mail and/or telephone. All registries had no structured information on p16/HPV status for the oropharyngeal cancers. Nevertheless, this information is available in pathology reports, other existing clinical registries or in the medical files of the patients. Additional resources and efforts are needed to obtain the necessary information with the issues that have to be tackled like linkage possibilities and privacy regulation.

For prospective cases, more complete clinical data will be available as the impact of the HPV status is now translated in the 8th TNM classification.