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Indispensable benefit of independent investigator-driven research in a changing clinical trial landscape

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To cite: Oosting SF, Fehrmann RS, de Vries EGE. Indispensable benefit of independent investigator-driven research in a changing clinical trial landscape. *ESMO Open* 2017;2:e000272. doi:10.1136/esmoopen-2017-000272

Received 7 September 2017
Accepted 9 September 2017

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In the Oxford dictionary, 'Independent' is defined as 'Free from outside control; not subject to another's authority'. Independence can be critical to identify important issues for patients. The authors of the paper 'Safeguarding the future of independent, academic clinical cancer research in Europe for the benefit of patients' are to be applauded for their strong plea for independent investigator-driven research. In addition, they use this paper to draw attention to the Clinical Academic Cancer Research Forum (CAREFOR) platform, raised to address funding and regulatory challenges faced by academic researchers and foster collaborative cancer research by developing novel approaches to do clinical trials.¹

Thanks to industry-driven studies, over the last decades, numerous effective drugs for treatment of patients with cancer have been registered.

Mounting costs leading to limited affordability as well as side effects of these drugs has increased interest in precise insight in the clinical benefit of these drugs for patients. Since 2015, two scales have been made available by, respectively, European Society of Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO), namely, the ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) and the ASCO Framework to grade the clinical benefit of drugs.^{2,3} Applying these scales made it clear that far from all studies executed to find relevant indications for new drugs had a high yield for the patient. According to Del Paggio and colleagues, only 15% of 277 randomised controlled trials evaluating systemic therapy for colorectal, breast, non-small cell lung and pancreatic cancer published between 2011 and 2015 met ESMO-MCBS thresholds for meaningful clinical benefit.⁴ These authors propose that

investigators, funding agencies, regulatory agencies and industry should adopt more stringent thresholds for meaningful benefit in the design of future randomised clinical trials. Independent research performed by academia might especially allow to focus on relevant clinical benefit.

Furthermore, several highly relevant clinical questions will not be addressed by the pharmaceutical industry. This applies to studies including surgery, radiotherapy, systemic treatment regimens with non-patented drugs and de-escalation studies.

Fortunately, there are already multiple beautiful examples of independent academic studies that indicated their relevance and changed treatment paradigms. Recently, 23 positive Southwest Oncology Group (SWOG) trials sponsored by the National Cancer Institute (NCI) from 1965 to 2012 were analysed in which a total of 12 361 patients were enrolled. It was estimated that 3.34 million life-years were gained from these trials through 2015. The return on investment was US\$125 per life-year gained. The authors concluded that NCI's investment in its cancer cooperative group research programme has provided exceptional value and benefit to the American public.⁵

The European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumour Group study 26951 is an example of a practice changing independent European academic study. This phase III trial demonstrated that adjuvant procarbazine, lomustine and vincristine administered after radiotherapy for anaplastic oligodendroglioma improved survival. This became only clear after long-term survival analysis with a median follow-up of 140 months.⁶

Such long-term follow-up is typically not reported for industry-sponsored studies.



► <http://dx.doi.org/10.1136/esmoopen-2017-000187>

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Funding of trials like these by a European fund or by several National Funds together is essential. There are in addition numerous unsolved clinical questions that could be of major interest for insurance companies and governments. Examples are studies investigating treatment de-escalation strategies or reducing maintenance therapy, in order to limit toxicity and costs while preserving efficacy. For example, the standard of care of patients with recurrent or metastatic head and neck squamous cell carcinoma, is six cycles of platinum-based chemotherapy with cetuximab followed by maintenance therapy with cetuximab until disease progression.⁷ The additive value of cetuximab maintenance treatment is unclear, while it leads to side effects and additional costs. In the Netherlands, costs for just the drug alone are €27690 for an average male patient with a length of 1.80 m and 80 kg body weight on maintenance therapy for 29.9 weeks, which was the median duration of maintenance therapy in the landmark study.⁸ A clinical trial comparing six cycles of chemotherapy plus cetuximab, with and without cetuximab maintenance would therefore be highly relevant. Such a study could be done relatively easy and quickly as an independent academic trial when funded for data management aspects. For studies investigating equivalence of shorter duration of immune checkpoint inhibition for approved indications, cost savings could be even more pronounced.

Moreover, investigator-driven studies could pay deserved attention to patients often excluded for clinical trials even though they could tremendously benefit from a clinical trial such as patients with second or third malignancies and patients with rare tumours or with brain metastases. Happily, there is activity in this field as exemplified by the EORTC 1206 study (ClinicalTrials.gov NCT01969578) in which patients with metastatic androgen receptor positive salivary gland tumours are randomised between hormonal therapy and chemotherapy.

The Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) trial is a very elegant and successful example of an ongoing independent academic study in which different pharmaceutical companies participate. Several experimental treatment arms are compared with an ongoing standard of care arm. Ineffective arms are closed early and new treatment arms can be added. The set up and basic structure of this innovative multiarm, multistage platform is funded by Cancer Research UK, Prostate Cancer UK and the Medical Research Council, with contributions of participating pharmaceutical companies. All information is freely accessible on the study website <http://www.stampedetrial.org> which supports participating centres and patients. Already more than 9000 patients have been included and two practice changing papers have been published.^{9,10} An European funding structure for independent academic trials, preferable connected with a cancer research organisation such as EORTC with expertise in conducting

multinational studies, could advance innovative trials after the example of STAMPEDE at the European level.

Not only a new structure for funding of independent clinical cancer research is important, also harmonisation and simplification of regulations will be important. Studies with drugs may become easier in Europe when the EU clinical trial directive is implemented.

In addition, we will have to nurture and educate the next generation of clinical researchers, for example, with workshops such as the *Methods in Clinical Cancer Research (MCCR) Workshop* jointly organised by EOCO, EORTC, American Association for Cancer Research (AACR) and ESMO. Researchers should have basic knowledge concerning data infrastructures created for assembly of so called 'big data', which can reiteratively be used multiple times to answer different research questions leading in potential to relative cheap scientific breakthroughs. It is clear that also patients need insight in this approach as they will be critical partners in bringing new approaches forward.

In the past, in trials only structured clinical data was collected enabling the researchers to assess efficacy of a therapeutic intervention or procedure. Nowadays, however, increasingly additional data such as biospecimen or omics data, and even patient's personal metrics data assembled with wearable technology, are collected to identify, for instance, potential predictive biomarkers for the therapy under investigation. This approach is rapidly expanding, and interest is also focusing on, for example, the ability of omics to predict short-term and long-term side effects. However, this data might dramatically increase in power when studies can be combined and used to answer other relevant questions not directly related to the main research question of the study. A clear example of an answer not related to the main research question is the development of the Response Evaluation Criteria in Solid Tumours (RECIST) for which the imaging and outcome data of patients were merged from industry as well as cooperative group trials. These criteria were developed because changes in tumour burden are frequently used as surrogates of survival/quality of life. In 2000, the RECIST Working Group simplified the 1981 World Health Response Criteria (WHO) 2 after validation in a large data warehouse. In 2009, RECIST was refined (RECIST 1.1) using an even larger warehouse and recently, based on data of 23259 patients, RECIST criteria for targeted agents were presented.¹¹

Happily, there are now several big initiatives on sharing data. With respect to reuse and merging of data, an important issue is the ownership of data collected in clinical trials. Four potential owners can be identified: the public, the participating patients, the investigators or the study sponsor. In the ideal setting, any anonymous data obtained within clinical trials including industry-sponsored trials should be available to other interested parties in accordance with the findability, accessibility, interoperability, and (re-)usability (FAIR)

principle, while observing ethical, legal and societal constraints.¹² The International Committee of Medical Journal Editors (ICMJE) recently proposed that authors include a plan for data sharing as part of clinical trial registration. Previously, it has been recognised that crediting data generators is a key incentive for data sharing.¹³ A proposal has been put forward to acknowledge persons who initially gathered the data with the concept called data authorship.¹⁴ It states that in order to be cited as a data author, a person must have made substantial contributions to the original acquisition, quality control and curation of the data, be accountable for all aspects of the accuracy and integrity of the data provided and ensure that the available data set follows the FAIR principle. This means that for merging data clinical studies we have to get used to very long author lists and create solutions as done by the Early Breast Cancer Trialists' Collaborative Group.¹⁵ Their studies already showed that pooling of data from multiple trials for so called big-data analyses that can lead to a more accurate and complete view of the complexity of the data and the problem under investigation. Ultimately, this can lead to faster advances in our medical knowledge for the benefit of the patient. Independent clinical researchers should be a major advocate for this data sharing approach.

A structure in Europe, in which we united can perform Independent, Academic Clinical Cancer Research as advocated by Negrouk *et al.*,¹ supported by the several European states, national charities, insurance companies, patient organisations and even pharmaceutical companies would be of major benefit for the patient with cancer and society.

Competing interests EGEDV has received research support from Amgen, Roche/Genentech, Chugai Pharma, Synthon, Astra Zeneca, Radius Health, CytomX and Nordic Nanovector made available to the institution.

Provenance and peer review Commissioned; internally peer reviewed.

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