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ESMO Clinical Research Observatory (ECRO): improving the efficiency of clinical research through rationalisation of bureaucracy

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ABSTRACT

During the last years, there has been a dramatic increase in the administrative and bureaucratic burden associated with clinical research, which has clearly had an impact on its overall efficiency and on the activity of clinical investigators and research teams. Indeed, the supervision of the adherence of clinical research to Good Clinical Practice (GCP) guidelines and legal regulations is of the utmost importance. Yet, while such regulations have remained largely unchanged during recent years, the number of administrative tasks and their complexity have grown markedly, as supported by the results of a survey performed among 940 clinical investigators that we report in this manuscript. Therefore, many investigators believe that it has become necessary to undertake a rigorous analysis of the causes and consequences of this issue, and to create a conduit to channel the advice from experienced investigators regarding clinical research procedures, in order to improve them. Based on these premises, ESMO has launched the ESMO Clinical Research Observatory (ECRO), a task force that will analyse different aspects of clinical research. ECRO will aim to provide the views of ESMO on clinical research procedures based on the feedback from clinical investigators, under complete adherence to the Declaration of Helsinki, the GCP guidelines and any other applicable legal regulations, while at the same time showing profound respect for all the stakeholders involved in clinical research. This manuscript provides the background and rationale for the creation of ECRO, its planned activity and an analysis of the current administrative burden in clinical research with recommendations to rationalise it. Indeed, we expect that this effort shall lead to a relevant improvement in the care of patients and in the development of clinical research.

The only thing that saves us from bureaucracy is its inefficiency.
Eugene McCarthy (1916–2005)

GROWTH OF THE BURDEN OF BUREAUCRACY IN CLINICAL RESEARCH

In recent years, the administrative and bureaucratic burden associated with clinical research in Oncology has grown along with its clinical success and technical complexity, generating a profound impact on the activity of investigators and clinical research teams. Indeed, regulation and monitoring are fundamental to guarantee the safety and the rights of patients and the quality of the data, according to the high standards that characterise clinical research, as defined by the Declaration of Helsinki,[1] the guidelines for Good Clinical Practice (GCP)[2] and the applicable regional and local legal regulations. Nevertheless, in the current scenario, physicians dedicated to clinical research have begun to feel overwhelmed by such administrative tasks, and it has become difficult for them to understand the appropriateness of certain procedures, to set a limit to the amount of time dedicated to administrative tasks, or even to perform their clinical role with an adequate level of autonomy.

While adherence to the Declaration of Helsinki, GCP guidelines and local regulations remains unquestionable, many experienced investigators believe that their overinterpretation and misinterpretation by Clinical Research Organisations (CROs), and their substitution by their own internal Standard Operating Procedures have significantly increased the administrative burden.[3–5] The number of processes that need to be documented and the complexity of the documenting procedures and templates have increased dramatically, creating an unsustainable pressure on the investigational site staff. Another layer of complexity has been added by the incorporation of cumbersome online platforms which require intricate procedures just to access them, and which generate myriads of emails that overwhelm the capacity of investigators and research

teams. Exhaustive training courses for administrative processes, which frequently involve examinations, are imposed on clinical research teams to qualify as trial site staff. Frequently, such trainings are requested even from individuals that are not related to those specific administrative tasks. The administrative overload even affects the medical records of the patients, which are frequently—and wrongly—considered as the most suitable place to document administrative procedures, thus distorting their true function. The number of meetings required during the development of trials has also increased relevantly, and once again, the focus of such meetings is often administrative.

Regrettably, investigators are unable to overcome, or even to discuss these situations.[3] The appropriateness of such procedures is justified by the *'necessity to comply with GCP and legislation'*, even though such regulations do not usually require such high levels of detail and complexity. Yet, the decisions are non-negotiable because the flow of communication is unidirectional and does not consider other opinions, including those coming from experienced investigators.

NEGATIVE IMPACT OF THE INCREASED ADMINISTRATIVE BURDEN ON INVESTIGATORS, RESEARCH TEAMS AND PATIENTS

This increased burden of bureaucracy makes poor use of the limited time physicians have available, generating frustration, loss of motivation and complaints from experienced investigators[3 4 6] as well as decreasing the interest of young physicians towards developing a clinical research career. In addition, non-essential administrative procedures significantly increase the economic costs of clinical research and contribute to delays in trial implementation,[7] thus negatively impacting the flow of drug development and hampering patient access to new drugs.[8] This is particularly relevant in the setting of independent academic clinical research,[9] which is critical for patient-focused drug development.[10]

More importantly, there is no evidence that this increased complexity leads to greater patient safety. A relevant example are pharmacovigilance procedures, which commonly consist of submitting all the available individual serious adverse events to investigators and documenting their reception, without any intent to summarise, prioritise or classify them. Sometimes, the events even include those observed during screening periods, when the patient has not yet received the investigational drug. This leads to an excess of information that becomes unmanageable and prevents investigators from being effectively updated on the safety of investigational drugs. Another example is the high number of informed consent versions generated in some studies and their complexity, which are difficult to understand by patients,[11] and may even generate distrust of the study and the research team.

CLINICAL INTERFERENCE OF PROTOCOLS WITH BEST MEDICAL PRACTICE

Finally, on limited occasions, discrepancies arise between investigators and sponsors or CROs regarding the most appropriate clinical management for some patients participating in clinical trials. For example, some study protocols mandate discontinuation of the study treatments based on the strict application of response criteria, disregarding the medical judgement of the investigators in clinically complex situations (eg, the possibility of maintaining treatment in the case of persistent clinical benefit; or to radically treat oligometastatic progressive disease while maintaining systemic therapy). Frequently, in these situations, the strict interpretation of the protocol prevails, generating *clinical interference* with the best clinical judgement of the physician, who is responsible for the care of the patient; and potentially compromising the rights, safety and well-being of trial participants, in clear contrast with the main goals of the Declaration of Helsinki and the GCP guidelines. Conversely, many protocols allow physicians to take the final decisions about these complex cases, either directly or after discussion with the medical coordinator of the study, thus confirming the validity of this approach.

ESMO SURVEY ON THE ADMINISTRATIVE AND BUREAUCRATIC BURDEN IN CLINICAL RESEARCH

In order to evaluate the opinions of clinical investigators on these issues, we developed an online survey that was distributed among ESMO members, ESMO faculty, oncologists selected for their wide experience in clinical research and investigators attending the ESMO 2019 meeting in Barcelona. The characteristics of the 940 responders are presented on table 1 and the responses are displayed on table 2.

The results clearly support that there is high agreement among investigators about the excessiveness of administrative procedures on clinical research (mean score: 8.3 over a 0–10 scale), which they consider an obstacle for the development of clinical research (mean score: 8.2). The survey also shows wide consensus about the feasibility to limit such procedures without compromising the safety and the rights of the patients and the quality of the data (mean score: 8.1); and about the necessity to incorporate the feedback from physicians about the procedures related to clinical research (mean score: 8.6). Interestingly, scores were higher among oncologists with more than 5 years of experience in clinical research (table 2).

While we acknowledge the limitations of surveys, we believe that these results accurately reflect the opinions expressed by the vast majority of oncologists dedicated to clinical research. Consequently, they should lead stakeholders to perform a profound analysis of the current situation and to implement the appropriate changes.

Table 1 Characteristics of responders to ESMO survey on the administrative and bureaucratic burden in clinical research

Characteristics	ESMO members (n=260)	ESMO faculty (n=66)	Oncologists with experience in clinical research (n=179)	Oncologists attending ESMO 2019 (n=435)	Overall (n=940)
Years of experience in clinical research (n/%)					
<5 years	54 (21)	2 (3)	19 (11)	175 (40)	250 (27)
5–10 years	60 (23)	10 (15)	31 (17)	114 (26)	215 (23)
>10 years	146 (56)	54 (82)	129 (72)	146 (34)	475 (51)
Type of institution (n / %)					
Academic	181 (70)	58 (88)	132 (74)	303 (70)	674 (72)
Community	66 (25)	6 (9)	40 (22)	113 (26)	225 (24)
Other	13 (5)	2 (3)	7 (4)	19 (4)	41 (4)
Country (n/%)					
European	203 (78)	59 (89)	177 (99)	221 (51)	660 (70)
Non- European	57 (22)	7 (11)	2 (1)	214 (49)	280 (30)

ESMO CLINICAL RESEARCH OBSERVATORY

Based on these premises, ESMO has decided to launch the ESMO Clinical Research Observatory (ECRO, https://www.esmo.org/research/esmo-clinical-research-observatory-task-force), a task force developed in 2019, with the objective of analysing the procedures of clinical research and incorporating the feedback from clinical investigators, as leaders in the development of research projects and those responsible for the care of patients. Indeed, we expect that this effort shall lead to an improvement in the care of patients and in the efficiency of clinical research.

ECRO will pursue the following areas of development, which are summarised in box 1:

1. Rationalisation of the bureaucratic burden associated with clinical research, based on strict adherence to current legal regulations and to any future amendments, and on showing respect to the time and expertise of clinical investigators and research teams, who should be mainly focused on clinical and research issues. Importantly, the ECRO will not enter into a debate on which administrative procedures are necessary and which are ancillary, but will rather support the following recommendations:
   a. Limiting the administrative documents required for trials to those required by GCP and legal regulations: We recommend that section 8 of the GCP guidelines (‘*Essential documents for the conduct of a clinical trial*’) is strictly followed, and that documents not included in that section are therefore considered non-essential. Of note, GCP guidelines only request that a small number of the essential documents be signed by the investigator; and they consider it “*acceptable to combine some of the documents, provided the individual elements are readily identifiable*” (GCP 8.1).
   b. Using simplified document templates: For example, while GCP guidelines merely—and reasonably—request that *“The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties”* (GCP 4.1.5), most study delegation logs have become extremely complex and labour-intensive to complete, and

Table 2 Results of the ESMO survey on the administrative and bureaucratic burden in clinical research

Statement	Mean score (0=strongly disagree, 10=strongly agree)	
	Overall score (n=940)	Research experience >5 years (n=690)
The current burden of administrative tasks in clinical research is excessive.	8.3	8.6
Current administrative and bureaucratic procedures in clinical research could be reduced without affecting the safety and rights of the patients and the quality of the data.	8.2	8.5
Current administrative and bureaucratic procedures represent an obstacle for the development of clinical research.	8.1	8.4
It is necessary to incorporate the feedback from physicians about the procedures related with clinical research.	8.6	8.8

Box 1 Initial areas of development and methods pursued by ECRO.

Initial areas of development

1. Rationalisation of the bureaucratic burden associated with clinical research:
   a. Limiting the administrative documents required for trials to those required by GCP and legal regulations.
   b. Use simplified document templates.
   c. Avoid redundant documentation.
   d. Avoid complex electronic resources.
   e. Avoid repetitive and unnecessary meetings and control their duration.
   f. Optimise the delegation of trial procedures from investigators to other members of the research team.
2. Avoid the *clinical interference* of protocols with best medical practice.
3. Rationalisation of pharmacovigilance procedures to improve its efficiency and effectiveness.

Methods

1. Establish an open channel of communication that allows physicians and research teams to deliver their feedback on general or specific issues related to clinical research procedures.
2. Foster the generation of data on clinical research procedures.
3. Issue recommendations regarding relevant topics related to clinical research.
4. Foster the involvement of experienced clinical investigators in the training of study monitors, to provide them with the clinical perspective of clinical research.
5. Collaborate with other national and international associations related to clinical research, especially in the area of Oncology, in order to endorse, revise and improve this initiative.

usually the investigator must assume this increased complexity. Instead, we recommend the use of simplified templates.

c. Avoid redundant documentation: A relevant example is the documentation process of the informed consent process. While GCP clearly state that the *"informed consent is documented by means of a written, signed and dated informed consent form"* (GCP 1.28),[2] it has become routine practice to request that investigators duplicate this documentation in the medical records, frequently including administrative details, such as the version code of the document and so on. Such a process is redundant and lacks any value, since it is not signed by the patient, as required by GCP.

d. Avoid complex electronic resources: Cumbersome applications with intricate access procedures should be replaced by user-friendly and intuitive systems, which should not require unnecessary trainings (ie, those dedicated to performing simple procedures, such as signing a document; or those dedicated to a resource that a particular member of the staff will not use). In addition, such resources should rely on single access platforms, rather than on multiple ones.

e. Avoid repetitive and unnecessary meetings, and control their duration: Start-up and monitoring meetings should focus on the core aspects of protocols and on clinical issues, and should avoid reviewing general aspects, ancillary administrative procedures and so on.

f. Optimise the delegation of trial procedures from investigators to other members of the research team: Indeed, the training and preparation of all the members of the research teams (ie, data managers, research nurses and so on) allows them to assume complex responsibilities. Therefore, optimising the delegation procedures will facilitate the development and monitoring of trials.

2. Avoid the clinical interference of protocols with best medical practice: Protocols describe the methodology that should be followed to conduct the trial, but they cannot foresee the whole variety of individual clinical situations that patients undergo and therefore they cannot substitute best medical practice. Consequently, protocols should avoid dictating strict and non-personalised instructions to manage clinically complex situations, such as discontinuation of an anticancer treatment whenever clinical benefit may persist, or when oligometastatic progressive disease may be controlled with radical treatment; or deny delivery of determined supportive therapy, such as palliative radiation. Protocols may consider such events as progression with regard to the interpretation of the study data, but treatment discontinuation should generally be decided by the investigators, after thorough discussion with their patients.

   Indeed, sponsors' recommendations regarding management of relevant toxicities, based on the centralised collection of information, should not be considered as clinical interference, particularly in the setting of early drug development. Neither should the decision to discontinue a study or a specific cohort of a study be considered as clinical interference. Nevertheless, the sponsor must inform investigators timely to avoid miscommunication with patients.

   Institutional Review Boards (IRBs) should specifically examine the existence of clinical interference in new protocols and should carefully review any potential situation of clinical interference in ongoing protocols, requesting appropriate amendments, as required by GCP guidelines (GCP 4.5.4).

3. Pharmacovigilance administrative procedures: Reporting the safety of medicines in the routine and clinical research settings is essential to maintain physicians updated about adverse events, with the objective of improving patient safety. In order to increase the efficiency and the effectiveness of the process, ECRO believes that current logistical and administrative pharmacovigilance procedures for reporting events from the sponsor to the investigators should be thoroughly revised and simplified. While the development of the optimal process is beyond the scope of this manuscript,

and should be defined through the collaboration and consensus of all stakeholders, we believe that the current practice of unstructured submission of all reports on individual serious adverse events to investigators is difficult to manage and may even dilute the desired effect of proper safety information. Adequate procedures, such as interpreting and periodically summarising the available information, should be evaluated.

ECRO will employ the following methods to attain its objectives (box 1):

1. Establish an open channel of communication that allows physicians and research teams to deliver their feedback on general or specific issues related to clinical research procedures. Relevant issues will be addressed by consensus panels including all the stakeholders of clinical research as appropriate, including sponsors, CROs, regulatory authorities and patient advocacy groups, in order to find solutions by mutual agreement.
2. Foster the generation of data on clinical research procedures: This includes obtaining balanced feedback from investigators through surveys targeting oncologists, especially ESMO members, reports from expert panels and so on; and fostering research and the publication of studies to characterise common problems related to clinical research procedures in ESMO publications, meetings and website. Already existing examples include studies that analyse the increasing complexity of clinical trials[12]; the occurrence and causes of excessive delays in starting treatment in cancer patients due to centralised molecular testing[13–15]; the broadening of eligibility inclusion criteria in clinical trials, to avoid disparities in care[16–18]; the consequences of outsourcing the monitoring of trials[7]; the need to simplify informed consents[11] and so on.
3. Issue recommendations regarding relevant topics related to clinical research. Importantly, ECRO will not evaluate specific cases, given the regional differences in legislations and patient management; and since decisions must depend on the structures that are legally in place in each country (eg, IRBs and other ethics committees). ECRO may contact local scientific societies to seek their advice about specific regional issues.
4. Foster the involvement of experienced clinical investigators in the training of study monitors, to provide them with the clinical perspective of clinical research.
5. Collaborate with other national and international associations related to clinical research, especially those in the area of Oncology, in order to endorse, revise and improve this initiative.

CONCLUSIONS

The ECRO will analyse different aspects of clinical research and will provide the views of ESMO on clinical research procedures based on the feedback from clinical investigators, under complete adherence to the applicable legal regulations, and showing profound respect for all the stakeholders involved in clinical research. We expect that this effort shall lead to a relevant improvement in the care of patients and in the efficiency of clinical research.

Indeed, we expect that all the stakeholders involved in clinical research will recognise the need to critically analyse these relevant problems and to assume their responsibility in implementing the necessary changes to overcome them. Consequently, rather than attempting to audit and to control clinical trial procedures, ECRO will publicly acknowledge the merits of those entities (ie, CROs, sponsors, IRBs, clinical research teams, regulatory authorities and so on) who succeed in reviewing and simplifying procedures without compromising—or even improving—the quality of clinical research, and consequently, the well-being of patients.

We also expect that our fellow physicians will support this initiative and that, while fully endorsing the need to stringently monitor clinical trials, they will demand respect of their time and their expertise and leadership in the organisation and completion of research projects and clinical care of patients

We would appreciate receiving your comments and opinions about this initiative at ecro@esmo.org. Please indicate if you would allow to make your comment public (ie, on the ESMO web page), and in such case, if you would prefer to include your name or not.

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trials, which are critical to develop new effective therapies to overcome human diseases.

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