Recommendations of the Coalition for Reducing Bureaucracy in Clinical Trials

Version: November 2021

Introduction

In September 2020 a broad cross-disciplinary coalition of medical societies and patient advocates issued the joint statement 'Reducing bureaucracy in clinical trials: now is the time!'

The statement[1] calls for urgent action to make clinical trials less bureaucratic and more patient-centred, efficient and cheaper. At stake are the quality of clinical trials, access to innovative treatments and, crucially, patient safety.

The Coalition calls on regulators, policymakers, sponsors, ethics committees and other stakeholders to collaborate to ensure that regulatory guidelines, safety reporting requirements and informed consent procedures do not harm what they are meant to protect: clinical trial quality and patient safety.

Over the past year, the Coalition has developed a series of concrete and consensus-based recommendations for reducing administrative burdens in clinical trials, laid out below in four clusters:

I. Safety reporting
II. Informed consent
III. Regulatory guidelines
IV. Harmonisation of requirements across the EU

These recommendations reflect, first and foremost, the views and needs of investigators and patients, but have taken in as much as possible the views of regulators, sponsors, ethics committees and other stakeholders. Their willingness to engage in dialogue and join the search for realistic, pragmatic and broadly-supported solutions has been invaluable in enhancing the quality and relevance of these recommendations.

The Coalition wishes to express its gratitude to all who have contributed, and – as we set out to spread awareness and promote uptake – to those that will be contributing, to this joint effort to make clinical trials more efficient, better, and safer.

I. Safety Reporting

1. Harmonising and simplifying submissions of adverse events

The Clinical Trials Information System (CTIS) is developed to be the single-entry point for submitting trial information in the EU. It will be operational in early 2022 and will be used by all sponsors, including academia. We recognise and welcome it as an impressive achievement with numerous functionalities. However, as it stands now, the system will be used by and facilitate clinical trial sponsors, while investigators will still have to collect data and submit safety reports to the sponsors – just without the facilities. In most cases the administrative burden for researchers only increases, with Clinical Research Organisations (CROs) acting as intermediaries between investigators and sponsors and requesting investigators to fill in time-consuming safety reports via different web-based systems.

Ideally, investigators should have to focus only on the medical aspect of adverse events – i.e., those elements directly related to the patient and the disease. All sponsors/CROs conducting clinicals trials across Europe should agree on a single harmonised investigator-friendly platform. For selecting the most appropriate interface, sponsors/CROs should seek input from investigators and advice from statisticians and IT services. To ensure that safety reports are as informative as possible, a proportionate stratified approach to the collection of adverse events should be adopted.

For the development of this single harmonised electronic system, we highlight the following priorities:

- **Simplifying the form for safety reporting**. Some medicines agencies have already approved useful simplified forms (e.g., the Australian Therapeutic Goods Administration model[2]). The endorsement of such forms by European authorities would give a clear signal to sponsors and CROs that there is no need to submit unnecessary information and would give investigators the confidence to submit reports that are less laborious and limited to what is essential.

  The list of core items to be included in the form needs to be agreed amongst all stakeholders, taking into consideration both industry and academic sponsors, as they may collect data in different ways.
- **Taking a paperless approach in clinical trials**. Paper-based clinical research systems are less efficient and unsustainable. Moving to fully electronic reporting and records would save time, space and waste to all parties involved in clinical research. Moreover, electronic signatures should be the rule for all submissions of adverse events.

2. Making use of the protocol to reduce excessive reporting, as per the new Clinical Trials Regulation (CTR)

The EU Clinical Trials Regulation No 536/2014 (CTR)[3], which will take full effect on 31 January 2022, establishes that the conditions of safety reporting between investigator and sponsor are dictated by the clinical trial protocol:

"T*he investigator shall record and document adverse events or laboratory abnormalities identified in the protocol as critical to the safety evaluation and report them to the sponsor in accordance with the reporting requirements and within the periods specified in the protocol.*"[4]

"*The investigator shall record and document all adverse events, unless the protocol provides differently. The investigator shall report to the sponsor all serious adverse events occurring to subjects treated by him or her in the clinical trial, unless the protocol provides differently*[5]

This means that investigators and sponsors can draft the protocol in a way that prevents excessive and unnecessary safety reporting. We recommend:

- **Listing the periodic reviews of aggregated safety data to ensure increased visibility of safety signals**

This approach also allows for better assessment of multiple complex toxicities in combination treatments. It can be done on a regular basis in studies through the MedDRA system[6]. It should be organised by organ classes, and severity should be graded (focussing especially on grades III/IV). This simplified procedure will improve in real time the Reference Safety Information, also for multidrug combinations. This is used widely by Data Monitoring Committees (DMCs) with the help of statisticians and can be blinded in randomised clinical trials.

This approach, if adopted, should be indicated in the protocol, in accordance with the CTR:

"The protocol shall describe the procedures for:

(a) eliciting and recording adverse events by the investigator, and the reporting of relevant adverse events by the investigator to the sponsor;
(b) reporting by the investigator to the sponsor of those serious adverse events which have been identified in the protocol as not requiring immediate reporting;
(c) reporting of suspected unexpected serious adverse reactions by the sponsor to the Eudravigilance database; and
(d) follow-up of subjects after adverse reactions including the type and duration of follow-up."[7]

The protocol could also widen the role of DMCs to pre-filtering suspected unexpected serious adverse reactions (SUSARs) before they are sent to investigators. Not only are DMCs scientifically qualified to review safety reports, but they also have access to unblinded data, which enables them to identify safety signals as the evidence emerges. The Coalition supports recommendations on the role of independent DMCs in evaluating safety and efficacy data from ongoing clinical trials, as formulated by the Good Clinical Trials Collaborative in its draft Guidance for Good Randomized Clinical Trials[8].

- **Listing anticipated events that do not require immediate reporting by the investigator to the sponsor**

The Clinical Trials Regulation states the following:

"*With regard to the notification of adverse events, the protocol shall identify the categories of:*
(a) adverse events or laboratory anomalies that are critical to safety evaluations and must be reported by the investigator to the sponsor, and
(b) serious adverse events which do not require immediate reporting by the investigator to the sponsor."[9]

It is thus possible to include in the protocol a list of anticipated serious adverse events (SAEs) that are expected and, therefore, not considered SUSARs. LUNGevity, working closely with the FDA's Oncology Center of Excellence, has proposed a list of anticipated events for patients with lung cancer with the purpose of reducing uninformative safety reports[10]. We encourage the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) to consider coordinating similar efforts in other disease areas and to help ensure that safety reporting issues are addressed globally.

- **Prioritising relevant toxicity data**

Safety reporting should be proportionate, stratified, coordinated and efficient. To prioritise relevant toxicity data, simple criteria (e.g., whether something is life-threatening or not) along with grading (such as MedDRA's) is recommended.

The clinical trial protocol could introduce a standardised grading system, which would enable prioritisation of the information flow within the chain of command. This grading system may operate along a scale with a minimum threshold for immediate single reporting:

- When adverse events are below the minimum threshold for immediate single reporting according to the protocol[11], the investigator can record and document adverse events or

laboratory abnormalities identified in the protocol[12] and compile them in a cumulative report to be sent to the sponsor at a recurrence specified by the protocol.

- When adverse events are equal or above the minimum threshold, the investigator shall notify the sponsor within 24 hours of obtaining knowledge of the events unless the protocol specifies otherwise. Where relevant, the investigator shall send a follow-up report to the sponsor to allow the sponsor to assess whether the serious adverse event has an impact on the benefit-risk balance of the clinical trial[13].
- When a SUSAR arises, the investigator shall notify the sponsor within 24 hours of obtaining knowledge of the events[14]. Following the investigator's report, the sponsor shall report to the regulators without delay[15].

3. Collection of patient views on what should be reported as adverse effects.

Implementing tools for patient-reported outcomes measures (PROMs) to complement clinicians' grading based on the Common Terminology Criteria for Adverse Events (CTCAE) will improve the assessment of tolerability and highlight toxicities that affect quality of life. The Med Safety App[16]is being deployed to facilitate the transmission of safety case reports into the database. However, with Individual Case Safety Reports (ICSRs) considered difficult to manage, a consensual approach to collecting and analysing PROs alongside clinician-graded adverse events needs to be developed together with patient organisations. The common goal must be to boost both the quantity and the quality of reporting and increase the ease of patient reporting.

II. Informed Consent

This Coalition is concerned about the increasing length and complexity of informed consent forms (ICFs) for clinical trials. The longer the form, the more challenging it can be for the patient to process information necessary to make an informed decision about participation in a clinical trial. Key considerations are whether the information is necessary, understandable, relevant and appropriate for lay people.

Long, complex and unclear ICFs may prevent potential participants from fully understanding the nature and purpose of the research. Therefore, when presenting an ICF to patients who are eligible to participate in a clinical trial, we find it important that the consent form **does not exceed 1 000 words**. This text can be accompanied by images to give further visual explanation. For example, the ICF could present a timeline/graph/histogram if multiple interventions or investigations will take place over the course of the patient's involvement. This should make it easier for the patient to understand his/her commitment.

The Council for International Organizations of Medical Sciences (CIOMS) international guidelines for health-related research involving humans, developed in collaboration with the World Health Organization (WHO), stipulate that the information leaflet going to all recruits should ideally not be longer than 2-3 pages[17].

1. **Recommendations for reducing ICF length:**

- **Using appendices**

We recommend focusing the ICF body text on the description of the study, including aims and risks, and moving ancillary information, **such as the GDPR[18] and legal clarifications**, from the body of the ICF to appendices[i]. The ICF body should include only the main points, as too much detail may distract and overwhelm the study participants[19, ii].

[i] The information to be provided to data subjects for GDPR compliance (implementing Articles 12-14 of the GDPR) can be annexed. However, if consent is chosen as the most appropriate legal basis for GDPR compliance, the ICF needs to include the details of the explicit consent for processing of health data.

[ii] The Clinical Trials Transformation Initiative (CTTI) provides helpful recommendations on informed consent, including a discussion tool which helps to guide the process. The aim is keeping the ICF itself as a tool to support the process, rather than making it the primary focus. The CTTI recommendations were made in the US regulatory context and would need to be revised with all relevant stakeholders, including European / international regulators, to agree on a format for the legally necessary component.

- **Listing study procedures**

We suggest transitioning from listing study procedures *by study visits* – which can result in repeatedly describing the same procedure in a single ICF – to grouping study procedures *by frequency*, thereby describing the study procedure only once and reducing the length of the ICF[20].

- **Providing ICFs in electronic format**

With the increasing use of digital health tools, especially in a pandemic and post-pandemic scenario, electronic informed consent should become a key component in medical research and routine clinical care. The availability of electronic formats can help shorten the ICF by making non-essential 'additional' information available via hyperlinks, instead of including it in the body text. COVID-19 has demonstrated that digital formats can work well for many. As technology progresses and e-signatures become more trustworthy, secure and feasible, it will be important to provide ICFs electronically to everyone who prefers this format. Providing ICFs in an electronic format would also make it easier for potential participants to share with family and friends, whose advice and comments they may want to seek. Of course, paper copies should also be provided to those patients that feel less comfortable with digital formats.

- **Use of images or audiovisual content**

Where feasible, the informed consent process may benefit from the use of digital and audiovisual content which can contribute to enhanced patient understanding, alongside the dialogue between patient and physician.

2. Recommendations on ethics committees

The CTR states that informed consent forms must "be kept comprehensive, concise, clear, relevant, and understandable to a layperson"[21].

Ethics committees play an important role in ensuring this provision is upheld. According to the CTR, Member States should ensure involvement of lay people including – and in particular – patient associations. Ensuring an active and strong role for patients and lay people in ethics committees is a way of ensuring checks and balances are in place for the informed consent process in a clinical trial. However, in practice this participation of lay people is not always ensured. The European Commission should consider appropriate measures to ensure that this provision is enforced throughout all Member States. One method could be to provide additional cross-border knowledge and expertise sharing among Member States ethics committees supported by the EU4Health programme.

3. Recommendations on key information

In the consent form there should be a key information section where essential information is highlighted concisely within the ICF, for instance as a boxed text, instead of adding a separate chapter that would increase the length of the ICF. The aim of the key information section is to make sure that patients reading the consent form can clearly and easily understand the benefits and risks of participation in the trial, to be able to make an informed decision.

An example of the information needed in the key information section would look like this:

Key information section:

- Name of the study
- Purpose/aims of the research study
- The reasonable duration of patient participation
- Voluntary participation
- The reasonably predictable risks to the patient participant in the study
- The reasonably expected benefits to the participant (or expected overall benefits of the study, in case there is no direct benefit for participating in the study)

To clarify what information principal investigators should summarise in the consent form ***in addition to the key section***, the Coalition has identified a number of elements that are considered essential which are in line with the additional protocol to the Oviedo Convention concerning biomedical research (Art. 13)[22] and the Guide for Research Ethics Committee Members[23]:

ICF BODY TEXT

- Brief description of the investigational treatment and the possible treatment alternatives (research versus standard of care)
- Brief description of study (including, when relevant only, patient population studied and approximate number of participants) and an explanation of general study procedures.
- Specify any additional examinations and/or interventions that are required by the protocol (and not part of the standard of care), e.g., additional imaging and tests
- Outline any minor risks, inconvenience or discomfort that could reasonably be expected to result from the study
- Principal investigator's name and/or affiliate institution
- Whom to contact with questions about the research?
- Whom to report a research-related injury including contact details
- Procedures for withdrawal from the study

- Participant´s responsibilities
- Research approved by Institutional Review Board or Independent Ethics Committee
- Steps to ensure privacy / confidentiality
- Opportunity to ask questions and to whom

AS APPENDICES

- Fertility warning
- Impact on quality of life
- What treatment will the patient receive when the clinical trial is ended, if applicable
- Alternative procedures or courses of treatment that might be advantageous to the patient, if applicable
- GDPR information, such as whether any personal information about the participant will be collected, processed and how and for what purpose and the right of the participant to request access to and rectification or erasure of personal data.

III. Regulatory Guidelines

The overarching solution proposed by the Coalition is the formulation of regulatory guidelines in a way that furthers a more harmonised, less heterogeneous interpretation. More clarity is needed on how regulatory guidelines need to be interpreted and utilised. Contradictory as it may sound, alleviating the administrative burden of regulation requires the introduction of more granularity. Key goals are (1) introducing a sense of proportionality, (2) the reduction of over-interpretation and (3) contributing to better trial designs.

While the consensus recommendations outlined below were developed independent of other initiatives, the Coalition has attached great importance to alignment with the Good Clinical Trials Collaborative (GCTC) which published its draft guidance in September 2021. Influencing the revision of ICH-GCP guidelines is an important shared objective of the Coalition and the Collaborative.

The Coalition acknowledges that while it calls, emphatically, for more detailed, concrete guidance to limit overinterpretation, a distinction needs to be made between the EU regulatory context (requiring a high level of specificity) on the one hand and the guidelines developed by GTCC and ICH, both global in scope, on the other.

Recommendations

1. All regulatory guidance should focus on safety of the participants and quality of the data and at the same time be formulated in a way that prevents overinterpretation and avoids regulatory overreach.
2. The patients' view should be an integral part of study design and conduct. Study participants should be partners at all stages of the clinical trial process, from protocol design and informed consent to trial conduct and formulating patient-relevant endpoints.
3. No distinction between academic and non-academic trials, but proportionality of safety reporting requirements according to the risk profile of the study. Whereas regulatory requirements should be the same for all trials, the academic view on how clinical trials should be performed needs to be reflected much better in the way trials are designed and in how regulatory guidance is formulated and interpreted, with the patient interest at the centre.
4. Guidance (guidelines) should be proportionate to the risks involved in the trial.

5. Reduce divergent interpretations by formulating guidelines in a more specific, less ambiguous way. The **wording** of guidelines needs to be clear and unambiguous, to limit room for (over)interpretation. In addition, the **scope** of guidelines (i.e., to what situations and types of trials do they apply?) should be defined as clearly as possible. Whereas guidance that aims to be universally applicable (ICH, Good Clinical Trials Collaborative) cannot be too narrow in scope, the need for clear and specific regulatory guidance at the EU level is evident so as to reduce divergent implementation and interpretation of EU legislation and regulatory requirements by Member States.

   Supplemental, living, example-based documents (such as Q&As) can help to guide the implementation of global, principle-based guidelines in the European context.
6. Guidelines must focus on mandatory requirements only. Mandatory should only be what is relevant for patient safety and data quality. Inclusion of non-mandatory 'requirements' should be avoided: something is either necessary and therefore required, or it is not.
7. Reduce the 'process burden': simplify interaction with regulatory bodies and ethics committees by introducing clear and harmonised guidance on how EU and international legislations and guidelines should be interpreted. Such 'interpretation guidance' should reduce, for example, the divergence in interpretation of GDPR and ethics committees' requirements by Member States.

   Harmonisation of guidance should not be an aim in itself: it must be based on good quality (not on the most restrictive cases) and multi-stakeholder consensus, and go hand in hand with simplification and clarification.
8. The same principles should apply to all interventions – drugs, devices, procedures – even if the specifics of the regulatory guidelines differ (necessarily so, due to different legislative frameworks).
9. Guidelines (guidance) must work for all stakeholders (patients, investigators, pharmaceutical companies, regulators and institutions) with as little regional divergence as possible. Patient organisations and medical societies have an important role in educating their communities about regulatory guidelines, and should be invited where possible to provide advice and to review study protocols.
10. Include learnings from clinical trial conduct obtained during the COVID-19 pandemic in respect to short set-up time and accelerated approval by regulatory bodies and ethics committees. Adopt simplification tools (e.g., remote training and monitoring, quality & risk management) that were developed when face-to-face study visits and trial follow-up had to be halted (due to lockdowns) and implement new trends in technology (electronic consent).

IV. Harmonisation of requirements across the EU

The drive towards patient-centric, high-quality, bureaucracy-light clinical trials in Europe requires harmonised interpretation and application of EU legislation, data frameworks and ethics requirements.

Specific recommendations:

1. The European Commission should encourage **aligned implementation of the Clinical Trials Regulation (CTR)** across EU Member states by ensuring that:

    a) national ethics committees meet the requirements for taking into account the views of lay people, in particular patients and patient organisations[24];

    b) members of ethics committees are independent ("of the sponsor, the clinical trial site, and the investigators involved, as well as free from any other undue influence")[25, 26];

    c) members of ethics committees have the necessary qualifications and experience[27].

    Considering that the role of ethics committees is to "safeguard the rights, safety, and well-being of all trial subjects"[28], members of ethics committees must be equipped, through education and training, with a broad and robust understanding of (the application of) all relevant guidance and legislation, including, but not limited to the ICH guidelines, Clinical Trials Regulation, Medical Devices Regulation, General Data Protection Regulation and the opinions and guidance (welcomed by the Coalition) of the European Data Protection Board[29] and the HMA/EMA Big Data Steering Group[30]."

2. The **governance and implementation frameworks for the European Health Data Space** should**:**

    a) help to enhance clarity, avoid duplication and align interpretation of relevant legislative, data and ethical requirements;

    b) provide legal clarity for secondary use of data for health research, in an already highly regulated sector;

    c) ensure the inclusion of lay people, patients, healthcare professionals and scientists/researchers as key stakeholders.

An EU body specialised in ethical and legal requirements for processing of data for health research purposes may be required to support decisions and guidance, to pool resources at EU member state level, draw together the relevant scientific expertise, educate and include the voices of patients and citizens, and to assist with aligned interpretation.

The Coalition for Reducing Bureaucracy in Clinical Trials

The Recommendations of the Coalition for Reducing Bureaucracy in Clinical Trials were developed by working groups of investigators, patient advocates and regulatory experts nominated by the organisations that signed the Coalition Statement (September 2020, bureaucracyincts.eu/statement).

Coalition leadership: Martin Dreyling (Coalition lead) and leaders of the core working groups Marcela Fajardo-Moser, Christian Gisselbrecht, Christoph Wanner, Natacha Bolaños, Sarah Collen, Rachel Giles and (until August 2021) Sara Badreh.

Coordination: Robin Doeswijk, Sara Román Galdrán and Gauthier Quinonez (EHA), Loredana Simulescu and Marieke Meijer (BioMed Alliance)

Listed below are the signatory organisations as well as organisations which have joined the Coalition more recently by endorsing its objectives and recommendations. The list of endorsements will be refreshed regularly.

Signatories

BioMed Alliance	Academic Clinical Trials Taskforce (chairs: Denis Lacombe, Martin Dreyling) Loredana Simulescu Marieke Meijer
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(List will be updated regularly)

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