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Informed Consent Writing: Facing the Patient Is in the Interest of the Sponsor

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ABSTRACT

This article analyzes the most common findings of the European Medicines Agency (EMA) and regulatory agencies regarding the quality of essential documents that led to delays in study approvals and major observations by EMA inspectors. The authors analyzed the content and length of informed consent forms used within clinical trials within the last 10 years and revealed a tendency toward increased length and complexity of the documents. Criteria for developing patient informed consent forms are suggested to implement in medical writing practice to make informed consent forms short and simple to read and understand by a layperson.

The quality of essential documents is one of the main factors affecting study approval by ethics committees (ECs)/institutional review boards (IRBs) and regulatory authorities (RAs). Deficiencies in the study protocol and/or informed consent form (ICF) content and structure might delay study approval by the EC/IRB and/or RA as well as negatively affect patient enrollment into the study, which would prolong study timelines.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) (R2) guideline[1] says that essential documents "serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements." Thus, the investigator's brochure, study protocol, and ICF(s) are always reviewed during the quality assurance audits or regulatory agency inspections.

According to the Annual Report of the Good Clinical Practice Inspectors' Working Group,[2] the most common findings of European Medicines Agency inspectors are issues related to essential documents: 7.5% of those findings were graded as critical and 59% as major.

In 2020, the American Medical Writers Association published data from an anonymized survey of reviewers at regulatory agencies evaluating the effect of study document quality on the regulatory review process.[3]

The main points of the survey were

- poor essential document quality can delay the study approval process or even lead to application rejection, and
- the most common issues related to document quality are
  - excessive length, repetition, and verbosity,
  - poor explanation of rationale, and
  - nonadherence to guidance and lack of clarity.

In addition, excessive document length, repetition, and verbosity were ranked as the main issues causing irritation for the reviewers or having a negative effect on regulatory review.

Thus, producing essential documents of high quality is a key factor affecting prompt study approval that would finally save sponsors' resources to allow for performing clinical trials within the predefined timelines and budget.

To achieve this goal, the essential documents produced by medical writers should meet the following criteria:

- provide clear scientific rationale for the study using available preclinical and clinical data, and
- be brief, clear, and unambiguous and avoid repetition.

In this article, we would like to share our observations and focus on items that should be considered when developing patient ICFs.

The main requirement referenced in ICH E6 (R2), section 4.8.6, states that information used in the ICF "should be as non-technical as practical and should be understandable to the subject."[1]

However, the current trend in modern clinical trials is toward a more complicated trial design with the involvement of various tests, procedures, questionnaires, etc, evaluated at multiple study visits. Such an approach also affects the length of patient ICF, which now contains a lot of medical information in addition to sections required by RA that are relevant to personal data protection, as per General Data Protection Regulation (GDPR)[4] for clinical trials

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conducted in the European Union (EU) or Health Insurance Portability and Accountability Act (HIPAA)[5] for clinical trials conducted in the United States.

The need to include all information required by RA in addition to data outlined in ICH GCP makes the ICF bulky and lengthy, which may lead to delay in regulatory review. We calculated the length of ICFs used within clinical trials run by patient safety indicators (PSI) within the last 10 years; the average length was 17 pages for pneumonia studies and 30 pages for breast cancer trials.

We have also noted a tendency toward increased length of ICF with time. Thus, for a series of clinical trials with the same investigational medicinal product (IMP) used for multiple myeloma treatment, a master version generated in 2016 was made up of 12 pages, an 18-page master version ICF was generated for another study with the same IMP in 2017, and in 2020, a master version ICF for the same drug and the same indication was made up of 25 pages.

Initially, we thought that the reason for the increase in the ICF length was the accumulation of safety data collected within 4 years of clinical trials with the IMP; however, our initial assumption appeared to be wrong.

When comparing the content of the ICF generated in 2020 against that issued in 2016, we found out that the 2020 version contained more detailed information on study procedures on a per-visit basis, which was an exact copy of the information available in the study protocol (eg, Eastern Cooperative Oncology Group [ECOG] status assessment), including medical terminology that makes no sense to a layperson (eg, "increase in blood level of creatine phosphokinase that could suggest heart damage").

It should also be pointed out that, in the ICF issued in 2020, safety information on the possible risks of glucocorticoid dexamethasone was described in a paragraph containing 15 lines as compared with a 6-line paragraph in the ICF from 2016.

When developing the master version ICF, the study sponsor should additionally keep in mind that in an international clinical trial, translation of the master version ICF into local languages will further increase the document's length, for example, the 25 pages of the master ICF for a multiple myeloma study translated into Spanish or Malay become a 42-page ICF for Argentina and Malaysia or Malay populations; translations to other languages resulted in the development of a 34-page ICF for Hungary and Taiwan and a 31-page ICF for Poland.

ICH E6 (R2), section 4.8.10, reads that the written ICF should include explanations of the trial procedures to be followed, including all invasive procedures. In practice, this requirement is considered to be an instruction to list all study procedures in the ICF.

However, the study protocol is developed to provide information on study procedures performed within the trial to the investigator/site team, and direct transfer of this information into the ICF seems unacceptable for a document developed for patients.

As an example, if the study protocol requires assessing patient ECOG status at each visit, it makes no sense to mention this procedure in the ICF, because ECOG status assessment in fact means the assessment of the patient's capability to perform activities and provide self-care; this assessment is done by the site team as part of the routine patient examination and does not require any additional procedure to be performed by the investigator or any additional action taken by the patient.

It should also be noted that some EU countries restrict the length of the ICF by local regulations. No longer than a 12-page ICF is allowed by the Czech Republic RA, which also requires that study procedures be provided in 1 table and on 1 page. The maximum length of ICF in Spain is 15 pages (written in Arial or Times New Roman font with a font size of at least 11 points, minimum line spacing of 1.5), which would probably mean no longer that 13 pages of the master ICF version in English.

The Spanish Agency of Medicines and Medical Devices (AEMPS)[6] has also introduced some reasonable requirements for the ICF that may be considered by medical writers when working on the master version of the patient ICF. These include:

- Infrequent adverse events can be summarized.
- Explanation of risks of common care procedures can be removed.
- In the case of marketed medicines, the wording "because it is a drug approved by the competent health authorities, there is information available to everyone in the drug information leaflet regarding the side effects of the drug XXX. Please talk to your study doctor in order to obtain this information" may be included.
- Lengthy wording describing study procedures in the related section should be replaced with a table: "The same tables that appear in the protocol should not be included; others that are simpler and easier to understand for the patient should be prepared."
- No need to repeat the same explanations for each visit, unnecessarily lengthening the document. Information regarding common routine examinations such as blood pressure, pulse, electrocardiogram, weight, height, etc, should be discarded.
- Exact activities to be carried out should be referenced, for example, as "blood sample collection" (details such as "determination of xxx biomarkers or quantifi-

cation of drug levels" are not necessary if it has already been explained that during some visits blood will be obtained for these purposes).
- Technical (medical) terms should be avoided (such as double-blind, randomization, etc); nontechnical description or direct explanation should be used instead.
- Data from animal studies should not be given when sufficient information is available for studies in humans.
- Risks and discomfort of the tests that are carried out as a result of participation in the study should be described. Excessive technicalities and wording containing excessive and unnecessary details should be avoided; however, it should be made clear if the time spent at the visits is prolonged due to additional procedures required by the study, such as questionnaires, kinetic samples, etc.
- If the risks and discomfort have been mentioned previously while describing study activities, they must NOT be repeated.

CONCLUSION

The current trend is that clinical trial design is becoming more complex, and regulatory requirements make it necessary to include additional information in the ICF (eg, GDPR requirements), which leads to the development of lengthy ICFs. The requirements of ICH E6 (R2) guidelines are not strictly followed, which results in the development of ICFs containing information difficult to understand by patients, such as medical terms. Excessive length of ICFs may lead to delays in study approval by ECs/IRBs and/or RAs. It may be helpful to implement into medical writing practice the list of requirements for ICFs developed by local regulatory agencies (eg, AEMPS) with the objective to make the ICF as short as possible and simple to read and understand by a layperson.

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