Informed Consent Matrix for Clinical Trials

This matrix aims to provide a minimum set of requirements for informed consent aimed at adults in the context of clinical trials. This Guide should be adapted to national settings and specific contexts. It mainly refers to multicentre interventional randomized clinical trials, but some suggestions can also be applied to non-interventional research. The Guide covers:

- the processing of information: context, language, setting;
- topics and proposed wording; and
- general suggestions on wording, format, length of the information sheet.

Processing of Information: Context, Language, Setting

Background:

As evidenced, many people participating in clinical trials:

- are not aware they are in a clinical trial, and do not understand the investigative nature of clinical trials;
- do not understand the meaning of randomization;
- think that they are taking the new treatment, and therefore expecting substantial benefit from the novel treatments (also known as “therapeutic misconception”);
- did not know they may be administered a placebo and what "placebo” means; and
- in case of a non-inferiority trial, do not understand the meaning of non-inferiority.

Legal information and ethical approval are among the most frequent information provided. However it is also necessary to ensure the general understanding.

Furthermore, one of the factors driving a potential participant’s decision to take part in a clinical trial, and the satisfaction with the decision made, is the trust in research in general, and in particular in the physician (as well as in the health care structure), who invites the individual to participate. In addition to the importance of providing relevant information about the study, we believe that trust involves reliability and willingness on the part of the physician to be in an open relationship with the invited individual. Health professionals inviting a person to take part in a clinical study should provide the information that is relevant to make the decision, which is also something that has to be covered in the information sheet. Although important, the information sheet should never replace the process of providing information through the relationship with the health professional.

Guiding Points

In order to ensure that information is processed correctly, it is important to ensure the person reaching consent is actually informed. The following factors can be taken into account to facilitate this process:

a) Provide information on the study according to individual informational needs; reading capability level; and the mindset of the individual.

Enough time should also be given when providing information, so as to let the individual reflect upon the invitation to participate in the clinical trial. Furthermore, information should be provided in an appropriate location and setting,

What does it involve?

- An open professional relationship, to ensure the individual feels free to ask questions, as well as to express doubts. The option of involving family and close friends in discussion, if requested by individual, is also important.
- Enough time and an appropriate venue dedicated to the task; aspects which have to be supported by both the physician and the health care structure.
- Trained research nurses to provide some of the information and/or gather questions from participants.

b) communicate using simple language, avoiding technical terms and jargon.

What does it involve?

- Communication and inter-personal skills on the part of the physician and health professionals involved.
- Supporting material in lay language to that gives general information on research and clinical trials.[1]
- Easily accessible and readily availableable information material, which addresses the needs of participants.
- Assessing the information flow and confirming understanding of potential participants. Possible ways of doing this include summarising the information, asking if there are any questions or doubts, as well as assessing comprehension and health literacy of potential research participants..

[1] As an example,the European Communication on Research Awareness Needs project (ECRAN) has developed tutorials and videos, in collaboration with patient representatives, on randomized clinical controlled trials, the independency of research, and its value for patients (http://www.ecranproject.eu)

Topics and Proposed Wording

Background:

Health professionals should provide information on the topics listed below, which should also be covered in the information sheet. A short and clear document should provide the main information points concerning the clinical, as listed below. A supporting document should be provided to further elaborate upon particular topics. It is also advisable to make the the information sheet available online so that it is more accessible according to the information needs of the individual. Below, you will also find examples of headings/explanations for the information sheet in *italics*.

The amount of information provided by the health professional should be a balance between the minimum amount of general information needed to make an informed decision, and further informational needs of the individual invited to participate.

Topics

General information

- The Protocol title - state the original title and use plain language
- The Sponsor - explain the meaning of this term and specify the role of the sponsor in the study:

> *"An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial"*

- The Principal investigator
- The Centre
- Contact information.

Introduction

- Brief summary of the clinical trial
- An invitation to participate
- Explanation that participation is voluntary
- Explanation that there is a right to withdraw at any time with no implication for care
- The EU trial registration number
- Information on the availability of the trial results on the EU database, with indication of when they will become available (if known)
- Information on the possibility (if any) to have a individual feedback of findings in the event that participants give permission to be contacted

- Specifying that the study results will be published and where they will be published, namely databases, scientific articles, etc., as well as how the results will be publicly disseminated, namely in public meetings, websites, lay press (if any)

Description of the Study

- The Context:

> *"What do we already know about condition x? / Why is this study needed?"*

- Objective of the study and its value for patients - the aims of the clinical study have to be clearly defined and explained, so as to allow potential participants to understand and assess if the aims are in conflict with their own values, personal beliefs, and/or religious beliefs:

> *"What benefits will the study bring?/ What is the specific research question being addressed? / Why is the study relevant and important to participants / patients and public?"*

- Reference to the research ethic committee's approval
- Participant selection:

> *"Who will be involved? / Who will be selected to participate in the clinical trial?"*

- Type of intervention and comparison:
  Participants must also be clearly informed that they may be in the control group (instead of the intervention group) as per the design of the trial:

> *"What drug, device or procedure is being tested?"*

- Outcome
- Methodology /type of study design, as well as sample size (in plain language)
- If relevant, special effort should be made to explain equivalent or non-inferiority studies, randomization, placebo, including why is a placebo control necessary.[2] For example:

> - *"A non-inferiority trial aims to demonstrate that the test product/new drug is not worse than the comparator by more than a pre-specified, small amount. This amount is known as the non-inferiority margin"*
> - *"A placebo or inactive medicine looks like real medicine but it is not. It's a 'dummy' or fake medicine"*
> - *"Participants and/or their doctor/research team will not know which treatment they are receiving [blinding/double blinding"]*

[2] Reference to the ECRAN video and tutorial could be useful (http://www.ecranproject.eu/en/content/tutorial; http://www.ecranproject.eu/en/content/sail-along-james-lind). The video is available in single modules focusing on individual topics, such as randomisation or blinding.

- The availability of alternative treatments – explain standard treatment (if this is relevant)
- Duration:

> *"How long will the study last? / When will it start and end?"*

- What taking part would involve - specify visits, examinations additional to standard care, included any indirect burden on participants, such as travels, work arrangements, etc:

> *"What will taking part in the clinical trial involve? What will the participant have to do?"*

- The sites where the study will be conducted
- The possibility of incidental findings (the meaning should also be explained) and how they will be managed and communicateds
- Sources of funding and potential conflict of interests

Benefits and Risks

- Benefits of the clinical trial to the participant and for society
- No guarantee of individual health benefits - a sentence noting that there is no guarantee that participants will receive any health benefit in this research study has to be included
- Side effects of treatments, which should be presented in odds or percentages. If odds are used, - *1 out of 100* - should be used. The base number should not be changed. Serious side effects should be stated first.
- Impact on possible pregnancy and breast feeding
- Status of the product, namely whether it is approved or not
- Specify that Possible profits - coming from the commercial exploitation of products related to the clinical study will be not shared with participants (except specific cases), even if their biological samples have been used, in accordance with patent laws and rules.

Confidentiality

This section should be adapted in order to meet the requirements of the national regulation/legislative framework. Topics to be addressed in this section include:

- Confidentiality of identity with an explanation of how information will be kept confidential
- Usage and storage of data
- Specifying which individuals can access the data whilst maintaining confidentiality
- The right to modify, oppose and revoke consent for the use of personal data
- Reuse of patients' data and samples (for further details on this topic, please refer to the biosample and data sharing sections as below)
- The possible need to release information to third parties in other countries

It should be noted that information on processing of personal data has to be separated from the information provided relating to the clinical trial. Therefore separate information sheets

have to be provided, except in the instance when the participant's identity is anonymised. Consent to the processing of personal data is a separate process from consenting to the clinical trial.

Processing of Personal Data - Information concerning the data protection rights of clinical trial participants

A separate information sheet and consent form should be provided for the processing of personal data. Participants should be informed as to how they can can exercise their rights under the General Data Protection Regulation by providing information on the following:

- Data controller, as well was Data Protection Officer - specify who is who
- Who will have access to participants' data, and under which conditions
- Rights to request correction of data, restriction of use of personal data, deleting personal data
- Pseudoymization of participants data – explain what this means
- Data portability

In the case of international trials, where they may be transfer of personal data to another country, the sponsor of the clinical trial is located in a different country, or is co-sponsorship, etc., participants should be informed how they can exercise their rights under the Clinical Trial Regulation. Further information to be provided includes:

- whether the data be anonymised or pseudonymised before the transfer.
- what would happen in case of personal data breach.
- who the data controller, and the data protection officer is in each of these cases.

Please be aware that the implementation of the European General Data Protection Regulation's provisions concering the processing of personal data for scientific puroposes might vary from country to country since they are subject to national adaptations.

Collection of biosamples for the purpose of the clinical study

The possibility to fully anonymise biosamples and data is increasingly impossible, particularly due to the advancement of available technologies and the sharing of information amongst different sources. Furthermore, pseudonymization of biosamples and data also implies a certain risk of identification of the participant, and related privacy risks, the implications of which will depend on the nature of the particular study and the condition.

This possibility of identifying a participant's data and biosamples can also mean there is opportunity for the clinician to inform the participant about any signifcant individual health information that results from the study. All these issues have to be stated in the information sheet:

- Specify that biosamples will be collected with related data, describing which data will be collected and why.
- Specify procedures of biosample collection and analysis, namely the kind of examations that will take place and the frequency, as well as how biosamples will be used, and the mode and duration of processing and storage.
- Participants have to be informed that the possibility to anonymise biosamples and data is increasingly impossible. The measures used to protect participant privacy and confidentiality have to be specified, along with the meaning and procedures of pseudonymization if relevant.
- Describe benefits and risks related to the collection of biosamples, i.e. benefits related to the improvement of scientific knowledge and potential benefits for society; the fact that the participant will not have any direct advantage; and possible clinical risks. Include the benefits and risks related to the pseudonymization of biosamples and data, as well as related privacy risks.
- Clearly state that there is a right to withdraw consent for the collection of biosamples and related data, which will not result in any loss of benefits, and that the current research study will not be affected in any way. Clarify if previously collected bio-samples can no longer be destroyed.
- Clearly state the name and contact details of the people responsible for the collection of biosamples.
- Clearly state who will have access to the bi-samples and data, and whether third parties will have access. If so, explain why they will be permitted to have access, and specifiy whether there are any transfer agreements with third parties.
- Describe how the study results will be disseminated, such as via scientific articles, meetings, public dissemination, etc.

In case of secondary use and sharing of biosamples

A separate information sheet and consent should be provided, covering:

- Reasons for sharing or secondary use
- How the biosamples will be used in the future (if known)
- Storage conditions – namely where, how and how longs samples will be stored for
- Specifiy the type of requests that will be considered and the scrutiny to which they will be subjected, for instance, which access model will be applied, such as through request/review mechanisms
- Who will use the biosamples (if known)
- Participants should have the possibility to state some selection criteria or exclusion areas for the sharing or secondary use of biosamples.

It is advisable to limit the secondary use of biosamples for studies that focus on the disease/disease group, or similar disease group, studied in the original clinical trial.

In case of Biobanking

A separate information sheet and consent for biobankng should be provided, covering:

- The meaning of biobanking
- The scope of biobanking
- The connection between the disease of the participant and biobanking, in the event that the participant is a patient
- balancing risk of profiling with rights due, responsibility and implication of participation
- respect and protection of genetic information
- clear information on results returning and samples traceability.

Key points:[3]

- a widespread and informative environment that enables invited persons to make decisions, transforming the biobanking for research into a process accessible to everybody
- the co-production of definitions, beginning from biobanking for research as a collaborative process
- transparency of the process.

Before the proposal of biobanking:

- diffuse information environment based on different sources and multimedia options

During:

- communication stages, with different levels of in-depth information also on-line
- an information path personalized (how and why "biobanking oncerns me") "customized" at least for a group of pathologies, and in context
- granularity of the consent

After:

- a clear, accessible interaction path both with the principal investigators and the biobank.

[3] This section is based on a used-cased from the Biobanking and BioMolecular resources Research Infrastructure (BBMRI) community.

In case of Secondary use of individual participant data (IPD) [4]

Background

A separate consent, meaning a separate signature for secondary use of data, on the same sheet related to the trial , is required . An appropriate consent process for secondary use of data should ensure that:

a. The reasons for asking about data sharing, and the general benefits of data sharing in clinical research, for science and medical practice, are made clear to the trial participant.

b. The nature of data preparation, storage and access is explained to participants, so far as they are known at the time the patient documents are produced.

The nature, purpose and destination of IPD data sharing that may occur after the trial is finished is impossible to predict. Therefore any consent for secondary use of data cannot be fully 'informed'. What should be sought from participant is 'broad' consent to their data being shared only for scientific purposes.

Information

Information should cover:

- Reasons for data sharing - benefits for society and research should be included
- Use of external repositories
- Data preparation for sharing – it should be stated that data will be de-identified
- How and where the data will be stored
- How confidentiality will be maintained, including the measures that will be used to protect participant privacy
- The type of requests that will be considered and the scrutiny to which they will be subjected, for instance which access model will be applied, such as publicly accessible web-based systems, or through request/review mechanisms, etc.
- Trial participants have to be informed that not giving consent to share their data will not affect their participation in the study or the care they receive.
- They should be informed that the lack of large amounts of data would invalidate all data sharing
- The right of participants to withdraw consent for secondary use – the practical difficulties of implementing this however, should also be made clear to participants and stated clearly in the information sheet.

[4] This section is based on the Corbel WP 3.3 principles and recommendations on informed consent process and form on data sharing.

Insurance

- Details of insurance/indemnity schemes:

- *"What kind of things would be covered in the insurance/indemnity scheme* (specify whether only direct adverse effect of treatment under study or other things would be covered)?"
- *"Who is responsible if something happens to you? "*

Economic aspects

- Responibility of the sponsor – explain that the sponsor is responsible for all costs, with no costs to participants for participating
- Travel expenses and reimbursement
- Compensation (if provided)

Additional Information and Sources

To explain concepts such as why clinical research is necessary, the importance of independent research done, we suggest to consider referring to the ECRAN - European Communication on Research Awareness Needs project - film, tutorial, and FAQs as additional sources of information, given in different formats (http://www.ecranproject.eu/en/content/tutorial; http://www.ecranproject.eu/en/content/sail-along-james-lind).

General suggestions

Wording

- Avoid technical terms and jargon
- Explain acronyms if they are needed
- Use short sentences
- Use the active voice
- Don't introduce more than one idea/point in a sentence.
- Keep the object of the sentence close to the subject of the sentence.
- If your next sentence does not directly follow the previous one, start a new paragraph.
- Avoid words and phrases that could be potentially misunderstood), including those with dual or nuanced meanings, for example ‘drugs’ or ‘diet’. (e.g. drugs; diet); particularly consider wording that is likely to cause difficulty to those that have a different first language
- Avoid longer words or with many syllables
- Avoid more than 2 difficult words in a sentence unless it is a term that is explained

Format

Use:

- Headings and sub-headings
- A question and answer format
- A font size of at least 12, 16 or 14, particularly the latter for older or visually impaired persons
- Non-justified text
- Do not useall CAPS or all italics.
- In general, provide different formats, such as language and pictures to effectively communicate information to the person invited to participate. The use of videos or multimedia could also be considered, especially for younger individuals.

Length

- Make sure that the information sheet is concise and easy to read. For example, it is advised that the section focusing on general description of the study should be no longer than 2 pages, with the context described in 5 lines.

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