

Summaries of Clinical Trial Results for Laypersons

Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use

Version 2

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Contents

1. Introduction	3
2. Scope.....	3
3. Responsibility of sponsor	3
4. General Principles	3
5. Health Literacy Principles and Writing Style	4
6. Readability and use of plain language	6
7. Numeracy.....	6
8. Visuals	7
9. Language	7
10. Communication of return of results to participants	8
References	9
Annex 1 – Templates with example wording.....	11
Annex 2 – Neutral language guidance in describing results	27
Annex 3 - Examples of readability tests by country	29

1. Introduction

The [EU Clinical Trials Regulation](#) 536/2014 (Article 37) (EU CT Regulation) requires sponsors to provide summary results of clinical trials in a format understandable to laypersons. These layperson summaries will be made available in a new EU database once it becomes available and is approved according to the timelines set forth in the Regulation. Prior to this Regulation and the creation of a new EU database, the EudraCT Results data model, launched in July 2014, had been used for posting of scientific results written in technical language under the Commission Guidelines 2012/C 302/03, which was not easily accessible or understandable to the layperson.

Annex V of the EU CT Regulation sets out ten elements that must be addressed in the lay summaries. This document includes guidance and templates to help authors writing these lay summaries. Consistency in the way trial results are presented will help improve familiarity and comprehension by the general public, participants, patients, and others.

2. Scope

This document provides sponsors and investigators with guidelines and templates for the production of summaries of clinical trial results for laypersons. These guidelines will only apply to lay summaries included in the EU database. The lay summary section of the EU database will be publicly available. The general public are expected to be the primary audience for the lay summaries. The lay summaries may also be accessed by others, such as research participants, healthcare professionals, and academics. Given this wide audience, the summaries will need to take into account the average literacy level of the general population, provide simple explanations, and apply other measures to support health literacy¹.

3. Responsibility of sponsor

It is the responsibility of the trial sponsor to ensure that the lay summary is developed and submitted to the EU database within the timelines required by applicable regulation.

4. General Principles

- Develop the summary for a general public audience and do not assume any prior knowledge of the trial, of medical terminology or clinical research in general.
- Develop the layout and content for each section in terms of style, language, and literacy level, to meet the needs of the general public.
- Keep the document as short as possible, avoid simply copying text from the technical summary. Explaining technical terms in a simple language may increase the number of words and translation to some languages will result in longer documents than others. All content must be

¹ “Health literacy is the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions.”
<http://health.gov/communication/literacy/quickguide/factsbasic.htm>

carefully considered for inclusion since additional content worded in plain language may add considerable length which in and of itself may decrease comprehension.

- Focus on unambiguous, factual information.
- Ensure that no promotional content is included (See neutral language guidance in Annex 2).
- Follow health literacy and numeracy principles (see section 5 'Health Literacy Principles and Writing Style' and section 7 'Numeracy').
- Consider involving patients, patient representatives, advocates or members of the public in the development and/or review of the summary to assess comprehension and the value of the information provided. This won't be feasible for some studies, but where it is a possibility, it may enhance the final version. Medical writers with particular experience of writing in plain language for the public who are also able to incorporate health literacy and numeracy principles may be helpful in developing summaries for the lay person.

5. Health Literacy Principles and Writing Style

Communications written for the public should use simple everyday language to ensure ease of reading and understanding.

- Text should be suitable for people with a low to average level of literacy. Across Europe, the average proficiency level is 2 -3². A proficiency level of 2 is defined as being able to identify words and numbers in a context and being able to respond with simple information, such as being able to fill in a form. A proficiency level of 3 is defined as being able to identify, understand, synthesize and respond to information, be able to match given information that corresponds to a question. This level corresponds roughly with high (secondary) school completion levels.
- Avoid long and complex sentences that include many clauses as these are difficult to understand.
- Use simple vocabulary familiar to non-medical people:
 - Avoid jargon, technical, medical or scientific language (for example, use "high blood pressure" rather than "hypertension")
 - Remove unnecessary or complex words (for example, "use" rather than "utilise")
 - Be consistent in the use of terms/words throughout the document, and define them
 - Ensure that the underlying concepts are clear and easy to understand. Where necessary, explain the underlying concept
 - Avoid ambiguous words and phrases (for example, "felt badly")
- Use active, rather than passive, voice:
 - Active voice: "Researchers studied the effect of tamoxifen on breast cancer"
 - Passive voice: "The effect of tamoxifen on breast cancer was studied by researchers"

² Based on research across Europe, text for the lay summary should be aimed at a literacy proficiency level of 2 - 3. The International Adult Literacy Survey (IALS) identifies five levels of proficiency ranging from level 1 (lowest level of proficiency in literacy, that is basic identification of words and numbers) to level 5 (highest level of proficiency in literacy, that is able to understand and verify the sufficiency of the information, synthesize, interpret, analyse and discuss the information. At level 5, the individual demonstrates sophisticated skills in handling information).

- Use the following elements to help improve comprehension:
 - Headlines and descriptive subheadings to organise information
 - Presentation of the “big picture” before the detail (inverted pyramid writing style)
 - Bullet points instead of paragraphs
 - Numeracy principles to describe data and statistics (see section 7 below)
 - Adequate “white space”. For example, separate topics by one or two lines
 - 12-point font should be used (where needed, readers may enlarge print when viewing electronically or print pdf in larger font)
 - The most readable colour combination is black text on a white background. Please avoid using white text on a coloured background as this can be harder to read. Keep in mind how documents will look when online or printed.
 - Links to additional information, and resources for online summaries and background information. Such links need to be minimal since hyperlinks can become out of date over time.
 - Limited use of unnecessary imagery that does not enhance understanding (icons, logos, etc.)
 - Avoidance of text in ALL CAPS and underlining
 - Use visuals (for example, simple graphs) to convey messages where helpful. Avoid overwhelming the reader with too much information.

Where possible, avoid using acronyms, abstract, medical/technical, or multisyllabic words (such as, “unanticipated”, “hematopoietic”). If such words are to be used (for example, where commonly used medical terms will also aid in finding other medically relevant information and referencing other documents), add clear language to define the word followed by the term in parenthesis. For example, cancer that has spread to another part of the body (metastases). Also, where medical terminology refers to defined stages of a condition, it may be helpful to express the stages as mild (stage 1), moderate (stage II), severe (stage III) and very severe (stage IV) as appropriate.

Finally, it is helpful to use language in a way that is respectful and empowering for patients. For example, words such as “demented” in dementia research should be avoided. Similarly, avoid using the words “sufferers” or “victims” that have negative connotations. A preferable term is “people living with ...” or “people affected by ...”.

Sponsors should note that there is no limit placed on the size of the lay summary document that will be uploaded as a pdf document. However, it should be as succinct as possible while relaying the required information in a form that is readily understandable. Whilst brevity is preferable, explaining technical terms and complex concepts in a simple language will often use more words than a technical term.

6. Readability and use of plain language

Sentences should be kept short and succinct. The summary should remain factual and objective, avoiding any promotional language (See neutral language guidance in Annex 2) or promotional perception through formatting or tone³.

Sponsors are encouraged to use a language-specific reading test to assess the literacy level of each lay summary produced. Sponsors should understand, however, that even though lay summary text may indicate an optimal reading level, the summary may not be clear or readily understandable. Many simple sentences together may explain little or nothing despite the fact that each sentence is simple, straightforward and grammatically correct. Nonetheless, these readability tests may be useful tools in striving to make often complex information understandable. While approaches were initially only developed for the English language, tools are now available in other languages (See Annex 3 for further information). These tools use a variety of metrics to provide a corresponding grade level (for example, average numbers of words per sentence and syllables per word).

A well written lay summary would normally be accessible by young people from the age of 12 years upwards. Sponsors of paediatric studies may consider developing a child-focused version of the lay summary, particularly where they have already developed child-focused Patient Information Sheets. Paediatric focused lay summaries may differ in terms of presentation and style (more illustrations or graphics) to assist children in understanding trial results, over and above what is required under the EU CT Regulation. Enabling increased understanding of results by the general public will also help parents and caregivers explain results to others, including children who have participated in a trial.

Where feasible, sponsors should consider testing the readability of the summary with a small number of people who represent the target population. Depending on the nature of the study, this could be patients with a particular disease or members of the public. Their feedback and suggestions could be helpful in developing a summary that lay people will understand.

7. Numeracy

Trial results summaries are likely to include a variety of numerical data that should be easily understandable by the target audience. Some key principles to consider when using numbers in a lay summary are:

- Present absolute numbers but also consider conveying numerical information in other ways such as a percentage, rather than relative risks, odds ratios etc.
- Use whole numbers rather than decimals to the extent this is possible without increasing confusion should the lay summary be cross referenced with the scientific summary.

³ See 'Recommendations for Drafting Non-Promotional Lay Summaries of Clinical Trial Results' <http://www.transceleratebiopharmainc.com/wp-content/uploads/2015/04/TransCelerate-Non-Promotional-Language-Guidelines-v10-1.pdf>. TransCelerate BioPharma (2015)

Further detail on how to apply principles of numeracy can be found in Appendix 4 of the [MRCT Return of Results Guidance Document](#), Version 2.1, July 13 2016 – Multi-Regional Clinical Trials Center of Brigham and Women’s Hospital and Harvard.

8. Visuals

Well-chosen and clearly designed visual aids can help enhance understanding of text and their use is encouraged. Summaries of clinical trial results that combine clear infographics with explanatory text can be a good way of presenting information. Basic principles to follow include:

- Where used, visuals should present a simple message and be clearly labelled with captions; consider how a visual aid helps to reduce the need for lengthy text. Visuals should always be accompanied by a simple textual explanation and placed near the text that they illustrate.
- Avoid using overly complex images, such as graphs showing several relationships, since they can be easily misinterpreted.
- Graphs using potentially misleading axes labels should be avoided. Consider the scales you are using in any graph and whether the axes need to start at zero to avoid confusion. Ensure that all your graphical images are clearly labelled.
- Creative solutions to ensure understanding could include cartoons and illustrations.
- Finally, although colour adds interest, any visuals or graphics should still be clear if printed in black and white.

For examples of clearly laid out visuals which aid understanding see the [Understanding Immunology for kidney cancer website](#) which uses infographics to display clinical trial results.

9. Language

As a minimum, the summary is expected to be provided in the local language of each of the EU countries where the trial took place. The specific local languages selected should match the languages employed in the Patient Information Sheet for that trial in each country (pdf versions of translated lay summaries will need to be uploaded separately). Where resources allow, sponsors should consider including an English version if the trial did not include the UK, the Republic of Ireland or Malta, as the use of a common language will allow greater accessibility across the EU and globally, however this is not mandatory.

Where translation is required for multi-country trials, care should be taken to ensure that the original meaning and non-promotional nature of the summary are maintained. Translated summaries should also take into account the cultural validity of the medical or technical terminology used.

10. Communication of return of results to participants

The summary for lay persons in the EU database should not be regarded as the only way of communicating with trial participants. Although not required by regulation, sponsors may provide trial results to investigators or third parties to feedback to patients who have taken part in their trials, along with an acknowledgement of their contribution and an expression of appreciation, rather than solely directing them to the lay summaries on the EU portal .

References

Health literacy:

Apter, A. J., Paasche-Orlow, M. K., Remillard, J. T., Bennett, I. M., Ben-Joseph, E. P., Batista, R. M., Hyde, J. & Rudd, R. E. (2008). Numeracy and communication with participants: they are counting on us. *Journal of General Internal Medicine*, 23(12), 2117-2124.

Center for Information and Study on Clinical Research Participation (CISCRP) (www.ciscrp.org)

Centers for Disease Control and Prevention. (2010). *Simply put: A Guide for creating easy-to-understand materials*. http://www.cdc.gov/healthliteracy/pdf/simply_put.pdf

DeWalt, D.A., Callahan, L.F., Hawk, V.H., Broucksou, K.A., Hink, A., Rudd, R., Brach, C. (2014). *Health Literacy Universal Precautions Toolkit*. <http://www.ahrq.gov/professionals/quality-patient-safety/quality-resources/tools/literacy-toolkit/index.html> Pages 49-59

Doak, C., Doak, L., & Root, J. (1996). *Teaching patients with low literacy skills* (2nd ed.). Philadelphia: J.B. Lippincott Company. <http://www.hsph.harvard.edu/healthliteracy/resources/teaching-patients-with-low-literacy-skills/>

Health Literacy Missouri Best Practices for Numeracy (www.healthliteracymissouri.org)

Houts, P.S., Doak, C., Doak, L.G., Loscalzo, M.J. The role of pictures in improving health communication: a review of research on attention, comprehension, recall and adherence. *Pat Edu Coun.* 2006; 61(2):173–190.

Jacobson, Kara L., and Ruth M. Parker. (2014) "Health Literacy Principles: Guidance for Making Information Understandable, Useful, and Navigable." Institute of Medicine of the National Academies, 22 Dec. 2014. <https://nam.edu/perspectives-2014-health-literacy-principles-guidance-for-making-information-understandable-useful-and-navigable/>

A synthesis of health literacy principles used to create health information that is better aligned with the skills and abilities of those using that information.

Jacobson, Kara L., and Ruth M. Parker. (2014) "Health Literacy Principles Checklist." Center for Health Guidance, 2014. <http://centerforhealthguidance.org/health-literacy-principles-checklist.pdf>

A user-friendly checklist to apply health literacy principles.

Kirsch, I. The International Adult Literacy Survey (IALS): Understanding What Was Measured. Educational Testing Service. December 2001. <https://www.ets.org/Media/Research/pdf/RR-01-25-Kirsch.pdf>

[MRCT Return of Results Guidance Document](#), Version 2.1, July 13 2016 – Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard.

[MRCT Return of Results Toolkit](#), Version 2.2, July 2016 – Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard.

Nielsen-Bohlman, L., Panzer, A., & Kindig, D., Eds. (2004). *Health literacy: a prescription to end confusion*. Washington, DC: The National Academies Press. <http://mbrcinc.org/wp-content/uploads/2016/03/10883.pdf>

Sroka-Saidi K, Boggetti B, Schindler T.M. Transferring regulation into practice: The challenges of the new layperson summary of clinical trial results. *Medical Writing* 2015, Vol 24, 1, p.24-27. <http://www.tandfonline.com/doi/full/10.1179/2047480614Z.000000000274>

Stableford, S. & Mettger, W. (2007). Plain language: a strategic response to the health literacy challenge. *Journal of Public Health Policy*, 28(1), 71-93.

For more information:

- [OECD \(2013\), OECD Skills Outlook 2013: First Results from the Survey of Adult Skills, OECD Publishing](#)
- <http://www.plainenglish.co.uk/free-guides.html>
- www.plainlanguage.gov
- <http://www.invo.org.uk/resource-centre/plain-english-summaries/>

- Health literacy: a prescription to end confusion: <http://mbrcinc.org/wp-content/uploads/2016/03/10883.pdf>
- <http://www.transceleratebiopharmainc.com/wp-content/uploads/2015/04/TransCelerate-Non-Promotional-Language-Guidelines-v10-1.pdf>
- The Centers for Disease Control and Prevention (CDC) has developed extensive health literacy resources including links to free training and an assessment tool:
 - Overview: <http://www.cdc.gov/healthliteracy/>
 - Free online training: <http://www.cdc.gov/healthliteracy/gettraining.html>
 - Assessment tool: <http://www.cdc.gov/ccindex/index.html>

Annex 1 – Templates with example wording

Annex V of the EU Clinical Trials Regulation contains 10 elements that must be included in the summary of the results of the clinical trial for lay persons:

1. Clinical trial identification
2. Name and contact of sponsor
3. General information about the clinical trial
4. Population of subjects
5. Investigational medicinal product used
6. Description of adverse reactions and their frequency
7. Overall results of the clinical trial
8. Comments on the outcome of the clinical trial
9. Indication if follow up clinical trials are foreseen
10. Indication where additional information could be found

This document provides detailed guidance on the information that could be provided for each of these ten elements. The template below has substituted the ten elements with user friendly equivalent headings. Sponsors should cover all ten elements but can, if they wish, combine categories where this makes sense. For example, some sponsors might wish to combine section 3.1 (where the trial was conducted) with 4.1 (the number of subjects included in the trial). Sponsors may also decide to change the order of the headings if they feel this is appropriate and add sub-headings to help reader find and understand the information provided.

The use of suggested wording is not mandatory but a consistent approach with a familiar layout is likely to make the summaries more accessible to the lay person. Sponsors should pick and choose those sections of text that they think might be of use. Suggested text is provided in [blue](#).

1. Study name

- This section should refer to the phase of the trial (see “[ICH Harmonised Tripartite Guideline General Considerations For Clinical Trials E8: General Considerations for Clinical Trials](#)” for descriptions of trial phases) and specify the fact that this trial is only one study in an overall drug development process or process for understanding how treatments can be improved. Some trials take place outside of the four phases and the rationale for these trials should be explained, for example, long term safety study, pragmatic trials of existing licensed products etc.

Example Language:

[Researchers look at the results of many studies to understand which drugs work and how they work. It takes lots of people in many studies all around the world to advance medical science. This summary only shows the results from this one study. Other studies may find different results.](#)

1.1 Study name

- It is important that the title is specific to the trial so that it can be directly linked with other information included within the EU database.

<ul style="list-style-type: none"> • If the full title is lengthy and/or complicated then also provide a shorter and/or simpler lay title upfront followed by the full title. A short title alone may lead to confusion with other similar studies. Avoid technical terms and explain them further down in the document if necessary. The title should focus on the basic aim of the study.
1.2 Protocol number
1.3 EU Trial number
1.4 Other identifiers <ul style="list-style-type: none"> • Other identifiers refer to EudraCT number, WHO ICTRP number, US NCT number, ISRCTN number if available, etc.
1.5 Abstract Inclusion of an abstract is not mandatory but will help the reader identify whether they wish to read the whole summary. Give a very short description of the trial including: <ul style="list-style-type: none"> • Purpose of the study • What was tested: the intervention and any comparators, the Phase of the trial where applicable • People taking part in this trial: including total number of participants across x countries • Topline results: Simple description of the result of the primary endpoint • Safety: overall statement about the the safety findings in the study. For example:

ABSTRACT:

Purpose of the study: To see if [medicine x] prevents the development of type 1 diabetes in children with a high risk of getting this disease.

What was tested: [Medicine x] was compared to [placebo] in a Phase 2 trial. In a Phase 2 study a new treatment is tested in a small number of patients [amend as appropriate].

People taking part: 350 children aged 7 to 16 years at high risk of developing diabetes took part in this trial across 3 countries.

Results: [Medicine x] did not prevent the development of type 1 diabetes in high risk children.

Safety: In this study, researchers found that [Medicine x] had more side effects than placebo

2. Who sponsored this study?

- Give the name of the organization, and how to contact (not a specific person in most cases).

3. General information about the clinical trial

3.1 Where was the study done?

- The countries in which the trial took place i.e. where participants were recruited.

For example:

This trial took place in the following countries:

- France
- Belgium
- Germany
- USA
- Canada
- China
- Japan
- South Africa

3.2 When was this study done?

- The overall trial start and end dates. For example:

This trial started in December 2014 and ended in March 2017.

- Where a clinical trial has had to close early, the information included in the summary should explain the reason for this, for example, evidence of lack of efficacy, safety events, poor recruitment etc.
- Sponsors may want to specify follow up periods here for some longer trials.

3.3 What was the main objective of this study?

This section should specify:

- The purpose of the trial (for example, finding a safe dose, comparing treatments, etc.) / why the trial was carried out.
- Why the comparator was chosen, for example, the comparator is regarded as standard treatment for this condition.
- Any critical changes made during the study. For example, if the dosage used was changed or if the trial stopped early due to efficacy or side effects this should be noted.
- Avoid the use of unfamiliar abbreviations, acronyms and medical terms, for example “RCT” for Randomised Controlled Trial. Explain the concept simply. If you wish to use a medical term, use it in brackets after the simple explanation.

Suggested wording for different phases of clinical trials:

Phase 1:

In this study, researchers looked at how this drug works in the human body. Researchers did medical tests on men and women before and after they took the drug. The researchers wanted to know if there were:

- Any chemical changes in blood or urine, and
 - Any unwanted side effects of the drug
- This trial did not test if the drug helps to improve health. [Patients/healthy volunteers] took part in this study.**

Phase 2 trial:

In a Phase 2 study a new treatment is tested in a small number of patients [amend as appropriate]. In this study, researchers gave medicine X to patients with diabetes to find out if medicine X lowered the amount of sugar in their blood.

Phase 3 trial:

In a Phase 3 study a new treatment is tested in a large number of patients [amend as appropriate]. In this study, researchers compared the test medicine to the standard treatment used for [disease/condition] or placebo (identical looking tablets but with no medicine in them).

Phase 4 trial:

This trial was carried out after the new treatment had been approved for use (meaning that the treatment can already be prescribed by doctors). Researchers looked at the effect of the new treatments in a larger number of people.

Randomisation:

“People with diabetes were put into 2 groups by chance (randomised) to reduce differences between the groups. Putting people into groups by chance helps to make the 2 groups equal Reducing differences between the groups in this way, makes the comparison between the groups fairer.

Blinding:

[If the trial was double-blinded, also add the following wording] This trial was also “double-blinded”. This means that neither patients nor doctors knew who was given which treatment/drug. This was done to make sure that the trial results were not influenced in any way.

[If the trial was single-blinded, use the following words]This trial was single-blind. This means that the patient did not know who was given which treatment they were given but the doctor did know.

[If not randomised, list how many patients/people were in each group, and how this was determined.]

4. What patients/people were included in this study?

4.1 the number of subjects included in the trial by country both within and outside of the EU

For example:

This trial included [specific population to whom this applies, including healthy volunteers and patients as appropriate]

The trial was run in the following [list country(ies) that enrolled patients]. In each country [name the country] [#] people were enrolled in this study. If there are a lot of countries involved, it may be easier to present this data in a table or pie chart. It may be helpful to combine the requirement under section 3.1 with those of this section presenting both together rather than separately.

4.2 Age group and gender breakdown

- Provide basic breakdown of participants by age and gender in the trial as a whole

Consider including a simple graphic that helps the reader understand the study.

4.3 Inclusion and exclusion criteria

- The number of inclusion and exclusion criteria can vary substantially, and long lists of technical criteria can be very difficult to understand. It is suggested that when there are large numbers of inclusion and exclusion criteria, the sponsor should only list the most important inclusion and exclusion criteria – and draw attention to those criteria that have the most impact on the population to be studied.
- If possible, sponsors should include references to age, gender, diagnosis, indication, disease stage or severity as this will help define the scope of the trial (for example, ‘very severe chronic obstructive lung disease’)
- Sponsors should also avoid using technical terms that lay persons might struggle to understand. For example, ‘myocardial infarction’ would be better described as a ‘heart attack’. Explain the concept simply. If you wish to use the medical term, use it in brackets after the simple explanation.
- Care should be taken not to provide information that might inadvertently identify specific individuals who have taken part. Particular care should be taken in trials for rare diseases where the number of potential participants will be relatively small.

5. Which medicines [or vaccines] were studied?

- This should include naming of the trial medicine (and comparator(s)) as used in the protocol and trial registration.
- For early phase trials it might not be possible to refer to a specific name and will need to use the internal compound code instead.
- If a placebo was used in the trial, this should be stated clearly and the term 'placebo' explained. See the description above in section 3.
- Randomisation and blinding arrangements should be described.

6. What were the side effects?

Sponsors should note that the lay summary calls for a description of adverse reactions whereas the technical summary refers to adverse events. This difference is intentional and means that text should not be simply copied across from one section to another. Whilst it is not always possible to establish an exact causal relationship between the investigational medicinal product and the adverse events in a single study, the sponsor should define 'adverse reactions' as those adverse events where the investigator has indicated that there is a possible causal relationship between the event and the investigational medicinal product.

- Consider using a simple term, such as "side effects" to refer to adverse reactions, explaining how 'side effects' are defined for the purpose of the lay summary.
- Serious adverse reactions need to be listed first, followed by other common adverse reactions listed by frequency (starting with the most frequent) and using a clearly communicated 'cut-off' where needed.
- Frequencies should be given in numerical terms as well as percentages (X out of X patients [x%]) following the principles of numeracy. Where specific adverse reactions coincide with endpoints, this should be stated.
- The number of serious adverse reactions including fatal adverse reactions should be clearly stated together with any adverse reactions that have led to the early closure of the trial or the withdrawal of patients. The classification of serious adverse reactions should be explained (for example, "reactions that are life threatening or require the individual to have to go hospital").
- Include clinical laboratory changes only if they are useful/clinically relevant.
- MedDRA (Medical Dictionary for Regulatory Activities) terms, or other similar terminology as appropriate, should be translated into lay language where necessary. This might mean using the preferred term and a lowest level term as a plain language descriptor.

Suggested wording to describe adverse reactions (also known as side effects) is as follows:

Side effects are unwanted medical events (such as a headache) that happen during the study, and are reported because the trial doctor (investigator) believes the side effects were related to the treatments in the trial. Not all the people [people/patients] in this trial had side effects.

Serious and common side effects are listed here.

[List the serious adverse reactions and most prevalent other adverse reactions for each trial drug(s) tested (excluding the serious in the latter section to avoid duplication). If possible, compare the number of people who had each event by dose level.] Where the adverse reaction profile is similar for both the intervention and the comparable arm(s) the sponsor should only have to list the adverse reactions once indicating the numbers in each arm of the study.

[Plainly state any objectives or statistically valid endpoints that dealt directly with adverse reactions.]

Side effects [in Group A] included:

[List the serious and most prevalent (excluding the serious) adverse reactions. Apply numeracy and health literacy principles.]

[Minimise acronyms/medical terms and explain any that are used.]

Side effects [in Group B] included:

Side effects [in Group C] included:

More side effects were seen in Group C than in Group B. Because so many side effects were seen in Group C, no higher doses were tested.

7. What were the overall results of the study?

This section should describe each of the trial arms including the name of the drug (generic only) as well as the outcomes (both positive and negative), using text and graphics where appropriate, including:

- A general high level statement summarising the overall results and their implications without using promotional language (See neutral language guidance in Annex 2).
- Information on whether the trial completed as planned, or was stopped and for what reason.

- The primary endpoint(s) and results by trial arm which were pre-specified by the statistical analysis plan as a primary endpoint.
- Additional safety data important to the overall results of the trial.
- Sponsors should reference the complete list of outcomes based on all endpoints available in the technical results summary for each clinical trial in the EU database including patient relevant secondary endpoints.

Describing numerical concepts to a lay audience can be difficult and sponsors should follow the following guidance:

- Outcomes should be described using numeracy (x out of xx people [xx%]) and plain language principles.
- Refrain from using technical terms such as ‘number needed to treat’, ‘odds ratio’, ‘confidence interval’ etc. If technical terms are included, then they need to be explained in simple language.
- If reference is made to numerical differences that are not statistically significant, this should be explained to the reader. For example:

Group A had lower blood sugar levels than Group B but the difference between the groups is likely to be by chance rather than a difference caused by the treatment.

- Further guidance on providing numerical information can be found at www.healthliteracymissouri.org/.

The following table lists common clinical trial endpoints in simple language. Terms are defined with general descriptions, followed by examples of simple, plain language that can be used in summaries of clinical trial results for laypersons. Please select those examples that relate to the type of outcome in your trial.

Endpoint	Original description of the type of endpoint	Example of desirable simple, plain language
Composite	A composite endpoint , as the primary endpoint, combines multiple outcomes (for example, death, getting sick again (relapse), serious event) and test results into one measure of how well the	“The XXX trial measured <i>[patients/people]</i> to see if those in Group A (ABC treatment) or Group B (XYZ treatment) lived longer, had fewer heart attacks, or fewer hospital visits for heart failure. These outcomes were measured together

	drug/therapy/device works. This is useful when there are many different outcomes that can happen during a trial. This can also be called a combined or multi-part endpoint .	(combined) because each one is quite rare. Researchers also wanted to see if the drug worked in patients who had all 3 conditions. The trial found that there was no change in the number of outcomes for [patients/people] in Group A or Group B."
Dose Escalation	Dose escalation is sometimes used in phase 1 studies to measure safety. People in the trial start with a low dose of the medicine (drug). If that dose does not cause safety problems, then more people are given a higher dose until there are too many safety issues. The highest dose that is tolerated is called the maximum tolerated dose (MTD).	"This trial was undertaken to find the highest [dose/amount] of treatment that people could safely take [or use] without having severe side effects."
Mortality / Overall Survival	The goal of this trial was to see if Treatment ABC or Treatment XYZ helped patients with [disease/condition] to live longer.	<p>"This trial compared patients in Group A (Treatment ABC) to those in Group B (Treatment XYZ) to see who lived longer.</p> <p>If there was no effect – "Patients in both groups lived about the same amount of time, no matter what treatment they got."</p> <p>If there was an effect (statistically significant) – "The times given below refer to the average amount of time that [patients/people] in this study lived. Some [patients/people] lived for a shorter time and some lived longer. People in Group A (ABC treatment) lived about 15 months. People in Group B (XYZ treatment) lived about 12 months.</p>

		This means that people in Group A (ABC treatment) lived on average 3 months longer than people in Group B.”
Morbidity	Morbidity endpoints are those that measure the severity of disease, or when the patient experiences a new disease or illness.	<p>“People with diabetes were put into 2 groups by chance (randomised) to reduce differences between the groups.</p> <p>Group A received drug X, Group B followed a diet and exercise program. All people were followed over time to test the health of their heart and blood system, including stroke, high blood pressure and heart disease.</p> <p>EFFECT – After x years both groups had similar health conditions and outcomes. There was no difference in the health of the heart for patients in Group A (drug X) compared to patients in Group B (diet and exercise).”</p>
Non-Inferiority	Non-inferiority endpoints are designed to show that a new treatment or drug is not worse than the control (or other comparison drug) by a pre-specified amount (also termed the non-inferiority margin). Efficacy can, in fact, be worse if there are other benefits (for example, fewer side effects).	<p>[Need to include some specific comparisons between the arms before stating the following sentence.]</p> <p>“Non-inferiority studies are conducted when it is not possible to compare the new treatment with an established treatment. In a non-inferiority trial, it is expected that the new treatment would work as well or almost as well as, the existing treatment but might have other advantages such as fewer side effects or offer a better quality of life.</p> <p>This trial showed that insulin A (Group A) was not different or at least not worse than standard insulin therapy (Group B) in lowering the blood sugar level in Type 1</p>

		diabetic patients. Patients in Group B had fewer side effects of upset stomach and feeling sick (nausea) than those in Group A."
Patient-Reported Outcomes	<p>This trial asked patients about their [list the main purpose of the questionnaire: for example, symptoms, activity level, quality of life, income and/or happiness] and if the measurement changed based on whether a patient got A or B.</p> <p>The primary endpoint is less XXX based on the YYY scale. This scale measures ZZZ and how this changes over time.</p>	<p>"Patients answered questions to measure pain, stiffness, and how well they could climb stairs, stand or bend over. Questions were asked during each trial visit.</p> <p>About 2 in 4 people (50%) in Group A had less knee pain.</p> <p>About 1 in 4 people (25%) in Group B had less knee pain.</p> <p>This means that fewer patients in Group A drug A had knee pain than patients in Group B (Drug B/placebo)."</p>
Prevention/ Incidence	<p>The incidence endpoint tells how many new cases of XXX occurred over a given period of time.</p>	<p>"Women who had a bone fracture after they stopped having their monthly periods (menopause) were put into 2 groups by chance (randomised) to reduce differences between groups. The trial was carried out using two different groups because no one knew if one treatment was better than another.</p> <p>1 in 20 women (5%) in Group A (bisphosphonates) had a break in their back bone (vertebrae).</p> <p>2 in 20 women (10%) in Group B (X Treatment) had a break in their back bone (vertebrae).</p> <p>Fewer patients in Group A had a break in their back bone."</p>

Progression-Free Survival (PFS)	<p>Progression-free survival endpoints measure how much time it takes from the beginning of starting a drug/therapy/device until a patient has a sign that the disease has progressed/spread/got worse. The goal of this trial is to measure whether people given drug XXX had longer PFS than those that did not get drug XXX.</p>	<p>“Patients in this trial were assigned to 2 groups by chance (randomised). This was done because no one knew if one treatment was better than another.</p> <p>The goal of the study was to measure the size of each breast cancer tumour to see if it had shrunk, stayed the same, or grew in a 1 year period.</p> <p>56 in 100 patients (56%) in Group A (ABC treatment) had tumours that stayed the same, while 12 in 100 patients (12%) had tumours that grew, and 32 in 100 patients (32%) had tumours that shrunk.</p> <p>33 in 100 patients (33%) in Group B (DEF treatment) had tumours that stayed the same, while 10 in 100 patients (10%) had tumours that grew, and 57 in 100 patients (57%) had tumours that shrunk.</p> <p>This means that more patients in Group B had tumours that shrunk.”</p>
Surrogate	<p>Surrogate markers may be used instead of a clear endpoint (for example, overall survival) when it is hard to measure the outcome or the trial would take too long to complete. Surrogate markers measure participants’ level of X over time. Doctors believe that measuring this level of X may show how severe the disease is or how likely something is to happen in the future.</p>	<p>“The main goal of this trial was to see if drug A lowered pressure in the eye (called intra-ocular pressure).</p> <p>Higher eye pressure could mean that vision may be lost faster than with lower eye pressure.</p> <p>This trial found that people in Group A (drug A) had lower eye pressure at the end of the trial than at the beginning.</p> <p>People in Group B (placebo) had no change in their eye pressure over the course of the</p>

		<p>study.</p> <p>Eye pressure may be linked to how much vision is lost due to glaucoma <i>[define the disease]</i>. This is not yet known.”</p>
<p>Further information on neutral language guidance in describing results can be found in Annex 2. This is based on the MRCT Return of Results Toolkit, Version 2.2, July 2016 – Multi-Regional Clinical Trials Center of Brigham and Women’s Hospital and Harvard</p>		
<p>8. How has this study helped patients and researchers?</p>		
<ul style="list-style-type: none"> • State if the results are applicable to a specific population (for example, if the treatment was tested only in healthy young male adults) • Describe the most important limitations of the study. If required, sponsors can refer to further detailed information in the technical summary. • Reinforce that the outcome of one trial reflects only one single clinical trial – and that other trials may show something different (either already done or future studies). It is worth spelling this out in an separate paragraph to ensure that readers take note of this important point. <p>[If appropriate, include a general comment on what this trial contributed to the relevant area of research and potential next steps to build on that knowledge.]</p> <p>[Include the state of result analyses (including dates of interim/final analysis stage, global end of trial date – describe as appropriate)]. Please note that sponsors are normally only expected to upload a lay summary of results after a trial has been completed. However some trials have a long follow up period during which it may be appropriate to upload some interim findings. Similarly some arms in multi-arm trials may close and publish results long before the overall trial closes. In these circumstances the sponsor may decide to develop multiple summaries for the same trial.</p> <p>Findings from this trial will be used [add general next steps to this sentence to help explain context. Suggestions include:]</p> <ul style="list-style-type: none"> • in other studies to learn whether [patients/people] are helped by this drug • in other studies to compare this drug with other treatments for [patients with condition/disease] 		

- to seek approval for using the treatment for [patients with condition/disease].

9. Are there plans for further studies?

This section should explain whether other related trials are ongoing already or provide public domain information about related trials. For example:

- Clinical trials with Drug X are ongoing and further trials are planned
- Further clinical trials with Drug X are planned
- No further clinical trials with Drug X are planned at the current time.

10. Where can I find more information about this study?

- Provide links to helpful websites with further information such as industry based websites as well as university websites and others.
- Care should be taken to avoid readers being unnecessarily exposed to any promotional language either on the linked pages or pages that readers might be exposed to in the process of accessing the relevant pages.
- Provide links to other generic sites of related interest such as other clinical trial registries, European Clinical Trials Register (EU CTR), the Cochrane Library etc.

Suggested wording might be:

To learn more about this study, you can find more detailed information on this website (EU database) – [include link to technical summary].

More information may also be available by going to

[list relevant websites that may have further information about this trial etc if appropriate.]

You can also find more details about this trial at:

[List all applicable citations and websites that are not listed in clinicaltrials.gov or EudraCT. This can include resources as well as articles.]

For general information about clinical trials, go to: [Below are some suggested sites. List appropriate sites whilst taking care not to overwhelm readers with links]

<http://www.testingtreatments.org>

<https://www.clinicaltrials.gov/ct2/about-studies/learn>

<http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm>

http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000489.jsp&mid=WC0b01ac058060676f

<http://www.nhs.uk/conditions/clinical-trials/pages/introduction.aspx>

http://www.ukcrc.org/wp-content/uploads/2014/03/iCT_Booklet.pdf

Annex 2 – Neutral language guidance in describing results

Sponsors, as well as individuals and groups, who intend to communicate summary results to trial participants and the public are sometimes concerned that the language used might be considered unduly positive, promotional, or serve a marketing purpose.

Below we offer terms to avoid and terms to consider that reflect objective, neutral descriptions of trial results. The first column in the table below lists possible statements that might be considered promotional. The second column with blue text suggests neutral language that provides neutral and objective information.

Examples of Promotional Language	Neutral Language – Consider this
This trial proved...	This trial found that... This does not mean that everyone in that group had these results.
This trial proved that using <drug A> to prevent <disease/condition> is effective.	This trial found that people with <disease/condition> who received or were treated with <drug A> had <primary endpoint>.
The combination treatment of <drug A and B> may also help <a different disease/condition than what was/was not studied elsewhere> as observed in new small studies.	When <drug A and B> are used together, people in this trial had <study endpoint>. The drugs may be helpful in other diseases/conditions, but this was not studied here. Further studies in <disease/condition> will be needed.
This means that <drug A> is better than <drug B>.	In this study, people who took <drug A> had more <study endpoint> than some people who took <drug B>.
<drug A> works better than <drug B>, but some people didn't tolerate it as well.	In this study, more people who took <drug A> had <trial endpoint> than those who took <drug B>. But they also had more side effects that may have interfered with their daily lives, <list specific adverse reactions>.

Examples of Promotional Language	Neutral Language – Consider this
<drug A> is better tolerated than <drug B>.	In this study, fewer patients who took <drug A> had <list specific adverse reactions> than patients who took <drug B>.
People taking <drug A> lived longer after they had <therapy> for <disease/condition>, even with more adverse reactions.	People who took <drug A> lived longer than those that took <drug B>. The patients who took <drug A> also had more side effects.
While the combined treatment of <drug A and B> did not extend life over <drug A> alone, people felt better and lived longer with the combined treatment.	People in both groups had the same kind of results (outcomes). People who took the combined treatment <drug A and B> had milder side effects <list specific adverse reactions> but did not live longer.
Trial groups had the same results. More studies are provided after acceptance for publication in a peer reviewed journal.	There was no effect in the treatment groups/there was no difference between the groups.
People in group <1> were able to tolerate the highest dose of <drug A> so more studies will be done.	People in group 1 were able to take the highest dose of drug A without side effects so more studies will be carried out with drug A.

Taken from MRCT Return of Results Toolkit, Version 2.2, July 2016 – Multi-Regional Clinical Trials Center of Brigham and Women’s Hospital and Harvard

Annex 3 - Examples of readability tests by country

Dutch

The Leesindex was developed by Brouwer in 1963 and is a modified version of the Flesch Reading Ease Score (see below).

English

Using Microsoft Word, writers can test the readability of writing in English by using the Flesch Reading Ease Test or the Flesch-Kincaid Grade Level Test based on counting syllables and sentence length. This can be helpful in multi-country studies where summaries are first drafted in English and then translated into other languages. The Flesch Reading Ease Test assesses readability on a scale from 1 to 100. The higher the Flesch Reading Ease test score, the easier the text is to read. Anything that scores 70 and above is easy to read.

The Flesch-Kincaid Grade Level Test uses an algorithm that includes both the number of syllables per word, as well as average sentence length and transforms the test score into a school grade equivalent based on the U.S. school grading system. An ideal reading grade level is 6th grade, which is close to the literacy level of the general population. Even if the writer cannot achieve this, strive to get as close to this as possible.

French

Kandel & Moles Modified Flesch Reading Ease has been adapted for French Texts. The Kandel & Moles scale ranges from 0 to 100 and scores of 60 to 100 indicate text, which is normal or easy to read. Text that scores below 60 is regarded as difficult to read.

German

There are a wide range of readability tools available for the German language. The Flesch Reading Ease Index has been adapted for the German language. This was done by keeping the original scale and newly calculating the word factor, taking into account the greater length of German words. (REF: Amstad T. Wie verstaendlich sind unsere Zeitungen, Universitaet Zuerich. Dissertation 1978). Text that scores 80 and above is defined as easy to read.

A more recent and frequently used tool is the Hohenheim Comprehensibility Index which operates on a scale from 0 (totally incomprehensible) to 20 (very comprehensible). The Index is generated with the support of a computer program for automatic text analysis (TextLab). The analysis takes into account the length of sentences and words, use of nested sentence, proportion of abstract terms. An easy to read text should have a score of 17 and up.

Italian

The GULPEASE formula is the first readability formula directly adjusted on the Italian language and considers two linguistic variables: the length of the word (in letters and no longer in syllables) and the length of the sentence compared to the number of letters (see Lucisano-Piemontese, 1988, and Lucisano, 1992).

The formula is the following:

$$89 + \frac{300 * (n^{\circ} \text{ of sentences}) - 10 * (n^{\circ} \text{ of letters})}{\text{number of words}}$$

The GULPEASE index (Lucisano and Piemontese, 1988) is seen as a suitable alternative tool for assessing readability of the Italian language. The GULPEASE index takes into account the length of a word in characters rather than in syllables, which proved to be more reliable for assessing the readability of Italian texts. The index ranges from 0 (lowest readability) to 100 (maximum readability).

Spanish

The Huerta Reading Ease, developed by Fernandez-Huerta, is a Modified Flesch Reading Ease for Spanish text. In this test, scores range from 0 to a 100 – a 100 represents the greatest ease of reading. A text with a result of <30 is considered very difficult, whereas a score of 70 is considered appropriate for adults.

In 2008 Barrio-Cantalejo et al proposed the use of the new Inflesz scale, which is a modification of both these scales for a more appropriate assessment of texts in Spanish. On this scale, a score of 55 marks the cut-off between a text that is accessible or not to an average person. “Normal” is defined as a score of between 55 and 65, “very difficult”, between 0 and 40, and “somewhat difficult”, between 40 and 55. Among the higher scores, “quite easy” is indicated by a score of 65 to 80 and “very easy” by a score above 80.

Swedish

LIX (The Lasbarhets index Swedish Readability Formula) is a readability measure to calculate the difficulty of reading a foreign text. The Lix Formula was developed by Swedish scholar Carl-Hugo Björnsson in 1968 and revised in 1983. As with other readability tools, LIX is based on a combination of word and sentence length. However LIX assesses word length by estimating the percentage of words with more than six letters. Scores below 40 are regarded as easy and scores of 50 and above indicate text that is difficult to read.