Consultation document

Summary 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

This document does not necessarily reflect the views of the European Commission and should not be interpreted as a commitment by the Commission to any official initiative in this area

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1. Introduction

The EU Clinical Trials Regulation 536/2014 (Article 37) requires sponsors to provide summary results of clinical trials in a format understandable to laypersons. These lay person summaries will be made available in the EU Portal and Database.

Annex V of the Regulation sets out the ten elements that must be addressed in the lay summaries. This document includes recommendations and templates to help authors when writing the lay summary. Consistency in the way that trial results are presented will help to improve familiarity and comprehension for participants, patients and others.

2. Scope

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

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.

4. General Principles

- Develop the summary for a general public audience and do not assume any prior knowledge of the trial
- 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.
- 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 6 ‘Health Literacy Principles and Writing Style’).
- Consider involving patients, patient representatives, or advocates in the development and review of the summary information to ensure that it truly meets their needs. This won’t be feasible for some studies but where it is a possibility, it may enhance the final version. Medical writers with experience of writing in plain language for the public may also be helpful.

5. Health Literacy[1] Principles and Writing Style

Research across Europe suggests that text for the public 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, analyze and discuss the information. At level 5 the individual demonstrates sophisticated skills in handling information **).**

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 -3 . 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 e.g. 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 which corresponds to a question. This level corresponds roughly with high 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"
- Use the following elements to help improve comprehension:
    - Headlines and descriptive subheadings to organise information
    - Presentation of the "big picture" before the details (inverted pyramid writing style)
    - Bullet points instead of paragraphs

[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

- Numeracy principles to describe data and statistics (see section 8 below)
- Adequate "white space" (for example, separate topics by one or two lines, a minimum of 12-point font)
- Links to additional information, and resources for online summaries and background information. Such links need to be minimal since hyperlinks may become out of date over time.
- Limited use of unnecessary imagery (icons, logos, etc.)
- Avoidance of text in ALL CAPS and underlining
- Limited use of acronyms, abstract, medical/technical, or multisyllabic words (e.g. "unanticipated", "hematopoietic"). If such words must be used, add clear language to define them
- Use visuals (e.g. simple graphs) to convey critical concepts.
- Avoid overwhelming the reader with too much information.

6. Readability and use of plain language

Sponsors should default to a minimum of size 12 sans serif font in the lay summary section. However, an appropriate larger font is recommended where the clinical trial relates to visual impairment or involves older people.

Sentences should be kept short and succinct. Keep the summary factual to avoid any promotional language (See neutral language guidance in Annex 2).

It is essential that the lay summary is drafted in a way that requires only a low level of literacy. Research across Europe suggests that text aimed at the public should be aimed at a literacy proficiency levels of 2 -3, based on the OECD Skills Outlook publication which reports on the first round of the Survey of Adult Skills, a product of the Programme for the International Assessment of Adult Competencies (PIAAC). Across countries in the survey, 38.2 % of adults aged 16 to 65 years score at Level 3, on average. In most countries, more adults perform at this level than at any other level. Although exceptions to this are France, Ireland, Italy, Poland and Spain, where a larger proportions of adults score at Level 2.

Sponsors are advised to use a language specific reading test to assess the literacy level of each lay summary that they produce. The readability of texts can be formally determined using different metrics. While approaches were initially only developed for the English language, tools are now also available for other languages. The following sections highlight the approaches available for the most commonly spoken languages in Europe .

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 6^{th} 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 scale ranges from 0 to 100 and scores of 60 to 100 indicate text which is normal or easy to read. Text which scores below 60 is regarded as difficult to read.

German

There are a wide range of readability tools available for the German language. The Flesh 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 most wide-spread formula in the world is the Flesch (Flesch Reading Ease Test) formula, a method designed for English. This has now been adapted to the Italian language by reshaping the parameters [206 – (0.65*S) – W, where S = syllables on a 100 words sample and W = average of words per sentence] (see Franchina-Vacca, 1972); it can also be used within Microsft Word. The new formula, however, still has the limitation of not being able to describe and reproduce the exact spelling of single words in a text, as it was designed for English and calibrated for the structure of that language.

Subsequently, in 1988 a group of linguists of the University of Rome 'La Sapienza' have defined a new formula, starting directly from the Italian language. The scale correlates the values returned by the formula with the reader's schooling degree and the values obtained are included, as for the Flesch index, in a scale ranging from 0 to 100. 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:

$$89 + \frac{300 * (n° \; of \; sentences) - \; 10 * (n° \; of \; letters)}{number \; of \; words}$$

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 which is difficult to read.

Other considerations

Readability scores are useful but not in themselves enough to ensure that a text is easy to understand. Where feasible, sponsors should consider testing the readability of an initial version of the study results 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 it could be members of the public. For example, studies which affect the general public such as vaccine studies would benefit from input from members of the public rather than patients. Their feedback and suggestions can be crucial in developing a summary that lay people will understand.

7. Numeracy

Study results summaries are likely to include a variety of numerical data that should be easily understandable by the target audience. Further detail on how to apply principles of numeracy can be found in Appendix 4 of the MRCT Return of Results Guidance Document, Version 1.0, March 19 2015 – Multi-Regional Clinical Trials Center at Harvard.

8. Visuals

Well-chosen and clearly designed visual aids can help enhance understanding of text. Patient friendly summaries of clinical trial results which combine clear infographics with explanatory text can be a good way of presenting complex information.

Where used, visuals should present one message per image and be clearly labelled with captions. Visuals should be placed near the text that they attempt to illustrate. Overly complex images, such as graphs showing several relationships, can be easily misinterpreted and should be avoided.

Graphs using misleading axes 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 videos, cartoons and animation.

For examples of clearly laid out visuals which aid understanding see the Drug Trial Snapshots created by the Food & Drug Administration (FDA) in the USA.

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. A pdf version in each language used will need to be uploaded separately. Where resources allow, sponsors should consider including an English version if the trial did not include the UK, as the use of a common language will allow greater accessibility across the EU, however this is not mandatory.

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. Whilst study participants may find the lay summary useful, sponsors should consider providing some direct feedback to patients who have taken part in their trials including an acknowledgement of their contribution and an expression of thanks for their time.

11. Acknowledgements

The Health Research Authority (HRA) (www.hra.nhs.uk), which was established in England to promote and protect the interests of patients and the public in health research, has led on the development of these recommendations, on behalf of the expert group on clinical trials, through an EU-wide taskforce comprised of representatives from industry, patient organisations and academia.

This document builds extensively on the MRCT Return of Results Guidance Document, Version 1.0, March 2015 – Multi-Regional Clinical Trials Center at Harvard, MRCT Return of Results Toolkit, Version 2, October 2 2015 – Multi-Regional Clinical Trials Center of Harvard and Brigham and Women's Hospital and also the paper "Transferring regulation into

practice: The challenges of the new layperson summary of clinical trial results" by Kamila Sroka-Saidi, Barbara Boggetti and Thomas M. Schindler. We would also like to thank Megan Rooney of Health Literacy Missouri for "Missouri Best Practices for Numeracy".

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For more information:

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- http://www.plainenglish.co.uk/free-guides.html
- www.plainlanguage.gov
- http://www.invo.org.uk/resource-centre/plain-english-summaries/

- www.nap.edu/catalog/10883.html
- 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

Annex V of the EU Clinical Trials Regulation contains 10 elements that should be included in the summary of the results of the clinical trial for laypersons. This document provides detailed recommendations on the information that should be provided for each of these elements.

It should be noted that the wording of the ten elements cannot be changed but that sponsors 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 as required.

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 which they think might be of use. Suggested text is provided in **blue**.

1. Clinical trial identification
• **This section should refer to the phase of the study (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 study 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 decide which drugs work best and are safest for patients. It takes participants 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 Title of the trial • **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.** • **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

- **Other identifiers refer to WHO ICTRP number, US NCT number, ISRCTN number if available, etc.**

2. Name and contact of sponsor

- **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 the trial was conducted

- **The countries in which the study took place**

For example:

This study took place in the following countries:

- **France**
- **Belgium**
- **Germany**
- **USA, Canada, China, Japan, Brazil, South Africa.**

3.2 When the trial was conducted

- **The overall study start and end dates. For example:**

  This trial started in December 2006 and ended in March 2010.

- **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.**

3.3 The main objectives of the trial and an explanation of the reasons for conducting it. This section should specify:

- **The purpose of the trial (e.g. finding a safe dose, comparing treatments, etc.) / why the study 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 Phase 1 trials:

In this study, researchers looked at how this drug works in the body. The researchers are able to get information on the effect that the drug has including side effects. This study did not test if the drug helps to improve health. [Patients/healthy volunteers] took part in this study.

Suggested wording for Phase 2 trials:

In this study, researchers were trying to find out if this new treatment could help patients with a particular condition.

Suggested wording for Phase 3 trials:

In this study, researchers compared the new treatment to the standard treatment used for [disease/condition] or placebo.

Suggested wording for Phase 4 trials:

This study was carried out after the new treatment had been approved for use. Researchers looked at the effect of new treatments in a larger number of people.

4. Population of subjects

4.1 the number of subjects included in the trial:

- **in each of the Member States concerned,**
- **in the EU and**
- **in countries outside the EU**

This study included [specific population to whom this study applies, including healthy volunteers and patients as appropriate]
The study was run in following [list country(ies) that enrolled patients]. In each country [name the country] [#] individuals were enrolled in this study. If there are a lot of

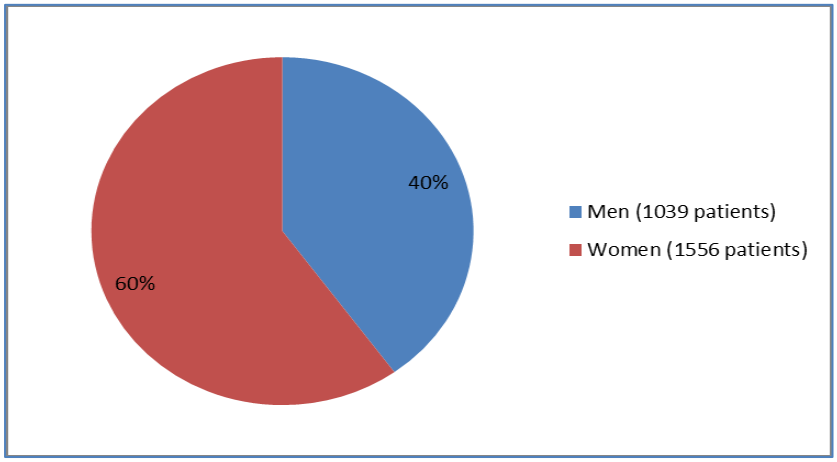
countries involved, it may be easier to present this data in a table.

4.2 Age group and gender breakdown

- **Provide basic breakdown of participants by age and gender in the EU (and non-EU if the studies includes countries outside of the EU)**
- **Consider including a simple graphic that helps people/patients understand the study. The Drug Trial Snapshots produced by the FDA provide a useful model.**

For example:
The figure below summarizes how many men and women were in the clinical trials

Figure 1. Baseline Demographics by Sex



Source: Company Trial Data

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 the criteria that have the most impact on the population to be studied, perhaps by highlighting them in bold.**
- **If possible, sponsors should include references to age, gender, diagnosis, indication, disease stage or severity as this will help define the scope of the study (for example, 'stage IV chronic obstructive lung disease')**
- **Sponsors should also avoid using technical terms which 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. Investigational medicinal products used

- **This should include both the interventional drug and any comparator products, and should refer to generic (international non- proprietary name (INN)) and all brand/trade names used in the countries where the trial took place. Subsequent references in other sections of the summary should use the generic name only to avoid long lists of names.**
- **For early phase trials it might not be possible to refer to a specific name and will instead need to use the internal compound code.**
- **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. Similarly if a study was blinded this should be simply explained.**
- **Randomisation and blinding arrangements should be described. For example:**

"People with diabetes were put into 3 groups by chance (randomised) to reduce differences between the groups.
[If the study was double blinded, also add the following wording] This study 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 study results were not influenced in any way.
[If the study was single blinded, use the following words]This study was single blinded, this means the patient did not know who was given which treatment/drug but the doctor did know. A single blinded trial may mean that the results may be biased by knowing who received each treatment.
[If not randomised, list how many patients/people were in each group, and how this was determined.]

6. Description of adverse reactions and their frequency

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.

- **Sponsors should follow guidance used for listing adverse reactions in patient information leaflets included in the European Commission's Readability guideline (http://ec.europa.eu/health/files/eudralex/vol-2/c/2009_01_12_readability_guideline_final_en.pdf) on how to comply with the legal requirement of article 59(3) of Directive 2001/83 and render a package leaflet that it**

is legible, clear and easy to use.

- **Providing very long lists of adverse reactions in technical language is not helpful. Consider using a simple term, such as "side effects related to the treatment" to refer to adverse reactions. There is still a requirement to refer to 'adverse reactions' so it might be helpful to state:**
  'adverse reactions also known as side effects related to the treatment'.
- **The side effects should be laid out as they would be in a regular Patient Information Leaflet. The most serious adverse reactions need to be listed first, followed by all other side effects listed by frequency (starting with the most frequent) and not repeating the most serious side effects listed above.**
- **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 and deaths should be clearly stated together with any adverse events which have led to the early closure of the trial or the withdrawal of patients. The classification of serious adverse reactions should be explained (e.g. "reactions that are life threatening or require the individual to have to go hospital"). Where deaths and adverse reactions may be attributable to the treatment rather than the condition, this needs to be made clear.**
- **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 (e.g. headache) that happen during the study, and are reported because they are thought to be related to the treatments in the study. Not all the people [people/patients] in this study had side effects.

Common and serious side effects are listed here.

[List the most serious and/or most prevalent adverse reactions for each study drug(s) tested. If possible, compare the number of people who had each event by dose level.]

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

Side effects [in Group A] included:
[List the most serious and/or most prevalent 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. Overall results of the clinical trials

This section should describe each of the study 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:

- **Information on whether the study completed as planned, or was stopped and for what reason.**
- **The primary endpoint(s) and results by study arm**
- **Patient relevant secondary endpoints and results by study arm**
- **Key patient reported outcome measures (PROMS) or other quality of life indicators of interest to patients (Any scales used for measurement should be explained).**

Dealing with multiple endpoints:

- **If there are only a small number of end points (both primary and secondary), they should all be reported.**
- **Sponsors should include patient relevant secondary endpoints as some of the quality of life measures and PROMs are likely to be of interest to patients.**
- **In some cases it might be possible to summarise closely-related endpoints jointly.**
- **Sponsors may wish to point out that a complete list of outcomes based on all endpoints is available in the technical results summary for each clinical trial is available on the website.**

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

- **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.**

- **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 which 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 (e.g. death, getting sick again (relapse), serious event) and test results into one measure of how well the 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**.	**"The XXX study measured *[patients/people]* 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 events were measured together (combined) because each one is quite rare. Researchers also wanted to see if the drug worked in patients who had all 3 conditions.** **The study found that there was no change in the number of events 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 study 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) or dose limiting toxicity (DLT).	**"This study was carried out to find the highest [dose/amount] of treatment that people could take without having too many side effects."**
Mortality / Overall Survival	The goal of this trial was to see if Treatment ABC or Treatment XYZ helped	**"This trial compared patients in Group A (Treatment ABC) to those in Group B (Treatment XYZ) to see who lived**

	patients with *[disease/condition]* to live longer.	**longer.** **If there was no effect –** **"Patients in both groups lived about the same amount of time, no matter what treatment they got."** **If there was an effect –** **"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.** **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 a new disease begins.	**"People with diabetes were put into 2 groups by chance (randomised) to reduce differences between the groups. This was done because no one knew if one treatment was better than another.** **Group A received drug X, Group B followed a diet and exercise program, All people were followed to test the health of their heart and blood system, including stroke, high blood pressure and heart disease.** **EFFECT – Both groups had similar health conditions and outcomes. There was no difference in the health of their heart for patients in Group A (drug X) compared to patients in Group B (diet and exercise)."**
Non-Inferiority	Non-inferiority endpoints are designed to show that a new treatment or drug is not worse than the control (or	**[Need to include some specific comparisons between the arms before stating the following sentence.]**

	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 (e.g., fewer side effects).	**"Non-inferiority studies are conducted when it is not possible to compare the new treatment with a placebo. This study showed that insulin A (Group A) was not different or at least not worse than standard insulin therapy (Group B) in lowering the level of red blood cells in Type 1 diabetic patients. Patients in Group B had fewer side effects of upset stomach and feeling sick (nausea) than those in Group B."**
Patient-Reported Outcomes	This study asked patients about their [list the main purpose of the questionnaire: e.g., symptoms, activity level, quality of life, income and/or happiness] and if the measurement changed based on whether a patient got A or B. The primary endpoint is less XXX based on the YYY scale. This scale measures ZZZ and how this changes over time.	**"Patients answered questions to measure pain, stiffness, and how well they could climb stairs, stand or bend over. Questions were asked during each study visit.** **About 1 in 2 people (50%) in Group A had less knee pain.** **About 1 in 4 people (25%) in Group B had less knee pain.** **This means that patients in Group A (tanezumab) had less knee pain than patients in Group B (x treatment/placebo)."**
Prevention/ Incidence	The incidence endpoint tells how many new cases of XXX occurred over a given period of time.	**"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 study was carried out using two different groups because no one knew if one treatment was better than another.** **1 in 20 women (5%) in Group A (bisphosphonates) had a break in their back bone (vertebrae).** **2 in 20 women (10%) in Group B (X Treatment) had a break in their back bone (vertebrae).** **This means that patients in Group A had fewer breaks in their back bone."**

Progression-Free Survival (PFS)	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.	**"Patients in this study were assigned to 2 groups by chance (randomised). This was done because no one knew if one treatment was better than another.** **The goal of the study was to measure the size of each breast cancer tumour to see if it shrunk, stayed the same, or grew in a 1 year period.** **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.** **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.** **This means that more patients in Group B had tumours that shrunk."**
Surrogate	Surrogate markers may be used instead of a clear endpoint (e.g. 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.	**"The main goal of this study was to see if drug A lowered pressure in the eye (called intra-ocular pressure).** **Higher eye pressure could mean that vision may be lost faster than with lower eye pressure.** **This study found that people in Group A (drug A) had lower eye pressure at the end of the study than at the beginning.** **People in Group B (placebo) had no change in their eye pressure over the course of the study.** **Eye pressure may be linked to how much vision is lost due to glaucoma *[define the disease]*. This is not yet known."**

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 2.0, October 2015 – Multi-Regional Clinical Trials Center of Harvard and Brigham and Women's Hospital

8. Comments on the outcome of the clinical trial

- **Write a general high level statement summarising the overall results and their implications without using promotional language (See neutral language guidance in Annex 2).**
- **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).**

[If appropriate, include a general comment on what this study contributed to the relevant area of research and potential next steps to build on that knowledge.]

[Include the state of result analyses (including dates of intermediate analysis date, interim/final analysis stage, global end of trial date – describe as appropriate)].

Findings from this study will be used [add general next steps to this sentence to help explain context. Suggestions include:]

- **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 combine with other treatments in [patients with condition/disease]**
- **to seek approval for using the treatment for [patients with condition/disease].**

Describe if there were any significant differences between sub-groups; in particular by age, gender and ethnicity where the sample size is sufficient to show statistical differences. The Drug Trials Snapshots produced by the FDA provide a useful model for this, for example:

Were there any differences in how well the drug worked in clinical trials?

- **Sex: Treatment A worked similarly in men and women.**
- **Ethnic group: Treatment A worked similarly in all groups.**
- **Age: Treatment A worked similarly in patients younger than 65 years and patients 65 years and older.**

Were there any differences in side effects?

- **Sex: Treatment A had a similar side effect profile in men and women.**
- **Ethnic groups: The number of patients from ethnic minority groups was limited. This means that it was not possible to make any conclusions regarding differences in side effects among ethnic groups.**
- **Age: All patients who took Treatment A had a similar side effects no matter how old they were.**

9. Indication if follow up clinical trials are foreseen

- **This section should explain whether other trials are ongoing already or if any further, related clinical trials are likely to be undertaken, and if so, what the foreseeable timelines might be.**

10. Indication where additional information could be found

- **Links can be made to a range of helpful websites with further information; such as industry based websites as well as university websites and others.**
- **Care should be taken to ensure that the readers are not 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.**
- **Links can be provided to other generic sites of related interest such as other clinical trial registries, European Medicines Agency (EMA), the Cochrane Library etc.**

Suggested wording might be:

To learn more about this study, you can find more detailed information about this study on this website.

More information may also be available by looking up the official number or title, or 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 study 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 [list appropriate sites, e.g.]

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 study 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 study results. The first column in the table below lists possible statements that might be considered promotional. The second column offers suggestions of neutral language that provides neutral and objective information.

Promotional Language - DO NOT USE!	**Neutral Language - USE THIS**
This study proved…	**This study found that... This does not mean that everyone in that group had these results.**
This study proved that using <drug A> to prevent <disease/condition> is effective.	**This study 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 study 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 <study endpoint> than those who took <drug B>. But they also had more side effects that interfered with their daily lives, e.g. <list specific adverse events>.**
<drug A> is better tolerated than <drug B>.	**In this study, fewer patients who took <drug A> had <list specific adverse events> than patients who took <drug B>.**
People taking <drug A> lived longer after they had <therapy> for <disease/condition>, even with more side effects.	**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 e.g. <list specific adverse events> and so felt better but did not live longer.**

Promotional Language - DO NOT USE!	**Neutral Language - USE THIS**
Study 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. All groups still had pain and numbness in their fingers or toes (called neuropathy).**
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 2.0, October 2015 – Multi-Regional Clinical Trials Center of Harvard and Brigham and Women's Hospital