August 30, 2016

To: Health Research Authority

From: The Center for Information and Study on Clinical Research Participation (CISCRP) and Synchrogenix Information Strategies, Inc. (Synchrogenix)

Re: Implementation of Regulation (Eu) No 536/2014; Comments on the "Summary Of Clinical Trial Results For Laypersons" Submitted For Public Consultation

CISCRP and Synchrogenix appreciate the opportunity to provide the Health Research Authority with comments on the Summary of Clinical Trial Results for Laypersons consultation document. This issue plays a significant role in honoring participants' contributions to medical research and in the responsible sharing and disclosure of plain language trial results that educate, inform, and empower clinical trial participants and the public.

We have identified several areas for further consideration and clarification:

- **Evaluation of readability:** within the guidance, the emphasis is placed on the assessment of readability through the use of metrics. However, there are dangers in using these formulas as the primary basis for anticipating document literacy levels. Readability formulas account for only a small portion of influences in reader understanding. Many other factors contribute to comprehension that readability formulas do not address, such as conceptual difficulty, graphical and other visual elements, organization of information, stress, illness, concern for afflicted loved ones, and familiarity not only with content but with the type of document provided. Greater emphasis should be placed on the critical role of patients, advocates, and representatives of the target population in reviewing lay summaries to ensure content is understandable and non-promotional.

- **Translations:** the consultation document does not specify whether a summary initially drafted in English, in line with the guidance, would need to further undergo readability verification when translated into other languages. The translators are obligated to maintain tone, level of literacy, and the meaning/representations expressed within the original summary document. A discussion of expectations for translation that incorporates quality and in-country review by native language speakers would alleviate additional administrative burdens for duplicative, multi-country language testing.

- **Numeracy:** the consultation document suggests the use of Appendix 4 of the Multi-Regional Clinical Trials Center at Harvard (MRCT) Return of Results Guidance Document, Version 1.0, March 19, 2015 for further details on how to apply principles of numeracy. We are concerned that the use of this guidance without further clarification may lead to information being presented in a promotional manner. Approaches to presenting entirely non-promotional numerical information specific to the context of layperson trial result summaries should also give special consideration to utilizing the expertise of medical, regulatory, and plain language writers and editors, in

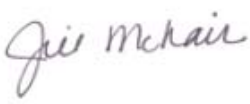
collaboration with statistical and medical experts, to determine the most appropriate use of these plain language strategies for sharing trial results data, on a case-by-case basis.

Granular feedback on particular language and a discussion of other issues are provided in the detailed comments section starting on page 3 of this letter.

We are grateful for the opportunity to contribute our comments in response to the European Commission's Public Consultation on The Summary of Clinical Trial Results for Laypersons consultation document. We appreciate the challenge the European Commission faces in collecting perspectives from the broader clinical trials community to identify responsible, transparent data sharing solutions that support the needs of the public and honors clinical research participants.

Please feel free to contact us for additional comments or if we may otherwise serve as a resource.

Sincerely,

Ken Getz, MBA	Jill McNair, MBA	Tatyana Wanderer, PhD	Lora Killian, MBA
Founder & Board Chair	Senior Director, Patient Engagement	Director, Strategic Partnership Alliances	Director of Transparency and Disclosure
CISCRP	CISCRP	synchrogenix A CERTARA COMPANY	synchrogenix A CERTARA COMPANY

CISCRP: 56 Commercial Wharf East, Boston, MA 02110; 617-725-2750; www.ciscrp.org

Synchrogenix: 2 Righter Parkway, Suite 205, Wilmington, DE 19803; 302-892-4800; www.*synchro*genix.com

DETAILED COMMENTS

Summary of Clinical Trial Results for Laypersons

Section 4 "General Principles", page 3, text lines 71-72:

Develop the summary for a general public audience and do not assume any prior knowledge of the trial

General Health literacy principles require tailoring language to the audience, giving essential and omitting extraneous information. Providing basic study information in accordance with the ten elements addressed by Annex V of the EU Clinical Trials Regulation 536/2014 (Article 37), including sufficient contact information and hyperlinks to make more detailed information accessible to both participants and more interested members of the public, satisfies effective literacy principles, while providing all audiences access to more detailed information that they may wish to learn about the trial. As long as the information is factual and non-promotional in nature, the ability to provide references for additional facts about the trial will assist sponsors in effectively sharing information, while keeping the document as short as possible, in accordance with recommendations for style.

Section 5 "Health Literacy Principles and Writing Style", page 4, text lines 88-94; 97-103 and Section 6 "Readability and use of plain language", page 5, text lines 148-155; 164-175:

The Adult International Literacy Survey (IALS) Levels (specifically Level 2-3) referenced in the consultation document to determine adult literacy and the recommended readability tools (e.g. the Flesch-English test) are difficult to apply in all geographic areas.

The guidance suggests that "text for the public should be aimed at a literacy proficiency level of 2-3" per International Adult Literacy Survey (IALS) and "research across Europe" [lines 88-89].

IALS Level of 2 is described [lines 98-100], but a corresponding grade level is not provided. IALS Level of 3 is described [lines 100-102], and a corresponding grade level is provided: "roughly with high school completion levels" [lines 102-103]. However, it is suggested that, for English language texts, a Flesch Reading Ease Score of "70 and above is easy to read" [line 170], and "An ideal reading grade level is 6th grade which is close to the literacy level of the general population" [lines 173-174].

Literacy at high school completion levels is enormously variable. It is difficult to quantify what "high school completion" means for literacy in areas like the United States (where there are programs like the Brearley School vs. college preparatory public high schools vs. rural public schools). Across the EU, and elsewhere, literacy at high schools is highly variable. As such, the use of the IALS Level 3 grade level, corresponding to a "high school completion" literacy level is unlikely to be a useful metric. The majority of readability experts advise against writing plain language documents at a Grade 12 of high school graduate reading level.

We have been addressing parameters required by Annex V in the lay language trial summaries produced, according to rigorous practices of health literacy and cultural competency. We feel that it is very possible to produce template summaries in English at a 6th grade level, which seems highly feasible for most

clinical trials. However, within the guidance, the emphasis is placed on the assessment of readability through the use of metrics. Kathy Everts Danielson's 1987 article on readability verification methods clearly illustrates that there are dangers to using these formulas as the exclusive basis for anticipating document literacy levels. Readability formulas account for only a small portion of influences in reader understanding. Many other factors contribute to comprehension that readability formulas do not address, such as conceptual difficulty, organization of information, reader stress, illness, or concern for afflicted loved ones, and familiarity not only with content but with the type of document provided. Additionally, non-text elements in a layperson summary, including tables, graphs, or charts, are unaccounted for in readability assessments but can significantly increase the cognitive demand placed on readers. In our experience, engagement of a panel consisting of plain language and patient communication experts as well as representative patients, patient advocates, and specialists during the drafting process is absolutely critical to ensuring that the summary has an appropriate level of readability and non-promotional messaging.

The consultation document suggests "Sponsors are advised to use a language specific reading test to assess the literacy level of each lay summary that they produce" [lines 156-157]. Additionally, with regard to drafting in English, the consultation document also suggests that testing the readability of writing in English by using the Flesch readability tests, then translating into other languages can be beneficial: "This can be helpful in multi-country studies where summaries are first drafted in English and then translated into other languages" [lines 167-168].

The application of language-specific readability testing seems highly variable from region to region, therapeutic area to therapeutic area, and from institution to institution. The consultation document does not specify that a template produced in English, written according to the parameters required by Annex V and completed according to a 6th grade readability level (as verified by the appropriate test for the country of origin), could be translated for end-country review without the need for additional, duplicative, readability verification methods. This may be an important process clarification, as translation companies have an obligation to maintain tone and level of literacy while also ensuring the representation of the meaning/ideas of the original document (including the level of terminology). A discussion of expectations for translation that incorporates quality and in-country review by native language speakers would alleviate sponsors of additional administrative burdens for duplicative, multi-country language testing.

Section 5 "Health Literacy Principles and Writing Style", page 4, text line 126:

- **Bullet points instead of paragraphs**

The consultation document suggests that bullet points be employed, instead of paragraphs, to improve comprehension. We would prefer that more explicit guidance be given regarding the use of bullet points to promote clarity. Bullet points are generally recommended for unordered lists, also known as groups of similar items. Text describing sequential actions is better in paragraph form, and text describing steps in order should be numbered. Bulleted lists should be 4 to 7 items maximum and should not be overused. In our experience, an 8-page lay summary should have less than 5 bullet points, at most.

Section 7 "Numeracy", page 7, text lines 243-247:

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.

The consultation document refers to Appendix 4 of the Multi-Regional Clinical Trials Center at Harvard (MRCT) Return of Results Guidance Document, Version 1.0, March 19 2015 document for further details on how to apply principles of numeracy. As plain language summaries should remain unbiased and "strictly factual", the CISCRP/Synchrogenix Partnership would like more explicit clarification on numeracy regarding how sponsors should be expected to address the following points from MRCT guidance:

"Do the math

- *Calculate or convert numbers. Readers are unlikely to conduct even basic math. Instead of "Lose 5% of your body weight," do the math for the reader, or show a few examples."*
- *Provide estimates for longer time periods. Cumulative or long-term risks often require readers to extrapolate information from 1 time period to another.*
    - *For example, if a patient knows the annual risk of taking a medicine, but intends to take it for many years, they must understand how the risk might change over a longer period of time. Do the math to help readers understand risk over time."*

Give numbers meaning and context

- *People have trouble extracting meaning from numbers, so always explain what the numbers mean—interpret the meaning of numbers for the reader. This can affect health judgments and choices.*
    - *For example, "This number means your blood pressure could be hurting your heart".*
- *Use evaluative labels and captions (such as "poor, fair, good, and excellent"). Combining these labels with numbers can result in greater use of the information in judgments, and changes in risk perception and behavioral intentions. But use them carefully and consider potential misinterpretations.*
- *Present numbers in context by using comparisons — this gives readers a reference point. Use a framework to compare choices and explain and highlight differences.*
    - *Show numbers as "high" or "low".*
    - *Compare numbers across ages or groups. Use a "harm anchor," which means to show patients where they are on a continuum in relation to a harmful or healthy state.*
    - *Give common equivalents, such as "about the size of your fist" or "about the chance of getting struck by lightning".*

This is an area where we agree that the public will not engage in completing calculations and will have difficulty in extracting meaning; thus, it is helpful for sponsors to complete mathematical conversions and provide a contextual basis to aide understanding. However, it is critical to exercise caution and utilize the collective expertise of health communication and medical professionals to give equitable representation, for example, to negative and positive values, so as not to introduce bias, and to ensure that estimates are not made in such a way that there is the appearance of any promotional interest or influence. The role of a representative panel of patients, patient advocates, and specialists in reviewing layperson summaries to ensure entirely non-promotional content similarly cannot be overemphasized and, in our experiences, is entirely feasible as a standard process step in the development of all lay summary documents.

"Use visuals…

- *Beware of using color to indicate important messages. Some readers may have difficulty assigning meaning to various colors.*
- *Use graphic images or text for emotional appeal when persuasion is acceptable. Affective reactions can influence risk perception and thoughts about behavioral change. Graphic images have been shown to create negative affect and encourage readers to consider behavioral change—especially among less educated and less numerate populations.*
- *Draw attention to important numbers through larger or bolder font, which can impact judgment, increase sensitivity to risk, and change decisions."*

Colors have different connotations for different cultures. Drawing attention to important numbers or visual elements by changing the color or font could influence or impact the judgement or bias the perception of a reader while reviewing study information, potentially changing their decision-making process. The CISCRP/Synchrogenix Partnership's method for creating lay language summaries attempts to avoid influencing the reader in any way possible, including the use of any graphical elements that do not provide clarity and may influence reader sentiment.

Annex 1 – Templates

Introduction, page 13:

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.

We interpret this text to suggest that the specific wording of the level 1 headings of the proposed template cannot be changed under this guidance. However, titles such as "investigational medicinal products used" and "description of adverse reactions and their frequency" are not themselves lay-friendly. In their extensive testing, the CISCRP/Synchrogenix Partnership found that organizing information under headings that mimic frequently asked questions has been easily understood by patients. Please consider more lay-friendly terminology, such as "what was the drug used in the study?" and "how many participants had adverse reactions during the study?"

Section 4.1, page 15:

the number of subjects included in the trial

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

The breakdown of the number of patients by country is not typically included in Clinical Study Reports. Although this information is understandably interesting to the Member States, for rare diseases (where there may only be a few patients with the disease who reside in a given country), this information may enable identification of the specific study participants and violate data privacy regulations.

Section 6 "Description of adverse reactions and their frequency", page 17:

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.

At this time, many sponsors are copying adverse events from the full technical summary in the Clinical Study Report (CSR) into the lay summary, without taking the additional step to parse out adverse reactions (an experience that has an association with use of the test article). When appropriate, consideration should be given to sharing aggregate adverse events from the full technical summary, at least in reference, with an explanation of context for the information, to prevent risk of non-disclosure. In some cases, such as early phase studies with smaller participant populations or in rare disease communities, adverse reaction information can also enable self-identification of specific study participants. It is critical to present safety findings fully and factually and to provide appropriate and clear plain language definitions for adverse reactions and/or adverse events to avoid raising undue concern regarding the potential safety of investigational medicines.

Section 6 "Description of adverse reactions and their frequency", page 18:

- **Include clinical laboratory changes only if they are useful/clinically relevant.**

We suggest a slight modification to this wording. Please consider adding bolded text as follows: "Include clinical laboratory changes only if they are useful/clinically relevant **based on the data gathered in the study**". Sponsors may omit discussion of laboratory changes that do not seem useful or clinically relevant at the time of study data analysis. However, at the stage when aggregate data become available, some laboratory changes may turn out to be important and may be reflected in the label. If the statement is left open-ended, omission of discussion of certain results in the study may be perceived as misleading or promotional once the aggregate information becomes available.

Section 7 "Overall results of the clinical trials", page 19:

- **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.**

Many studies have too small a sample size to evaluate certain endpoints adequately. However, efforts to assess these endpoints are of interest to study volunteers. As such, we recommend disclosing these results but clearly indicating when the results have not been measured robustly. We suggest adding clarification in the guidance that a lay language explanation be included to indicate where the sample size is insufficient to show statistically significant differences between subgroups.

Section 8 "Comments on the outcome of the clinical trial", page 24:

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 punctuation used in this sentence as shown may lead to an important misinterpretation of the guidance. Our interpretation is that the guidance aims to suggest that the discussion of subgroups is only required when it is scientifically appropriate, i.e., if the sample size is sufficient and the study is appropriately powered for statistical analysis of subgroups. Typically, that is not the case. Study-level subgroups are typically small, and any conclusions that may be drawn from the results could be misleading to patients. If we understood the intended meaning correctly, we suggest revising as follows: "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."

Annex 2 – Neutral language guidance in describing results

The CISCRP/Synchrogenix Partnership did not have comments on this section.

About the CISCRP and Synchrogenix Partnership

About CISCRP: The Center for Information and Study on Clinical Research Participation (CISCRP) is an independent, non-profit organization, dedicated to educating the public and patients about clinical research and to engaging study volunteers as partners in the clinical research process. CISCRP has been developing and providing patient-centric, plain language clinical trial results summaries since 2009.

About Synchrogenix: Synchrogenix Information Strategies, Inc. (Synchrogenix), a division of Certara Company, is a 30-year-old global medical, regulatory, and scientific writing company. Synchrogenix's regulatory writing expertise complements CISCRP's lay language expertise. This synergy is complimentary to Synchrogenix's complete and integrated support of all transparency and disclosure activities.

Partnership: Using a well-established, transparent, flexible, and scalable process, the CISCRP/Synchrogenix Partnership has become the leading provider of lay language clinical trial results summaries to patients.

CISCRP: 56 Commercial Wharf East, Boston, MA 02110; 617-725-2750; www.ciscrp.org

Synchrogenix: 2 Righter Parkway, Suite 205, Wilmington, DE 19803; 302-892-4800; www.*synchro*genix.com