

Draft FDA Guidance on Provision of Plain Language Summaries

Issued by: Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, and Center for Devices and Radiological Health

Intended Audience: Sponsors, Investigators and Institutional Review Boards

Disclaimer: *This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA) on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the number listed on the title page of this guidance.*

I. Introduction

This guidance¹ is intended to facilitate the voluntary provision of plain language summaries (PLS)² of aggregate results to research subjects³ and to the general public.

This guidance provides recommendations and points to consider in sharing PLS for sponsors (e.g., industry, non-profit entities, government, academia), investigators, and institutional review boards. This guidance does not address the provision of individual “patient-level” results to individual research subjects or the disclosure of incidental and secondary findings to individual research subjects.

FDA’s guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance’s describe FDA’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidance’s means that something is suggested or recommended, but not required. The use of the word *must* in FDA guidance’s means that this is required under the FDA regulations.

1 FDA notes that the provision of PLS is mandatory in the EU under the EU clinical Trial Regulation No.536/2014 and voluntary in the US. In general, FDA intends this guidance to facilitate the return of PLS in a manner that enables compliance with international regulations.

2 Also known as layperson summaries (EU) or non-technical summaries (FDA)

3 FDA is aware that individuals who participate in clinical research trials generally prefer the term “participants” to “subjects.” However, the term “subjects” is used in FDA regulations and is therefore used here.

II. Background

For nearly two decades, FDA has made efforts to increase transparency of clinical study information. In 1997, the Food and Drug Administration Modernization Act (FDAMA) required the establishment of a data bank of information or registry of federally- and privately-funded clinical trials for drugs for serious or life-threatening diseases and conditions. In addition, the statute stated that the data bank “may also include information pertaining to the results of clinical trials.”⁴ The National Institutes of Health (NIH) through its National Library of Medicine (NLM) launched ClinicalTrials.gov in February 2000 that serves as a repository of clinical trial information and results.

FDAMA only partially addressed the need for transparency of clinical trial information. The US Food and Drug Administration Amendments Act (FDAAA) of 2007 broadened the scope of trials for which information had to be submitted and expanded the types of information required for each trial.⁵ The statute required the “responsible party” (usually the sponsor or designated principal investigator) to register certain clinical trials of drugs, devices, and biological products (referred to in FDAAA as “applicable clinical trials”) and to submit summary results to the government-operated clinical trials data bank, www.ClinicalTrials.gov, within a certain time period.⁶ Moreover, FDAAA included a provision which would require “ a summary of the clinical trial and its results that is written in non-technical, understandable language for patients, if the Secretary determines that such types of summary can be included without being misleading or promotional.”⁷ However, 42 CFR Part 11⁸ did not mandate submission of PLS and thus it remains voluntary.

In addition to the need for transparency to the general public, provision of aggregate research results in plain language is helpful for research subjects to: 1) be informed about the study results, 2) understand that their participation in research is respected and appreciated, and (3) recognize that their contributions to science and public health are valued. Further, PLS may help to inform research subjects and the general public regarding clinical study results, ultimately increasing public trust and awareness of medical research efforts.

Clinical research subjects, patient advocacy groups, FDA, other federal agencies, clinical investigators, industry groups and others have a growing interest in, and support for, sharing study results with the general public and with

4 U.S. Food and Drug Administration Modernization Act of 1997, Title I, Subtitle B, Section 113(a)(3)(B)(i) and (ii).

5 U.S. Food and Drug Administration Amendments Act of 2007, Title VIII, Section 801.

6 U.S. Food and Drug Administration Amendments Act of 2007, Title VIII, Section 801(a).

7 U.S. Food and Drug Administration Amendments Act of 2007, Title VIII, Section 801(a).

Also see FDA’s Draft Guidance, Informed Consent Sheet Information Sheet, available at:

www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM405006.pdf.

8 <https://www.federalregister.gov/documents/2016/09/21/2016-22129/clinical-trials-registration-and-results-information-submission>

research subjects, and an increasing appreciation of the importance of these communications.⁹ FDA believes that clarifying the agency's perspective with regard to the content and distribution methods will help enable the routine preparation of PLS for FDA-regulated studies, while simultaneously supporting a harmonized approach across regulatory jurisdictions.

III. General Considerations of the PLS

A. Content

Care should be taken to communicate effectively in a manner that is understandable to the research subject and to general public (see Section C). Content should remain concise, non-promotional, fair and balanced. Each PLS should be factual, describing the results of a single clinical study and including both the positive and negative findings of the study.

The PLS should contain:¹⁰

- Recognition of the contributions of subjects
- Study title
 - A short study title in plain, non-scientific language
 - The full title (official title) of the study
 - Include US NCT number (and other identifying information as appropriate, for example the protocol number)
- Study purpose
 - Why the study was conducted
- Study information
 - The FDA-regulated product under study and any comparators (the names for each being the name used in the study registration)
 - Start and end dates of the study
 - Countries where the study took place
 - The number of subjects enrolled
 - The type and phase of the study
 - The date the PLS was produced with a statement that the PLS is current as of this date

⁹ For example the Institute of Medicine (now the National Academies of Science, Engineering, and Medicine) report, "Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risks," concluded that there "are compelling justifications for sharing clinical trial data to benefit society and future patients." The committee formulated and considered "four guiding principles for responsible sharing of clinical trial data: 1) Maximize the benefits of clinical trials while minimizing the risks of sharing clinical trial data; 2) Respect individual participants who data are shared; 3) Increase public trust in clinical trials and the sharing of trial data; and, 4) Conduct the sharing of clinical trial data in a fair manner." Available at: <http://www.nap.edu/catalog/18998/sharing-clinical-trial-data-maximizing-benefits-minimizing-risk>

¹⁰ The content of the PLS does not have to follow the exact order of, or terms for, items as they are listed here.

- Study overview
 - A high-level description of the study design, treatment(s) and other pertinent information that may be helpful to understanding the results
 - A picture or diagram as appropriate
- Study population
 - Demographics (e.g., age, gender, and race)
 - Key inclusion/exclusion criteria
- Primary outcome(s)
 - Describe the results for the primary endpoint(s) for each study arm
 - Describe the outcome measures in plain, non-technical language
 - Present the data in simple tables using both absolute numbers and percentages as appropriate
 - Differences that are **not** statistically significant should be indicated
- Safety:
 - Provide the incidence of investigator determined “drug-related adverse events” to indicate a potential causal relationship between FDA regulated products under study and an adverse event
 - The plain language term “side-effects” may be used in this context to indicate “drug related adverse events”
 - Serious “side effects,” including participant deaths, should be listed as well as non-serious “side effects” using a reasonable and disclosed cut-off for those that are common
 - Include a link to the reported scientific results for a listing of additional safety information
 - Additional safety data important to the overall results of the study may be included so long as inclusion is balanced and there is reasonable justification
- Comments on outcome of the study
 - High level statement(s) regarding the study
- Additional information
 - A statement that patients should consult their physicians and/or study doctors with further questions about their individual care and should not make changes in the treatments based on the results of this study
 - A statement that the summary includes the results of a single study and that multiple studies are used together to assess the risks and benefits of an FDA-regulated product
 - Where additional information may be found (include a link the scientific summary posted on www.ClinicalTrials.gov)
 - Whether further research is anticipated, as appropriate and as available in the public domain

- Contact information for and the name of the study sponsor or call center if applicable.

B. Ensuring Appropriate Communication for the PLS Audience

FDA is concerned with the risks to the public from uses of products not shown to be both safe and effective through adequate and well-controlled clinical studies including unapproved, unlicensed products. These concerns are also relevant to new intended uses for previously approved or cleared products.

The selection of studies for which PLS are provided should be fair, transparent, and balanced. In general, the decision to provide a PLS should be made either prospectively and before the results are known or by criteria that do not take study outcome into consideration. If PLS will be prepared for some studies and not for others, the rationale for doing so should be open and accessible. For example, FDA considers it appropriate to provide PLS for all studies that conclude after a certain date, or for all studies of a certain phase, but would consider inappropriate the provision of PLS for studies with “positive” outcomes only.

The overall intent of each PLS is to present clinical study information in a truthful and non-misleading manner, and this intention should guide the selection of text and presentation style. The PLS should not make characterizations or conclusions regarding safety or effectiveness of a product that go beyond the results of that study.

Some general recommendations for sponsors to help ensure that the PLS is truthful and not misleading include:

- Noting that the summary provides results of a single clinical study and that new information or different results may be obtained from other studies;
- Ensuring that the overall tone of the PLS is factual, objective, and accurate;
- Avoiding superlative and enthusiastic words;
- Avoiding statements that describe the product as being better, more effective, or useful in a broader range of conditions or patients than that study has demonstrated;¹¹
- Avoiding statements that describe the product as being safer, having fewer, or less serious side effects or contraindications than that study has demonstrated;¹²
- Avoiding statements that represent the product as being safer or more effective than another product other than demonstrated by that study;¹³

¹¹ See 21 CFR 202.1(e)(6)(i).

¹² See 21 CFR 202.1(e)(6)(1).

¹³ See 21 CFR 202.1(e)(6)(ii).

- Avoiding using statistical statements in a misleading way,¹⁴ and
- Providing a link to the scientific summary for further information.

Examples of language to avoid or consider are provided in the following table.¹⁵

Language to avoid	Language to consider
This study proved...	This study found that... This does not mean 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 got <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 necessary.
This means that <Drug A> is better than <Drug B>.	In this study, people who got <drug A> had more <study endpoint> than some people who got <Drug B> with the same health conditions.
<Drug A> works better than <Drug B>, but some people didn't tolerate it as well.	In this study, more people received or were treated with <study endpoint> with <Drug A>. They also had more side effects that interfered with their daily lives, like <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 adverse events.	People who took <drug> had more time before their <disease/condition> came back and they lived longer. These patients also had more safety events.
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 had fewer serious side effects like <list specific adverse events>.
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 done with drug A.

¹⁴ See 21 CFR 202.1(e)(6)(xv).

¹⁵ From *MRCT Return of Results Guidance Document* <http://mrctcenter.org/wp-content/uploads/2017/03/2017-03-13-MRCT-Return-of-Aggregate-Results-Toolkit-3.0.pdf>.

C. Health Literacy and Numeracy

Information, whether oral or written, in English or translated, that is intended for general audiences should be in language understandable to research subjects and the general public. “Understandable” means that the information presented is in plain language; uses literacy principles,¹⁶ including health literacy¹⁷ and numeracy;¹⁸ and applies cultural sensitivity.

D. Timing of the PLS

As a general matter FDA suggests that provision of a PLS occur within 1 year of study end (which is last subject last visit, unless otherwise defined in the protocol together with appropriate scientific rationale).¹⁹ Public release of the PLS should be aligned with release of the study’s scientific summary to enable cross referencing.

For some studies, sponsors may be interested in communicating results after the primary endpoint has been reached but while the study remains open for the completion of the secondary endpoints. Sponsors should consider whether provision of a PLS while a study is ongoing may introduce bias and compromise the integrity of the research data. PLS should be postponed until study completion if communication of interim results could compromise study integrity.

E. Methods of delivery of PLS

As a general matter, sponsors may choose to use one or more methods of delivery of the PLS. Different situations, including study characteristics and populations, study setting, and indication, can influence the selection of delivery method(s). The consistency of the message content is better maintained in one-way communication methods (mailing of hard copies, email, or posting to a website), but comprehension and follow-up questions may be facilitated by two-way interactive discussion between investigators and subjects. In all settings, participant privacy and confidentiality should be appropriately maintained.

¹⁶ Definitions and resources available on literacy. See also FDA’s Draft Guidance, Informed Consent Information Sheet, available at: <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM405006.pdf>

¹⁷ Definitions and resources on health literacy can be found in Appendix 3 of *MRCT Return of Results Guidance Document*, <http://mrctcenter.org/wp-content/uploads/2017/03/2017-03-20-MRCT-Return-of-Aggregate-Results-Guidance-Documents-3.0.pdf>

¹⁸ Definitions and resources on numeracy can be found in Appendix 4 of *MRCT Return of Results Guidance Document* <http://mrctcenter.org/wp-content/uploads/2017/03/2017-03-13-MRCT-Return-of-Aggregate-Results-Toolkit-3.0.pdf>
<http://mrctcenter.org/wp-content/uploads/2016/07/2016-07-13-MRCT-Return-of-Results-Guidance-Documents-Version-2.1.pdf>

¹⁹ This would harmonize return of PLS with the EU regulations.

Communicating the PLS should occur separately from the delivery of information that is commercial in nature (e.g., if PLS is posted to a sponsor's website, there should be no links from or to web pages that include product commercially-oriented content.)

Examples of potentially acceptable methods of delivering PLS are:

- One-way communication methods to general public: web-enabled communications;²⁰ such as posting of the PLS to a publically available internet site or web-based portal;
- One-way communication methods to subjects: (e.g., video summary, printed materials) that respects the confidentiality of the recipient. For example, if a letter is sent to the research subject, the outside envelope should not mention the topic of the study or describe the contents of the envelope;²¹
- Two-way interactive methods (e.g., face-to-face meeting(s), telephone call(s), online meeting(s), dynamic email exchange), Of note, industry sponsors of clinical trials typically do not have access to personal participant information; in this method of communication, therefore, arrangements with the investigators or healthcare providers may need to be made. FDA realizes that it is difficult to control the content of these communications and recommends that a written PLS be provided as a guide.

F. Role of Sponsors and Investigators

Sponsor and sponsor-investigators who elect to provide a PLS should explain the process to site investigators and any roles and responsibilities investigators are expected to have.

The involvement of the investigator will vary depending on the method and timing of the PLS distribution. For example, the investigator should know how the PLS will be communicated and whether he or she is expected to have a role (e.g., face-to-face meeting) or not (e.g., web-enabled communication) in the actual distribution.

It should be emphasized that the provision of PLS does not absolve the sponsor, investigator or IRB of any of their responsibilities for protecting the rights, safety, and welfare of research subjects, including adequate risk-based monitoring of the clinical study, and providing subjects with information about significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation in the clinical study. Further, PLS

²⁰ Use of a study-specific website for the return of PLS has some advantages including the ease by which: research subjects can elect to review PLS, anonymization of aggregate results can be achieved, communication with research subjects can occur through push notification when the site is updated, and distribution of the website URL can be handled.

²¹ Consideration of participant death or incapacity may limit options for one-way communication.

should not replace or substitute for other communications (e.g., adverse event notification) that would normally take place during the conduct of a study.

G. Institutional review boards

The primary purpose of an IRB is to assure the rights and welfare of research subjects during the clinical study.²² FDA anticipates that the role of the IRB will generally be limited to review of the method of communicating the PLS to research subjects but not the content of the PLS itself given that PLS is not expected to be available until a year or more after the last site has conducted the last patient visit unless otherwise defined and justified in the protocol. Communication of the PLS to the public at large, after a study has concluded, does not require IRB oversight.

The reviewing IRB should consider whether the plan to provide a PLS to subjects will affect the applicable criteria for IRB approval at 21 CFR 56.111, similar to any other component of research. Generally, plans for distribution to research subjects of the PLS would not impact IRB approval nor be a reason for deferral of the study as a whole. IRBs may review the proposed methods to ensure that patient autonomy (e.g., ability to opt-in or opt-out of receiving PLS), privacy, and confidentiality are respected. IRBs may evaluate the potential of unintended harm resulting from the distribution method itself.²³ In addition, if the planned method of distribution to research subjects changes from that which is reviewed and approved by the IRB, the IRB may need to be informed.

In addition to review of the planned method of distribution, the IRB may wish to review and approve any communication that will be provided to research subjects describing the general intent and proposed method of communication of a PLS. For example, a sponsor may develop a written communication that explains the intent to provide, and timing of, a PLS and the uniform resource locator (URL) or the Internet address to which PLS will be posted when available.

In certain circumstances where the provision of interim results and a PLS are being considered during an ongoing study, the IRB should be notified. The IRB may consider whether the communication will impact data integrity or the overall study results. Further, when more than one reviewing IRB is involved in the study, the IRBs should consider whether each IRB is required to review and how alignment among IRBs may be achieved.

According to FDA Guidance, IRB Continuing Review after Clinical Investigation Approval, IRB's continuing review of the research is generally no longer required

²² See 21 CFR 56.102(g).

²³ For instance, in the rare circumstance in which results will be returned to the individual or the research is of a sensitive nature (eg, HIV/AIDS research, research on illicit drug addiction), the IRB should ensure that adequate provisions to protect the participant's privacy and prevention of other harms are considered.

once the data collection from all study sites is complete, the overall study results database has been locked, and the only remaining activities is the analysis of the aggregate data by the study sponsor.²⁴ FDA endorses a similar approach regarding the provision of PLS. Thus, the IRB would not need to review the content of the PLS after study close-out. IRBs or institutions are encouraged to establish written procedures²⁵ regarding their role in the PLS process.

Nothing in this guidance is intended to restrict or impede the open communication between a research subject and the investigator when the investigator is serving as the health care provider. Further, communications, including communications about the study results, after the study is closed are considered part of the practice of medicine and are not regulated by FDA.

IV. Special Considerations of the PLS

A. Studies that close prematurely

Research subjects remain interested in the outcome of the study in which they participated, even if the study closed prematurely. In fact, there may be increased interest on the part of the research subject and the general public if a study is terminated for reasons of efficacy, futility, or safety.

B. Participant privacy

In general, patient privacy and confidentiality do not pose challenges to the PLS, provided that only aggregate results are described, no personal identifying information of research subjects is included, and care is taken to anonymize rare events. In special situations, for instance in very small studies (e.g., rare diseases, N of 1 studies) or for rare adverse events that may be challenging to anonymize, extra consideration may be needed to protect individuals from the risks of re-identification.

Privacy concerns may be a factor in the distribution method as described above.

C. Notification of results to a legally authorized representative and other third parties

While the option to obtain a PLS is generally provided directly to research subjects, subjects may wish to involve another person (e.g., a family member,²⁶

²⁴ See FDA's Guidance, IRB Continuing Review after Clinical Investigation Approval, available at: <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294558.pdf>

²⁵ See 21 CFR 56.1079(f).

²⁶ Under FDA's regulations, 21 CFR 50.3(m), a family member means, "any one of the following legally competent persons: Spouse; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters;

friend, or legally authorized representative) in the communication of a PLS, particularly in situations in which an interactive method of delivery is envisioned. Research subjects may opt to include a designated third party in this process.

D. Vulnerable populations

Vulnerable research subjects that may have special considerations in receiving PLS (i.e., children, prisoners, or mentally disabled persons)^{27,28} may be included in research described in a PLS. In some cases, these individuals (depending on their individual capacity to understand) or their legally authorized representative may require special consideration for receiving the PLS. The sponsor, investigator and IRB should consider whether the provision of results presents any specific or additional risks (e.g., psychological, behavioral, social, or legal) to the individual and whether the proposed method of communicating the PLS may mitigate or aggravate those risks.

If a child²⁹ is to be enrolled in research, the parent(s) or legal guardian must provide permission, with the assent of the child when appropriate. In general, if a child is of an age when assent is possible, then the child may be involved in the decision as to whether to receive the PLS of the study, and in the case of a teenager, both the parent(s) or legal guardian and the child should be involved in the decision to receive the PLS. As stated above, the methods of communicating PLS should be reviewed and approved by the IRB before implementation.

and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship." In the context of the implementation of the Supreme Court's invalidation of the Defense of Marriage Act in the case of *United States v. Windsor*, FDA's policy is to recognize same-sex marriage based upon the laws in effect in the state where the marriage was celebrated. That is, FDA applies a jurisdiction of celebration rule of recognition of a same-sex marriage.

²⁷ See 21 CFR 56.107(a).

²⁸ Pregnant women and physically handicapped persons are intentionally removed from this list as no special protections are necessary for receiving PLS.

²⁹ See 21 CFR 50.3(o). "Children" means, "persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted."

APPENDIX: Suggested Template(s)

[See MRCT ROR Toolkit, <http://mrctcenter.org/wp-content/uploads/2017/03/2017-03-13-MRCT-Return-of-Aggregate-Results-Toolkit-3.0.pdf>

Consider including an appendix with suggested templates]