

Plain Language Summaries

Keeping the End in Mind: Key Considerations for Creating Plain Language Summaries

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Executive Summary

Plain language summaries (PLS), also known as lay summaries and trial results summaries, educate participants and the public about clinical trial results in an easy-to-understand manner. Creating a PLS involves translating complex, technical information from regulatory documents into a short summary using non-promotional and unbiased language. These summaries are generally written at a 6th-to-8th-grade US reading level and avoid medical terminology and industry jargon. Current challenges sponsors face include the creation of a consistent and transparent PLS portfolio that revolves around the development of a reliable template. This template should consider both regulatory requirements and patient-centric health literacy principles that increase understanding. Sponsors preparing to meet short deadlines for PLS submission can incorporate best practices and implementation strategies presented in this white paper that allow for PLS drafting ahead of clinical study report (CSR) finalization.

Why write a PLS?

Doing the Right Thing

Patient-forward transparency builds and maintains public trust in clinical research. In a digital world where information is increasingly available at our fingertips, life science companies should consider the patient empowerment that comes from transparency initiatives. The availability of a PLS at the end of the clinical trial process provides not only closure, but also valuable information that may change the course of a participant's disease journey. Patient engagement initiatives as a whole, including PLS dissemination, may also increase participant recruitment and retention in clinical trials^{1,2}.

Nevertheless, clinical trial participants typically do not receive results of their clinical trial results, despite a desire to have them. A 2019 survey³ found that 85% of participants were willing to participate in clinical research, while 68% of those surveyed said a summary of study results was the most important information they would like to receive. Yet, nearly 61% of participants did not receive a summary of their study's results, with 39% noting that they never received a follow-up response from anyone¹. Healthcare professionals may also find a PLS extremely valuable for communicating current clinical findings of a particular treatment option to their patients. The same survey found that the top two sources from which individuals learned about clinical trials was either an advertisement or from their primary care physician (PCP) or specialist. 64% of the participants surveyed noted that their preferred method to learn about clinical research was during

discussions with their PCP or specialist about treatment options¹. Oftentimes, there may be a knowledge gap when a patient confers with a PCP about a certain condition and what clinical research is available on treatments. A PLS can be useful in these situations to help PCPs explain current clinical trial findings in lay terms to patients who may be interested or have questions about the effects of their clinical trial participation on their health⁴.

Regulatory Requirements

Beyond writing PLS documents as a best practice, sponsors must also consider regulatory obligations in the development of these summary documents. The new European Union (EU) Clinical Trial Regulation (CTR) No. 536/2014 includes a mandate for the creation of PLS for all clinical trials conducted in the EU, irrespective of the trial's outcome⁵.

Though the EU CTR was enacted in 2014, it has not been applied yet due to delays in development of the EU clinical trials portal and database. The regulation will become applicable six months after the portal goes live, and sponsors will be required to submit a PLS for all new Phase I through IV interventional clinical trials. For clinical trials in adults, sponsors will be required to post a PLS within 12 months of the end of the trial; this timeline is further shortened to within six months for pediatric trials. Implementation of the regulation will go through a three-year phase-in. In the first year, PLS submission will be optional, while after the second and third years, it will become mandatory for new trials⁶.



Outside of the EU requirements, other countries have shown awareness and support of PLS development. For example, PLS provision is encouraged in both the Netherlands⁷ and the United States⁸, but is not yet explicitly required. As transparency initiatives and public interest increase, sponsors will need processes and policies in place to meet these requirements.

Key Considerations for PLS Implementation

Centering PLS Consistency and Scalability Around a Compliant Template

Sponsors best positioned for managing PLS across their portfolios are prioritizing the creation of a PLS template ahead of the EU portal and database release. The most effective PLS templates align with current EU guidance and include key health literacy principles for increased understandability. Annex V of the EU CTR⁹ notes the essential elements required in all PLS. Including headers within the template that align with these required elements and are written in plain language further augments reader comprehension of each element covered (Table 1).

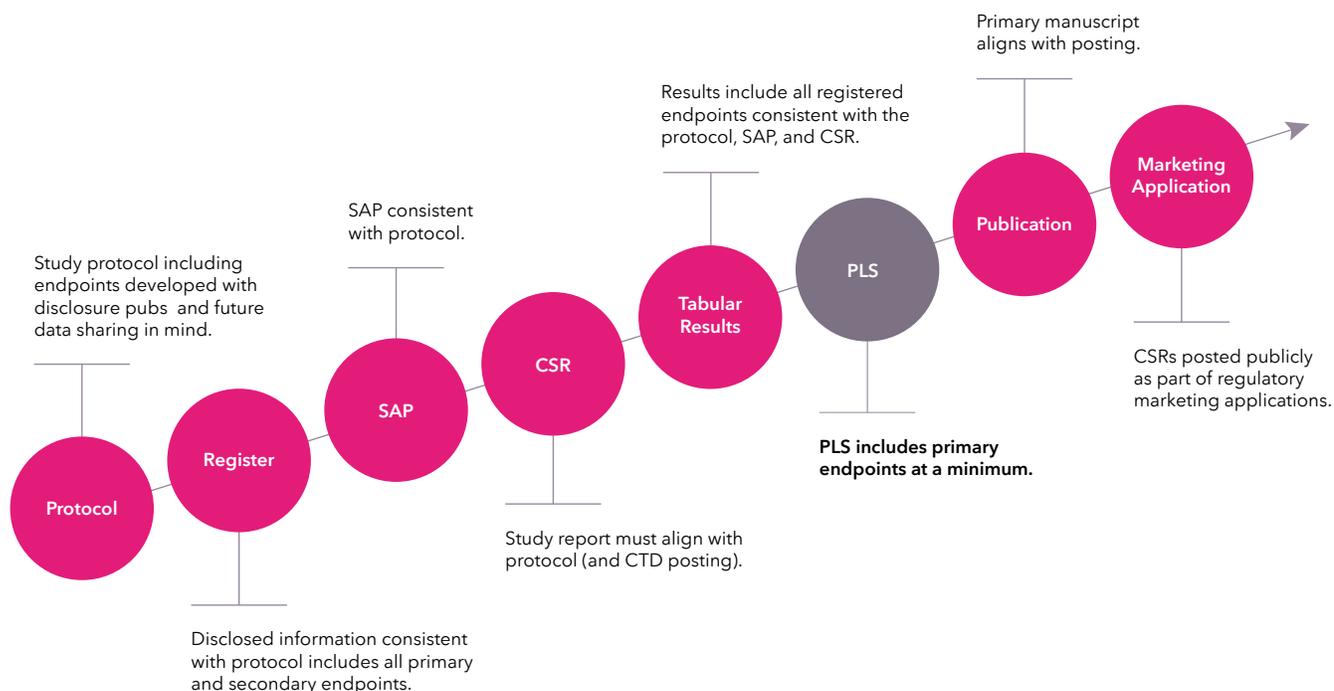
Sponsors best positioned for managing plain language summaries across their portfolios are prioritizing the development and piloting of a PLS template ahead of the EU portal and database release.

Planning for The PLS Through Endpoint Continuity and Specificity

During early trial development, study planners determine key hypotheses for the study design, whereby information from the protocol drives transparency obligations—particularly primary and secondary endpoints that form the basis of most clinical trial disclosure reporting worldwide (please see PRA’s Requirements & Strategy Considerations Whitepaper [here](#) for more information and guidance on trial disclosure requirements). Keeping the end in mind during protocol development protects against unanticipated exposure of proprietary information. As seen in Figure 1, the endpoint continuum should build from protocol development through the final stages of a clinical trial in a consistent matter. Writing specific endpoints and analyses in the protocol ensures that consistent scientific aims are communicated from trial registration to final publication. While most trial registrations require disclosure of all primary and secondary endpoints, only primary endpoints are specifically called out for inclusion

CTR Annex Essential Elements	Plain Language Headers
<ul style="list-style-type: none"> • Sponsor details and contact information • Study identification • Purpose and general information about the study, including the investigational medicinal products (IMP) used • Population of study participants • Overall results of the study, including primary outcome data, and the overall outcome of the study • Description of the adverse events/reactions and the frequencies • Indication as to whether follow up studies are foreseen • Where additional information about the study can be found 	<ul style="list-style-type: none"> • Thank you message to the participants • Why was the study done? • Who was in this study? • When and where was the study done? • How was the study done? • What adverse reactions did the participants have? • What were the main results of the study? • How has this study helped patients and researchers? • Where can I learn more about this study?

Table 1: The structure of a PLS



CTD: clinical trial disclosures; CSR: clinical study report; PLS: plain language summary; SAP: statistical analysis plan.

Figure 1. Transparency Lifecycle and the Endpoint Continuum.

in a PLS.

Endpoint continuity goes hand in hand with endpoint specificity. Guidelines set forth by various expert working groups have already aimed to facilitate improved transparency and disclosure in clinical trial reporting. The 2013 SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) outcome measure recommendations¹⁰, along with the 2010 CONSORT (CONSolidated Standards Of Reporting Trials) checklist¹¹ both recommend completely defining primary and secondary outcome measures. This includes the name of the outcome, the time point of interest, and the metric or method used to assess the outcome. Ultimately, writing protocols with specific and clear outcome measures determines future disclosure obligations.

Endpoint specificity is particularly important for a PLS. In the examples in Table 2, vague endpoint descriptions result in a muddled interpretation, leading to a more challenging endeavor when translating those endpoints into plain language. This can result in delays in an already tight timeline

for PLS development and the involvement of a potentially disbanded study team after trial conclusion, as well as added costs for sponsors. Additionally, this could potentially weaken public trust and engagement with clinical research due to a perception of shifting endpoints from the initial disclosure of the trial.

By including specificity within endpoints at the beginning of the process, sponsors can avoid confusion and maximize efficiencies at the end of the process when transparency and disclosure deliverables are needed. Protocol templates that incorporate disclosure guidance help promote full transparency and avoid challenges in reporting results after trial completion.

The decision on endpoint inclusion should be transparent and consistent across a sponsor’s lay summary portfolio.



Endpoint	Possible Interpretations
Overall survival (OS)	<ul style="list-style-type: none"> Median overall survival (months) Overall survival rate at X months (%) Number of OS events
Change from baseline in daily and 7-day mean composite scores over Weeks 1-12 of treatment	<ul style="list-style-type: none"> Change from baseline score at Week 12 Change from baseline score at Weeks 1, 2, 3... 12 Change from baseline score at Days 1, 2, 3... 84
Safety and tolerability as measured by vital signs	<ul style="list-style-type: none"> Number of subjects with vital sign abnormalities Percent of change from baseline in systolic/diastolic blood pressure, resting heart rate, body temp, etc. Measurements at each time point for systolic/diastolic blood pressure, resting heart rate, body temp, etc.

Table 2. Vague endpoint descriptions result in multiple interpretations

Considering the Balance in PLS Endpoint Inclusion

The current EU guidance¹² for PLS development specifically notes the inclusion of primary outcome data. Currently, PLS templates vary across the industry in whether they include secondary endpoints. While sponsors may consider the inclusion of secondary endpoints as a way of providing more information to the reader, this can often come with the risk of “cherry picking” or purposely selecting specific data for presentation. Anticipating PLS requirements while writing protocols helps mitigate this risk. A 2019 Food and Drug Administration (FDA) draft guidance on clinical trials with multiple endpoints suggests keeping the list of secondary endpoints short, because the chance of demonstrating an effect on any secondary endpoint after appropriate correction for multiplicity becomes increasingly small as the number of endpoints increases¹³. Thus, in the event a sponsor decides to include secondary endpoints in their PLS, portfolio-wide, it is advisable to keep the list of secondary endpoints short while also not sacrificing the scientific integrity of the trial.

A flexible PLS policy may help account for complex trial designs. In the example in Table 3, a mix of primary and secondary endpoints span three parts of a trial. If the sponsor’s PLS policy only includes primary endpoints, it may leave out information for certain parts of the trial, resulting in a piecemeal and potentially confusing message to the reader. Including all of the endpoints, however, could lead to a very lengthy and dense summary that loses the reader’s interest and understanding.

	Part 1	Part 2	Part 3
Primary Objectives	To evaluate the safety and tolerability of ascending single i.v. doses of Drug X	To evaluate the safety and tolerability of ascending single subQ doses of Drug X	To evaluate the safety and tolerability of repeated subQ doses of Drug X
		To assess the bioavailability of ascending single subQ doses of Drug X	To assess the PK of repeated subQ doses of Drug X
Secondary Objectives	To assess the PK of ascending single i.v. doses of Drug X.	To assess the PK of ascending single subQ doses of Drug X	To assess the bioavailability of repeated subQ doses of Drug X
	To assess the immunogenicity of ascending single i.v. doses of Drug X	To assess the immunogenicity of ascending single subQ doses of Drug X	To assess the immunogenicity of repeated subQ doses of Drug X

Table 3: Overlapping primary and secondary objectives in multi-part trials

i.v.: intravenous; subQ: subcutaneous; PK: pharmacokinetics



In creating a PLS template, sponsors should consider best practices that align with regulatory requirements and keep the participants' best interests in mind. PRA recommends aligning with the EU guidance in that sponsors include primary outcome data only to avoid bias when selecting secondary endpoints. In the event sponsors would like to include secondary outcome data, PRA recommends establishing guidelines at a program level on which secondary endpoints will be included across the portfolio. If a sponsor's clinical trials will always have a multitude of secondary endpoints, a policy that includes patient-focused secondary endpoints should be considered. For example, pharmacodynamic endpoints and patient-reported outcomes typically hold more interest to participants compared to pharmacokinetic endpoints. This goes hand in hand with the current EU guidance for PLS creation, which notes that sponsors should reference the complete list of outcomes based on all endpoints available in the technical results summary for each clinical trial in the EU database, including patient relevant secondary endpoints¹². While the implication of *patient relevant secondary endpoints* remains unclear within the life sciences industry, most sponsors interpret these as patient-reported outcomes and any clinically relevant endpoints, such as overall survival in an oncology trial. The decision on endpoint inclusion should be transparent and consistent across a sponsor's PLS portfolio. This is especially important for avoiding scenarios where it may seem the sponsor is biased by selecting positive outcomes only.

The significance of *patient relevant secondary endpoints* should also be considered when planning the hierarchy of endpoints in a trial. In order for these endpoints to be disclosed in a PLS, they should not be classified as an exploratory endpoint. This bears even more significance in terms of consistency between disclosure platforms, as exploratory endpoints are not disclosed on ClinicalTrials.gov and EudraCT. Additionally, discussing exploratory data can be extremely confusing and affect comprehension, as no true conclusions can be drawn from the results. While developing a trial's protocol, sponsors are encouraged to remember that endpoints intended to serve the purpose of hypothesis generation should not be included as secondary endpoints, but rather categorized as exploratory endpoints¹³. While hypothesis-generating exploratory endpoints can be extremely valuable for the science behind clinical research, they fall out

of the scope for inclusion in a PLS. Nonetheless, if an endpoint is clinically meaningful to a patient but may not be powered enough for analysis due a small sample size, consider making it a secondary endpoint that can be disclosed in a PLS and other disclosure platforms.

Incorporating the Patient Voice

Healthy Literacy Principles

Patient centrality in a PLS can be partly accomplished by following health literacy principles. Writing a PLS requires a highly developed and experienced skill set. The writer must have the medical or scientific experience to decipher regulatory documents, while also having the ability to communicate these technical messages using health literacy principles. These summaries are generally written at a 6th-to-8th-grade US reading level. In terms of writing style, a PLS looks very different from typical regulatory documents. The best written PLS documents use active voice, shorter sentences, and avoid the use of parentheses and other complex symbols. Big picture messages and conclusions should be stated first before distilling down the details. The text should also not include any medical jargon, with any medical terms defined in plain language if included.

From a visual perspective, plenty of white space should be prevalent in the PLS. When creating a graphical template, sponsors should keep the colorblind population in mind. Sponsors should also remember that documents in print may look very different from documents uploaded online. Moreover, graphics should be used to help the reader understand the study design and the primary results. However, graphics should not be used for the sake of inclusion, but rather to improve understanding of the key concepts in the PLS. When using a chart, like a bar graph to show differences between treatment groups, consider the importance of Y-axis scaling. While a result may not be statistically significant, the difference between two treatment group values may seem large to a lay reader who has no background in statistics. Moreover, graphics should be appropriately chosen. For example, though commonly used to generally indicate medication use, an icon of a capsule should not be used when a trial drug's route of administration was through an infusion.



Assessment of Plain Language Friendliness

In most countries, readability tools exist to help assess the reading level of a document. For example, the Flesch Reading Ease Test or the Flesch-Kincaid Grade Level Text in Microsoft Word can easily tell a writer the ease and grade level of readability of a document. While these tests are user-friendly methods of assessment, they are merely based on syllables and sentence length. While shorter sentences and words with fewer syllables are indeed needed in a PLS, these tests fail to grasp a lay reader’s comprehension of the concepts explained. They also do not account for the necessity of long drug names or any complex terms that must be included, despite the inclusion of a plain language-friendly definition.

Consequently, sponsors should consider an independent plain language review of each PLS. While not required, the EU guidance still notes that sponsors should consider testing the readability of the summary with a small number of people who represent the target population. Depending on the nature of the study, this could be patients with a particular disease or members of the public¹². Ideal plain language reviewers could include a variety of people: patients with the target disease, patient representatives, healthcare professionals, patient advocates, and general members of the public. Patient advisory boards, patient advocacy groups, and other third-party organizations can provide this kind of support during PLS development. Beyond the obvious benefits of testing plain language readability, this type of external review lends further evidence to the PLS being as unbiased and non-promotional as possible.

Current Approaches to Accommodate PLS Timeline

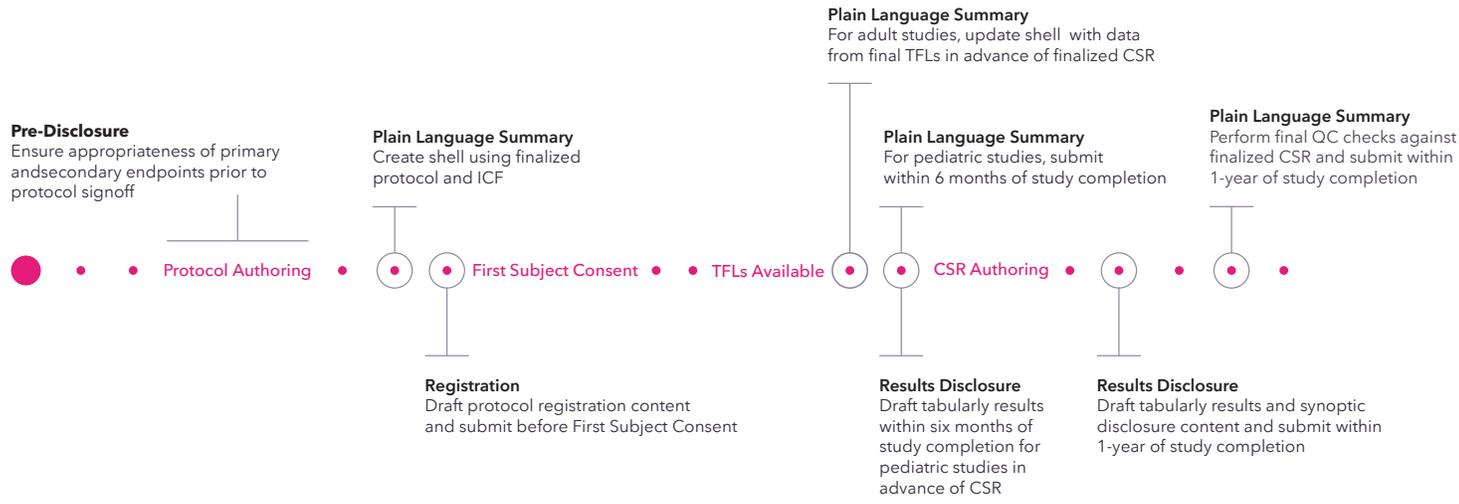
Best practices in terms of source information for a PLS remains using a finalized clinical study report (CSR). However, some sponsors are already anticipating the challenge of having a finalized CSR ready in time for a 1-year deadline for PLS submissions, especially with the 6-month deadlines for pediatric trials. Currently, sponsors have started piloting new processes where a PLS “shell” is created based on the protocol and ICF. A majority of the PLS can be populated with these two sources, leaving the data itself to be inserted when it’s finalized later in the process (Table 4). However, this should only be considered when the summary data files can be finalized ahead of CSR finalization.

For some sponsors, this may be a departure from the typical medical writing and programming processes of CSR development. Thus, a concerted effort must be made between medical writing, biostatistics/programming, and the PLS writing team to ensure that the protocol, ICF, and finalized summary tables can be made available before PLS creation. It can also greatly maximize efficiencies to include PLS writers

A collaborative effort in prioritizing finalized data sets and discussion of key messaging ahead of CSR finalization helps sponsors meet 1-year PLS deadlines.

PLS Content Pre-TFL Finalization	PLS Additions Post-TLF Finalization
<ul style="list-style-type: none"> • Thank You message to participants • General PLS templated language throughout • Partial sections that be inserted: <ul style="list-style-type: none"> - Who was in the study? (general inclusion criteria and disease under study) - Headers for main results (plain translation of endpoints) • Whole sections that can be completed: <ul style="list-style-type: none"> - Why was this study done? - How was this study done? - Where can I learn more about this study? 	<ul style="list-style-type: none"> • Partial sections that can be completed: <ul style="list-style-type: none"> - Age ranger and gender breakdown of randomized trial participants - Data and associated conclusions for main results • Whole sections that can be completed: <ul style="list-style-type: none"> - What adverse reactions did the participants have? - How has this study helped patients and researchers? • Any updates to planned trial conduct (early termination, actual trial dates, etc)

Table 4: PLS shell creation ahead of TLF finalization to accommodate 1-year (or 6-month) timeline



CSR: clinical study report; TFL: tables, listings, and graphs (data); ICF: informed consent form; QC: quality control

Figure 2: PLS Lifecycle and Clinical Trial Timelines

or members of a clinical trial transparency (CTT) group in any “key messaging” meetings. That way, PLS writers can learn the major conclusions the study team is planning to draw in the CSR, which is not found in the tables, listings, and figures (TLFs) outputs that are generated ahead of CSR finalization. Once the final CSR is ready, it can be used for quality control checks to ensure that all final data in the PLS are accurate (Figure 2). A collaborative effort in prioritizing finalized data sets and discussion of key messaging ahead of CSR finalization can help sponsors meet the 1-year PLS deadline.

Methods to Inform Participants and the Public About a PLS

Many sponsors are already in the practice of disseminating a PLS for each clinical trial, either through an online portal or directly through email or a mailing. However, sponsors should also consider the benefit of communications throughout the clinical trial process, again keeping the end in mind from the start. Conveying a clear message of transparency from the beginning helps participants trust the process and understand their role throughout. This can be accomplished through a variety of sources. Typically, an informed consent form (ICF) is the first form of communication a participant sees in the clinical trial process. As reading and understanding an ICF is required prior to enrollment in a trial, sponsors should consider

inserting language into the ICF that alerts the participant of their choice to receive a PLS in the future, including its approximate timing of availability. Consequently, trial participants can be prepared to make an informed decision on receiving a PLS or not by the end of the trial. Sponsors should also consider sending “Thank You” letters to trial participants throughout the process, including after the ICF is signed and after the participants’ last visit. In this letter, a note about the timing and distribution of the PLS should be reiterated for those who have agreed to receive a PLS, including how the PLS will be accessible.

While direct communications are necessary, the role of investigators or healthcare providers in communicating results is also important. Sponsors should also consider providing cover letters to investigators when providing the PLS for distribution. This can help re-aquaint investigators with the requirement of the PLS and the importance in distributing the PLS to trial participants at their site. Lastly, online portals already exist for many sponsors for PLS posting, ahead of the availability of the new EU portal and database that will house the PLS. Sponsors should consider leveraging their portals to include more information about the availability of a PLS, potentially using alerts that can be sent to trial participants and interested members of the public throughout the process.



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