Lay summaries for Phase I trials in healthy volunteers

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Abstract
Lay summaries of Phase I trials in healthy volunteers pose a challenge because their endpoints are complex, the targeted indication may not be known when they are conducted, their results are often reported years after the trial ended, and the majority of substances tested in Phase I never reach the market. Nevertheless, the European Union Clinical Trials Regulation (EU CTR) mandates that lay summaries are to be provided for all clinical trials regardless of clinical phase. As lay summaries are intended to inform the public about the results of clinical studies, they need to be understandable to people without specific knowledge of the disease or the clinical research process. It is challenging to write lay summaries for Phase I trials that are both meaningful for the public and in line with the requirements of the EU CTR. We have developed a template to facilitate writing of lay summaries of Phase I trials in healthy volunteers. Using a template ensures that study designs and endpoints are described in a consistent lay-friendly manner across different types of Phase I trials.

Introduction
A lay summary is a short document that provides important information about a clinical trial in language that the public can easily understand. Providing lay summaries enables transparency and ensures that the clinical trial results are accessible to participants and the public. The European Union Clinical Trials Regulation 536/2014 (EU CTR) mandates that lay summaries are to be provided for all clinical trials regardless of clinical phase, therapeutic area, and trial outcome. Thus, the provision includes Phase I trials in healthy volunteers (in the text we will use "Phase I trials" as a shorthand for Phase I trials in healthy volunteers; this article does not address lay summaries for Phase I trials in patients such as those in oncology). The content of lay summaries is specified by Annex V of the EU CTR in the form of a list comprising 10 items.[1] Lay summaries are to be posted on a web-portal that will serve as a database for information on clinical trials, together with other trial documents such as the scientific summary, the protocol, and the clinical study report (§67 of the EU CTR).

Following the publication of the EU CTR in 2014, an expert group of stakeholders developed guidance on the structure and content of lay summaries (referred to as "expert recommendations" in the text).[2] The expert recommendations state that the primary audience for lay summaries is the general public, who should not be assumed to have any prior knowledge of medical terminology, clinical research, or the specific context of the study. Lay summaries need to be written in a way that they are understandable to people with low literacy skills. Literacy levels within the general population are typically at level 2 to 3 on the International Adult Literacy Survey (a scale from 1 to 5), with level 3 roughly corresponding to a level attained after completing secondary school.[3–5]

It is a considerable challenge to transfer complex information about a clinical trial into a short summary that is both accessible and relevant to a lay audience. Lay summaries of later phase trials (Phase II and above) may provide results that are relevant to patients because they include data on a new therapeutic principle or confirm the efficacy of a new substance in a large group of patients. Phase I trials, on the other hand, address clinical questions that are only of indirect relevance to patients. Phase I trials are generally conducted in early stages of clinical development and usually evaluate the pharmacokinetic and pharmacodynamic properties of a new compound and assess initial tolerability but do not evaluate clinical endpoints. In this article, we outline some of the challenges associated with writing lay summaries of Phase I trials and provide recommendations.

Challenges in writing lay summaries of Phase I studies
To help readers understand a Phase I trial, a lay summary needs to describe it in a way that shows its contribution to the overall clinical development process. The evaluation of a new substance in humans usually starts with single and multiple rising dose trials, progressing through drug-drug interaction trials, food-effect trials, and bioavailability and bioequivalence trials until the pharmacokinetic and pharmacodynamics properties are established. Occasionally, Phase I trials are conducted in the later stages of clinical development (for example, bioequivalence trials for fixed-dose combinations).

Endpoints assessed in Phase I trials have limited meaning for readers
A characteristic feature of Phase I trials is that the endpoints are usually not as meaningful to lay readers as the clinical endpoints in higher phase trials. Endpoints assessed in Phase I trials pertain to uptake, metabolism, and excretion of a new substance and essentially consist of a series of measurements of blood concentrations of the new substance and its metabolites at various time points. Such endpoints include, among others, the maximal concentration (C_{max}) and exposure (area under the curve, AUC), half-life, and concentration at steady state. These endpoints are complex and often require mathematical derivation. Generally, individual pharmacokinetic endpoints cannot be interpreted in isolation but need to be evaluated in conjunction with each other. Both the individual endpoints and their

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overall interpretation are difficult to explain in lay language. In addition, usually none of these endpoints corresponds to a physical or psychological experience of the study participants. Lay summaries of Phase I trials therefore need to summarise and aggregate pharmacokinetic and pharmacodynamic endpoints at the appropriate level to facilitate understanding. Providing details may impede, rather than enable, comprehension of the results. Therefore, it is more informative to summarise the trial results in a qualitative statement.

Another key objective of Phase I trials is the initial evaluation of the tolerability of new substances. However, the assessment of tolerability in Phase I trials is always preliminary because the participants do not have the target disease and because the small number of participants does not allow infrequent adverse events to be detected. The safety signals seen in Phase I trials need to be confirmed in later phase studies. Therefore, the safety results of a single Phase I trial may be of limited value to a reader who is interested in the possible side effects of a finally marketed medicine.

The indication for substances tested in a Phase I trial may not be known when the trial is conducted

Unlike in later phase clinical trials, the intended indication of a new substance may not have been determined at this early stage. In most instances, new molecules that are tested in humans will be designed to modify a certain biochemical entity that characterises a particular disease. However, some substances that act on the immune system, such as antibodies to interleukins, affect many pathways that are relevant for different diseases. Hence, the target disease may not have been established when the substance is tested in Phase I. If the disease area is not known when the lay summary is written, or the one provided in the lay summary changes during the course of further clinical development, its usefulness for the public is limited.

Many substances evaluated in Phase I trials do not reach market authorisation

It is very hard to obtain reliable estimates of the number of Phase I trials conducted in Europe or in the US. This is mainly because registration obligations for trials in healthy volunteers differ from those in patients. Either no registration is required (ClinicalTrials.gov) or registered trials are available to authorities only but are not made public (EudraCT). However, the overall number of clinical studies in healthy volunteers is likely to be very high, outnumbering the trials in other clinical phases by far. The high number of new substances in early phase trials is in great contrast to the number of molecules that reach market approval after full clinical development. Recent calculations show that across all therapeutic areas only 13.8% of all drug development programmes lead to approval.[6] Most substances that are evaluated in Phase I trials never become available to patients. Therefore, lay summaries of such trials are likely to be of limited or no value to the public. However, the workload and cost associated with their generation is considerable for both commercial and academic sponsors.

Results of Phase I trials in healthy volunteers are not made available immediately

At the time of the first testing in humans, the details of an investigational substance are kept

Table 1. Key issues and proposals for writing lay summaries of Phase I trials in healthy volunteers

Issue	Solutions
To avoid misleading conclusions, readers must understand that the purpose of the trial was not curative and that it was not conducted in patients with a disease.	• Specify in the lay title that trial participants were healthy people. • Add a statement to emphasise that the trial was done in healthy people who volunteered to participate. • Visually distinguish lay summaries of Phase I trials from those of higher phases.
Readers may not have the knowledge to understand the purpose of the trial.	• Explain why the trial is conducted in healthy volunteers, e.g.: *"When we develop a new medicine, we need to understand how the body processes it. Studies in healthy people help us answer this question"*.
Pharmacokinetic endpoints are the focus of Phase I trials in healthy volunteers but are unlikely to be of immediate relevance to a lay reader.	• Describe the underlying trial design in lay language, e.g.: *"This study tested whether there is a difference in how the body processes <<medicine A>> and <<medicine B>> when they are taken as 1 single tablet or as 2 separate tablets"*. • Avoid technical terms like *bioequivalence*.
Intended indication(s) of the investigational product may not be known at the time of writing.	• Include a broader statement about the target organ or group of diseases instead of a specific indication, e.g., "diseases of the brain" instead of "Alzheimer's disease".
Phase I trials may have complicated designs, details of which may confuse readers.	• Provide details of the trial design and procedures sparingly. Do not use technical terms (e.g., *two-sequence crossover study*). • Example: *"We measured the amount of <<medicine A>> and <<medicine B>> in the blood when the participants took them as separate tablets and combined in a single tablet. The doctors took blood samples at different times during the study. The doctors also collected information about the participants' health."*
Numerical data for endpoints typically evaluated in Phase I trials in healthy volunteers may be not meaningful to readers.	• Describe the results qualitatively, e.g., *"This study showed that the amount of <<medicine>> in the blood was about the same, no matter whether it was taken as <<formulation 1>> or <<formulation 2>>."*

confidential to protect the sponsors' intellectual property. Unlike later phase trials, the results of Phase I trials are usually not made available within 1 year after study completion. In major clinical trial registries, Phase I trial results only need to be made publicly available once a drug receives marketing approval and this is usually many years after the Phase I trial is conducted. Even after the EU CTR comes into effect, it will be possible to defer Phase I study results from publication for 30 months, and sponsors are likely to make use of this option.[7] Hence, when a Phase I trial is completed, the participants will not be informed about the results in a timely manner.

A standardised approach to writing lay summaries of Phase I trials

As outlined above, writing a lay summary for a Phase I trial presents specific challenges, particularly making it relevant for the public. On the other hand, there is considerable scope for harmonising lay summaries of Phase I trials in terms of wording, structure, and overall appearance. This is because Phase I trials tend to have similar types of designs and endpoints, independent of the therapeutic area or intended indication. Therefore, for each Phase I trial design, standardised lay-friendly wording could be used to describe the background, methodology, and results for any investigational substance.

A template for writing lay summaries of Phase I trials

To establish an efficient, lean, and cost-saving process for writing lay summaries of Phase I trials, we designed a template. We based the template on the proposals in the expert recommendations and on our standard for lay summaries of higher phase trials. Our template not only provides the structure of the lay summary and annotated guidance for the writer, but also includes standard text that the writer can select depending on the trial design. The template aids the writing and ensures that lay summaries are harmonised with regard to the overall structure, the level of detail given, and the lay language used. Table 1 shows our approach according to this template and Figure 1 provides an example lay summary.

Title and statement that the trial was conducted in healthy volunteers

We routinely develop lay titles for all clinical studies based on the full scientific title. A good lay title allows the reader to judge quickly whether the trial is relevant for them. For Phase I trials, readers should understand that the trial was not conducted in patients with a certain disease. Therefore, our lay titles always specify that trial participants were healthy. To highlight this fact, we add a statement immediately below the title (see Figure 1). The lay titles are also used for other trial-related documents such as informed consent forms and for the posting on ClinicalTrials.gov.[8]

This was a study in healthy volunteers

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This study in healthy people tested whether taking a low strength of empagliflozin, linagliptin, and metformin together in 1 pill is the same as taking them in separate pills

This is a summary of results from one clinical study.

We thank all volunteers who took part in this study. You helped to answer important questions about the combination of empagliflozin, linagliptin, and metformin.

What was this study about?

The purpose of this study was to find out about the amount of 3 different medicines (empagliflozin, linagliptin, and metformin) in the blood. We wanted to know if the amount is different if they are taken as separate tablets or as combination tablets.

Why was this study needed?

Before testing a new medicine in patients, we need to know how the body processes the medicine. Studies in healthy people can help us answer this question.

Empagliflozin, linagliptin, and metformin might be taken together. A new combination tablet contains all 3 of these medicines. We wanted to know about the new combination tablets. Are they taken up by the body in the same way as when each medicine is taken as separate tablets?

Which medicines were studied?

We studied the medicines called empagliflozin, linagliptin, and metformin. These are all medicines that can help to lower blood sugar in patients with type 2 diabetes.

All 3 medicines are taken as tablets that patients swallow. The combination of all 3 medicines is also taken as a tablet that patients swallow. The metformin was extended release in both types of tablets.

This was a study in healthy volunteers

Boehringer Ingelheim

Who took part in this study?

A total of 30 healthy people took part in the study. This included 19 men and 11 women. The youngest participant was 24 years old and the oldest participant was 55 years old.

This study was done in Germany.

How was this study done?

All participants were to receive the empagliflozin, linagliptin, and metformin as separate tablets and also as combination tablets. The participants were divided into 2 groups.

One group started by taking separate tablets of 10 mg empagliflozin, 5 mg linagliptin, and 500 mg metformin as a single dose. Then they switched to take combination tablets of the same amounts of each medicine, again as a single dose. The other group started by taking the combination tablets, and then switched to take the separate tablets. The participants had to wait at least 35 days between taking the separate tablets and taking the combination tablets.

The participants and doctors knew which tablets of medicine the participants were taking.

We wanted to find out how much of each of the medicines (empagliflozin, linagliptin, and metformin) was in the blood. We also wanted to know the highest amount of each medicine in the blood. To find out, the doctors took blood at different times before and after participants took the medicines. The blood samples were collected after they took the separate tablets and after the combination tablets.

What were the results of this study?

This study showed that the amount of each medicine (empagliflozin, linagliptin, and metformin) in the blood was about the same if taken as separate tablets or as combination tablets.

Did the participants have any unwanted effects?

Yes, participants had unwanted effects while taking the medicines as separate tablets and as combination tablets. Unwanted effects are any health problems that the doctors think were caused by empagliflozin, linagliptin, or metformin.

This was a study in healthy volunteers

Boehringer Ingelheim

During this study, 7 out of 29 participants (24%) had unwanted effects while taking the medicines as combination tablets. 6 out of 30 participants (20%) had unwanted effects while taking the medicines as separate tablets.

The table below shows the unwanted effects.

Unwanted effect	Empagliflozin, linagliptin, metformin - combination (29 people)	Empagliflozin, linagliptin, metformin - separate (30 people)
Nausea	4 people (14%)	3 people (10%)
Headache	4 people (14%)	2 people (7%)
Decreased appetite	1 person (3%)	2 people (7%)
Vomiting	1 person (3%)	1 person (3%)
Diarrhoea	1 person (3%)	1 person (3%)

None of the unwanted effects were serious.

Where can I find more information about this study?

You can find further information about the study at these websites:

1. Go to http://www.trials.boehringer-ingelheim.com/ and search for the study number 1361.11.
2. Go to www.clinicaltrialsregister.eu/ctr-search and search for the EudraCT number 2018-001266-42.
3. Go to www.clinicaltrials.gov and search for the NCT number NCT03629054.

Boehringer Ingelheim sponsored this study.

The full title of the study is: 'Bioequivalence of a low strength fixed dose combination tablet of empagliflozin/linagliptin/metformin extended release compared to the free combination of empagliflozin, linagliptin, and metformin extended release tablets following oral administration in healthy male and female subjects (an open-label, randomised, single-dose, two-period, two-sequence crossover study)'.

This was a Phase I study. This study started in September 2018 and finished in November 2018.

This was a study in healthy volunteers

Boehringer Ingelheim

Are there additional studies?

If we do more clinical studies with empagliflozin, linagliptin, and metformin you will find them on the websites listed above. To search for these studies, use the words empagliflozin, linagliptin, and metformin.

Important notice

This summary shows only the results from one study and may not represent all of the knowledge about the medicine studied. Usually, more than one study is carried out in order to find out how well a medicine works and the side effects of the medicine. Other studies may have different results.

You should not change your therapy based on the results of this study without first talking to your treating physician. Always consult your treating physician about your specific therapy.

Boehringer Ingelheim has provided this lay summary in accordance with European Union transparency obligations.

Figure 1. A lay summary for a phase I trial in healthy volunteers, also available at the Boehringer Ingelheim Trial Results page:
https://trials.boehringer-ingelheim.com/public/trial_results_ documents/1361/1361–0011_english_136111laysummaryenglishpdf. pdf#page=1_or search for Trijardy

Background to the trial

This section should provide the reader with sufficient information to understand what the trial was about and why it was needed. It should start with a purpose statement followed by an explanation as to why the trial was conducted in healthy volunteers. We keep the text about the trial rationale at a high level and omit scientific details that are not relevant for lay readers. For the trial rationale, we developed standardised text covering different trial types (e.g., dose escalation, drug-drug interaction, or bioavailability/bioequivalence trials). As the name of the investigational product (usually a code number or International Nonproprietary Name, INN) is linked with the trial rationale, we provide it in this section. With regard to the intended indication, we only include a general statement (e.g., "diseases of the brain" rather than "Alzheimer's disease").

Trial participants

We include the total number of participants and their breakdown by age and sex. We list key inclusion or exclusion criteria if relevant, e.g., if participants had to be within a certain BMI range. We also provide the country in which the trial was conducted. We use the term *participant* instead of *subject* because we feel that this term is the most appropriate factual description.

How the trial was done

To help the readers understand the trial and in the interest of transparency, we provide some detail on procedures performed during the trial. This includes dose groups and dosing intervals, whether some participants received placebo (and a definition of placebo), the mode of administration of the investigational medicine(s), and information about blood sampling (or other sampling) and any special procedures (e.g., imaging). This section also includes a statement that the overall health of the participants was regularly monitored during the trial.

The results of the trial

In line with the expert recommendations, the results of the primary endpoint are given. Pharmacokinetic endpoints are difficult to translate into lay language. Furthermore, in consideration of the low- to medium numeracy of the general population,[5] we try to limit the amount of numerical information. We therefore recommend providing the results of the primary endpoint in a qualitative statement addressing the purpose of the trial. An example from the results section of a drug-drug interaction trial is shown below:

This study showed that taking medicine A did not affect the removal of medicine B from the blood. When the participants took medicine B with medicine A, the amount of medicine B in the blood was about the same as when they took medicine B alone.

In some Phase I trials, the primary endpoint is a safety endpoint, e.g., the frequency of drug-related adverse events. In this case, the results section and adverse reactions section (described below) may be combined.

Description of adverse reactions and their frequency

We usually list the most frequent adverse reactions by treatment group in a table. We use the term *unwanted effects* because this is more lay-friendly than *adverse reactions*. If very few adverse reactions are reported, it may be sufficient to provide them in a sentence or bulleted list rather than a table. The Medical Dictionary for Regulatory Activities (MedDRA) preferred terms are often not lay-friendly, therefore we additionally provide a lay term. Retaining the MedDRA term provides consistency with other sources such as postings in registries, publications, and clinical study report synopses. We add the number of serious adverse reactions in each treatment group if any have occurred.

Discussion and conclusion

Results of a Phase I trial are not as relevant to patients as the results of Phase III trials that investigate efficacy and safety in specific indications. Indeed, even the Multi-Regional Clinical Trial guideline on returning results to participants suggests that lay summaries of certain types of studies may not be warranted because the results may not be informative, or because the benefit may not justify the administrative burden and expense.[9] Also, in a comment on the EU CTR, the European Federation of Exploratory Medicine (EUFEMED), an association of organisations involved in early clinical development, proposed publishing lay summaries of Phase I trials only once trial information has ceased to be commercially confidential.[10] Nonetheless, lay summaries for Phase I trials remain mandated by the EU CTR and serve the overarching objective of making the entire clinical research process transparent, which was one of the driving principles of the EU CTR. Therefore, sponsors need to find efficient ways for providing these lay summaries.

The challenge for writing lay summaries of Phase I trials is to achieve a balance between providing meaningful information about trial

design and results, making the information accessible without over-simplification, preventing the release of commercially sensitive information, and finding an efficient way of writing these documents. Our template for lay summaries of Phase I trials provides standards for structure, content, and wording for the different types of Phase I trials. It provides information that is informative for lay readers with the aim of maximising the value of these documents for the public.

Disclaimers

The opinions expressed in this article are the authors' own and not necessarily shared by their employer or EMWA.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (Text with EEA relevance). 2014 [cited 2020 Oct 19]. Available from: http://eur-lex.europa.eu/legal-content/EN/TXT/ ?uri=uriserv:OJ.L_.2014.158.01.0001.01. ENG
2. Summaries of clinical trial results for laypersons; recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use. Version 2. 2018 [cited 2020 Oct 21]. Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017v01_26_summaries_of_ct_results_for_laypersons.pdf
3. OECD Literature in the information age: Final report of the International Adult Literacy Survey (IALS). 2000 [cited 2020 Oct 21]. Available from: http://www.oecd.org/education/skills-beyond-school/41529765.pdf
4. Kirsch IS. The International Adult Literacy Survey (IALS): Understanding what was measured. Educational Testing Service. 2001 [cited 2020 Oct 21]. Available from: https://www.ets.org/Media/Research/pdf/RR-01–25-Kirsch.pdf
5. Rampey BD, Finnegan R, Goodman M, et al. Skills of U.S. unemployed, young, and older adults in sharper focus: Results from the Program for the International Assessment of Adult Competencies (PIAAC) 2012/2014: First look (NCES 2016–039). U.S. Department of Education. Washington, DC: National Center for Education Statistics. 2016 [cited 2020 Oct 21]. Available from: https://nces.ed.gov/pubs2016/2016039 rev.pdf
6. Wong CH, Wei SK, Lo AW: Estimation of clinical trial success rates and related parameters. Biostatistics. 2019;20(2):273–86.
7. European Medicine Agency: Appendix, on disclosure rules, to the "Functional specifications for the EU portal and EU database to be audited – EMA/42176/2014". 2015 Oct 5 [cited 2020 Oct 21]. Available from: https://www.ema.europa.eu/en/documents/other/appendix-disclosure-rules-functional-specifications-eu-portal-eu-database-be-audited_·en.pdf
8. Leithold LHE, Brown CM, Schindler TM. Lay titles for clinical trials: A balancing act. Med Writing. 2018;27(2):55–8.
9. MRCT Return of results guidance document. Version 2.1. 2016 Jul 13 [cited 2020 Oct 21]. Available from: https://mrctcenter.org/wp-content/uploads/2016/07/2016–07–13-MRCT-Return-of-Results-Guidance-Document-Version-2.1.pdf
10. European Medicines Agency: Overview on comments on EMA/641479/2014. Draft proposal for an addendum, on transparency, to the "Functional specifications for the EU portal and EU database to be audited – EMA/42176/2014". 2015 November 6 [cited 2020 Oct 21]. Available from: https://www.ema.europa.eu/en/documents/comments/overview-comments-ema/641479/2014-draft-proposal-addendum-transparency-functional-specifications-eu-portal-eu-database-be-audited/42176/2014_en.pdf

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Thomas M. Schindler studied biology and linguistics in Germany and the UK, obtained a PhD in molecular physiology, and did postdoctoral research in the UK. Thereafter, he became an editor of popular science. He turned to medical writing and has now gained some 23 years of experience in both medical affairs and regulatory medical writing. He was a member of the TransCelerate Return of Results work stream, is contributing to the Good Lay Summary Practice initiative and the Plain Language Summary guidance from Patient Focused Medicines Development. He is the head of Innovation Medical Writing at Boehringer Ingelheim Pharma.