Layperson summaries of clinical trial results: Useful resources in the vacuum of regulatory guidance

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Abstract

To meet the requirements of the clinical trial regulation, preparation for the publication of lay summaries on the European database should be undertaken as soon as possible. However, as of July 2015 (at the time of writing this article), no regulatory guidance has been produced. The main goal of this article is to raise awareness of other resources that writers can use in the interim. This includes templates, guidance, and examples published by the Harvard Workgroup and the Center for Information and Study on Clinical Research Participation, whose work is supported by the EMA and FDA.

Keywords: Disclosure, Layperson summary, The Harvard Workgroup, The Center for Information and Study on Clinical Research Participation

People want to access trial results for various reasons. As participants, they may want feedback on the scientific research to which they have contributed. They may seek information to decide whether or not to start or continue with a treatment, interpret symptoms, or find an alternative treatment. Others may want to find out if a trial exists in which they could participate, or seek information to inform others (loved ones, doctors etc.).

There is evidence to show that unless patients are informed about results they may not participate in future trials,[1] and that at the end of a trial they no longer feel valued.[2]

Informing patients of trial results may not only provide a more positive experience for patients but also improve low clinical trial (CT) recruitment rates.

EU legislation

In the EU, the CT regulation (Regulation (EU) No 536/2014[3]), stipulates that a layperson summary should accompany the summary of CT results. Both are to be submitted to the database within 1 year from the end of a CT in all member states (MS) concerned: Article 37 [4].

The regulation will apply 6 months after the European Commission publishes a notice in the Official Journal of the European Union to verify that the EU portal and database are fully functional; this is predicted to be on 28 May 2016 at the earliest (Article 99). If submission of results within 1 year is not possible (e.g. the CT is ongoing in non-EU sites), they should be submitted as soon as possible; and the protocol should specify this together with a justification.

The informed consent used to enrol patients must explain that the technical and lay summaries will be available in the database and, to the extent possible, *when* these will become available: Article 29 [6]. Within the EU database, the summary, layperson's summary, protocol, clinical study report (CSR), and data from other CTs using the same investigational product will be linked together: L158/8 [67].

Annex V of the CT regulation lists 10 items that must be included in lay summaries. These were discussed by Sroka-Saidi et al.,[4] including the comment that it can 'hardly be considered a guidance document.' However, Annex V is not guidance but a regulation, and in the EU it is important to distinguish between regulations, directives, and guidance. Regulations are binding, inflexible legislative acts that must be applied in their entirety across the EU and leave no room for interpretation. In contrast, although directives set out a goal that all MS must achieve, individual MS devise their own laws on how to implement these. The consequent wide interpretation of the CT directive (Directive 2001/20/EC[5]) by different MS led to disharmony in CT application procedures including the documentation required, approval timelines, and

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assessments performed. This logistical nightmare was one of the main drivers that led to the replacement of the CT directive with a regulation. Guidelines are the most flexible. They represent the agency's current thinking on a topic in more detail, but are not mandatory and can be deviated from (with justification). For example, there was a far-reaching misconception that the ICH E3 guidance for writing CSRs represented a fixed template that could not be deviated from – a misconception that the ICH E3 Q&A document[6] sought to correct.

Therefore, we can say that Annex V consists of 10 mandatory items that legally must be included in lay summaries for CTs occurring in at least one MS. It is not intended as guidance or a template. It is sparse, precisely because it is a regulation. Too much legislation would limit the flexibility needed for such documentation, and throw up roadblocks on a journey just begun.

According to the European Patients' Forum (EPF), which has published its own responses and requests regarding Annex V,[7] these 10 items were added by the European Council at the last stage of negotiations, without consultation from patient groups.

In April 2015 at the DIA Clinical Forum, I spoke informally with an EMA representative; they mentioned that although regulatory guidance may not be produced for some time, in the interim it may be helpful to review the work done by the Harvard Workgroup into lay summaries (discussed below).

US legislation

Much of the discussion on lay summaries has been focused on the EU. Back in 2007, however, the US FDA Amendments Act[8] not only expanded CT.gov to include basic results posting but also introduced a provisional requirement allowing for the dissemination of 'a summary of the clinical trial and its results that is written in non-technical, understandable language for patients … without being misleading or promotional' (Title VIII, §801). However, since this is not mandatory by US law, and a final ruling is currently pending, it was widely ignored.

Despite this, the FDA encourages returning results to CT participants and, like the EMA, supports the work done by the Harvard Workgroup and the Center for Information and Study on Clinical Research Participation (CISCRP) mentioned below.

Harvard Workgroup guidance and templates for lay summaries

The Multi-Regional Clinical Trials (MRCT) Center at Harvard Return of Results Workgroup is a multi-stakeholder group comprising 54 members. The group includes individual pharma companies such as Pfizer, Merck etc., the Pharmaceutical Research and Manufacturers of America, the European Federation of Pharmaceutical Industries and Associations, academics, patient advocacy groups (including the EPF mentioned earlier), and non-profit centres including the CISCRP (mentioned below).

From January to September of 2014, the Harvard Workgroup convened to agree on some guidance that sponsors could use to encourage the return of results. They refer to these documents as 'research result summaries,' and although the focus is on returning results to trial participants, they state that their recommendations are 'congruent with the EMA mandate to post results on the EU database.'

In March 2015, they published 2 documents: the Return of Results Guidance[9] and the Return of Results Toolkit.[10]

The Return of Results Guidance document is a practical guide to returning results. It includes advice on process development (from before the study begins, to delivering results and obtaining feedback), timing, document reviewers, format, content, style tips, how to convey numerical results and risk/benefit information, and readability (user) testing. It is a comprehensive document that contemplates the logistical challenges in delivering results and how such challenges can be tackled.

Linked to the guidance is the MRCT Return of Results Toolkit, which includes templates for Phase 1 and Phase 2/3 studies, and early CT closure, and a reviewer checklist. Suggestions for translating endpoints into lay language (Table 1) are provided, along with practical examples on neutral, non-promotional language (Table 2).

Language that could be perceived as being promotional is clearly of concern, so although medical writers are good candidates for writing lay summaries, regulatory and legal input may be warranted.

A disclaimer is included to say that while the documents consider the perspectives of the FDA and the EMA, they are not intended to 'supplant or interpret any regulation or official guidance.'[9]

CISCRP examples of lay summaries

The CISCRP is an independent non-profit organisation dedicated to educating the public and patients about clinical research. In 2011, they began piloting programs with Pfizer and Eli Lilly to return results to trial participants and obtain their feedback. CT

Table 1: Endpoint table with simple language (abbreviated version)

Endpoint	Description of The Type Of Endpoint	Example in Simple, Plain Language
Mortality/ Overall Survival	The goal of this trial was to see if Treatment ABC or Treatment XYZ helped patients with [disease/ condition] live longer.	**If there was NO EFFECT** Patients in both groups lived about the same amount of time, no matter what treatment they got. **If there was an EFFECT** The times given include the middle (average) amount of time that patients in this study lived. Some patients lived for a shorter time and some lived longer. People in Group A (ABC treatment) lived about 15 months. People in Group B (XYZ treatment) lived about 12 months. This means that people in Group A (ABC treatment) lived about 3 months longer than people in Group B.
Non-Inferiority	Non-inferiority trials seek to show that any difference between the two treatments is small enough to allow a conclusion that the new drug has at least some effect or, in many cases, an effect that is not too much smaller than the active control. Non-inferiority endpoints are designed to show that a new treatment or drug is not worse than the control (or other comparison drug) by a pre-specified amount (also termed the non-inferiority margin). Efficacy can, in fact, be worse if there are other benefits (e.g., fewer side effects).	This study showed that the new insulin formulation (insulin A) was not much worse than standard insulin therapy in reducing the level of HbA1c in Type 1 diabetic patients.
Patient-Reported Outcomes	This trial studied patient answers about their [list the main purpose of the questionnaire, e.g. symptom (e.g. pain), quality of life, psychosocial, burden, economics] and if the measurement changed based on whether a patient got A or B. The primary endpoint is less XXX based on the YYY scale. This scale measures ZZZ and how this changes over time.	Pain levels were measured on a known scale. It measured pain, stiffness, and how well people can climb stairs, stand or bend. Questions were asked during each study visit. Patients in Group A (tanezumab) had less knee pain than patients in Group B. Knee pain was lowered by about 1 in 2 people (50%) in Group A. Knee pain was lowered by about 1 in 4 people (25%) in Group B.'

Source: MRCT Return of Results Toolkit March 19, 2015 - Version 1.0.[10]

results were translated into lay summaries written at a validated sixth–eighth grade reading level (ages 11–14).

Four examples of these lay summaries have been published on the CISCRP website: 2 for Pfizer, and 2 for Eli Lily and Company.[11] Their research found that there was a dramatic improvement in the understanding of the CTs by the participants after reviewing the lay summaries, and that over 90% of volunteers were satisfied with their level of understanding.

The FDA suggested the CISCRP program was one that should be adopted industry-wide; the EMA stated that the clinical research industry has a binding legal obligation and a strong moral one to communicate the results to individuals in trials.

Table 2: Neutral language guidance (abbreviated version)

Language to Avoid	Language to Consider
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>.
<Drug A> works better than <Drug B>, but some people didn't tolerate it as well.	In this study, more people got <study endpoint> with <Drug A>. They also had more safety events 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>.
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 milder safety events like <list specific adverse events>. The amount of time they lived depended on how they felt when they started either treatment.
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 arms/there was no difference between the groups. All groups still had pain and numbness in their fingers or toes (called neuropathy).

Source: MRCT Return of Results Toolkit March 19, 2015 - Version 1.0.[10]

Other resources

Other lay documents already produced and approved can be consulted for lay terminology. Descriptions on methodology may be taken from the applicable informed consent document, and lay glossaries used for adverse events.[12]

Patient information leaflets (PILs) provide examples of lay safety information and can be accessed from the electronic Medicines Compendium[13] or sponsor websites. Regulatory guidance on PILs is available, including advice on lay terminology, preferred formatting (e.g. use bold rather than italics and underlining) and readability testing.[14]

On the EMA's website, lay language on risk and benefit can be reviewed in the European public assessment reports (EPARs), which contain the final assessment for centrally approved (or rejected) products, and in lay summaries for risk management plans.[15]

User testing conducted on PILs and EPARs greatly improved the presentation of these documents for lay audiences,[16] and will likely be of similar importance for lay summaries.

In addition, patient-oriented websites may be helpful to consult such as Cancer Research UK, which publishes lay descriptions of oncology studies for patients.[17]

Closing remarks

Lay summaries will play an important role in educating patients about clinical research. There is some evidence that too much safety information may negatively impact compliance and that primary health care workers may be inundated with questions.[18] However, there is hope that improved transparency will help regain patient trust by restoring a sense of autonomy in their own treatment decisions, and may improve CT recruitment. For better or worse, they are likely to be influential documents and need to be written with care.

Generalisations that could be perceived as promotional must be avoided and communicating specific findings in lay terms will be challenging, as will keeping the document to a manageable size for improved readability.

Although regulatory guidance is pending, guidance cannot address all situations, and precedents may be of more value. Until these are available, the work done by the Harvard Workgroup and CISCRP should provide a solid foundation for the lay summary 'lift-off'.

Postscript

I am currently conducting some research into the publication of CT results and would welcome any thoughts, comments, questions or information you have on this topic e.g. describing your experience of writing lay summaries, basic results, disclosure summaries etc., and/or whether you would be interested in participating in any short future questionnaires or interviews. Please feel free to contact me on this topic.

Conflicts of interest and disclaimers

The findings and conclusions in this paper are those of the author and do not necessarily represent the views of PAREXEL International GmbH.

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