EPF position: Clinical trial results – communication of the lay summary

02/03/2015

This position paper received funding under an operating grant from the European Union's Health Programme (2014-2020).

Contents

Introduction: The importance of communicating scientific research to patients and the public

In order to achieve meaningful patient involvement in research, it is crucial that at every stage of the research process, information is available to patients in a way that enables them to understand it. So-called "lay summaries" are needed for example at the stage of seeking funding and ethics approval, and they are important not only for patients but also for lay persons and non-specialist medical professionals. The summary may need to be to be drafted differently according to its purpose and target audience.

The lay summaries that will be published on the EU database are only one type of lay summary: they are intended for the general public, including patients, who seek information about the results of a specific trial. Currently, some published research includes a lay summary, but these are of variable quality, and there is no single agreed standard for producing summaries.[1]

If the EU database is to become the main point of reference for patients for information about clinical trials, then it needs to establish a high standard of patient-friendliness for the information that is presented, the way it is presented, and the user experience of the electronic interface. Summary results should be communicated in a way that is unbiased, comprehensive, relevant, and understandable to patients.

A set of "core quality principles" for information to patients was developed by the High-Level Pharmaceutical Forum (2008) and endorsed by Member States. These principles are general criteria intended to be applicable to all kinds of information to patients. They include criteria relating to the evidence base, factual correctness, source and verifiability of information; criteria to check information is focused on issues that patients consider important, ideally with patients' involvement; and criteria to check information is understandable by lay persons and accessible to everyone.[2]

Transparency provisions of the Clinical Trials Regulation

The new EU Clinical Trials Regulation (Regulation 536/2014) introduces a number of improvements to the transparency of clinical trial results:

- compulsory registration of all trials
- principle of public access to the EU clinical trials database developed and maintained by the European Medicines Agency
- publication of all trial results, irrespective of the outcomes, on the EU database
- summary results must include a summary "understandable to lay person".

[1] Denegri and Faure (2013)."It's plain and simple: transparency is good for science and in the public interest." *Trials* 2013, 14:215.

[2] http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/itp_quality_en.pdf

The summary results, including the lay summary, will be published within one year after the end of the trial, irrespective of the outcomes of the trial.

If it is not possible to submit the summary results within one year, this can be delayed but only for scientific reasons; which must be justified in the protocol. In such a case the protocol must say when the results will be published.[3]

Patients participating in a trial must be told that a lay summary of the results will be available on the EU database, and they should also be told when the summary results will become available, as far as that is already known (Article 29 (6)).

Why do patients look for information on clinical trials?

Patients look for information on the results of a clinical trial for a number of reasons:

- to know more about the latest scientific research in the field;
- to know more about trials for future involvement;
- if they have participated in the trial, to know the results;
- to spread the information to friends, other patients, physicians, and various other stakeholders
- to help recruit participants;
- to see what therapeutic development is taking place that may be better than the current therapeutic options;
- to know about access to the newest medicines.

In the rare disease community there are often very few or no effective treatments for a given condition. Therefore, this patient community takes a particular interest in medicines that are undergoing trials. Patients want to know whether that medicine has been effective in reducing symptoms, slowing the progression of their condition or reducing mortality.

Patients and patient organisation are interested in many of the same details as other stakeholders, including the start and end dates of the trial; the eligibility criteria for participation; a description of the medicine, intervention of device; what methodology was used, and what the end points of the trial were. Patients in rarer conditions and where the therapeutic options are limited, are particularly interested in possibilities to participate in a clinical trial.

“Primarily, though, the patient community wants a straightforward explanation of what the trial found: what was expected from the intervention under consideration and how it performed against these expectations.” (Patient representative)

[3] This consultation deals only with the lay version of the summary results. However, if a clinical trial is done with the aim of gaining a marketing authorisation in the EU, then the *clinical study report* (CSR) must also be published. This happens 30 days after the completion of the assessment procedure. (Article 37 (4)) the clinical study report is therefore published substantially later than the summary results, because of the time needed to conclude the assessment procedure. The CSR must be published regardless of the outcome of the application (approval, rejection, or withdrawal).

Information contained in the lay summary

The content of the summary is set out in Annex V of the Clinical Trials Regulation.[4] However, this is only a list of elements the lay summary must contain. It says nothing about how, or in how much detail, they should be described. This list was added by the Council at the last stage of negotiations, without any consultation with patient groups. It is therefore far from clear how the list of items in itself will meet patients' information needs.

Box 1: Information specified in Annex V of the Regulation

i. Clinical trial identification (including title of the trial, protocol number, EU trial number and other identifiers);
ii. Name and contact details of the sponsor;
iii. General information about the clinical trial (including where and when the trial was conducted, the main objectives of the trial and an explanation of the reasons for conducting it);
iv. Population of subjects (including information on the number of subjects included in the trial in the Member State concerned, in the Union and in third countries; age group breakdown and gender breakdown; inclusion and exclusion criteria);
v. Investigational medicinal products used;
vi. Description of adverse reactions and their frequency;
vii. Overall results of the clinical trial;
viii. Comments on the outcome of the clinical trial;
ix. Indication if follow up clinical trials are foreseen;
x. Indication where additional information could be found.

EPF believes these points must be clarified in order to arrive at the lay summary that makes sense for lay patients.

As a priority, patients want to know the objectives of a trial and its main outcomes; milestones and endpoints; what patients from which countries participated; which companies or academic researchers or sponsors were involved (including what relationships exist between researchers and pharmaceutical companies). Patients also want to know that the protocol was of good quality and was implemented properly; and they want information about safety and efficacy of the treatment.

We believe at least the following information needs to be integrated, while bearing in mind that it should be expressed in a simple and easily understandable manner:

[4] The Regulation in all EU languages is available here: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2014.158.01.0001.01.ENG

ADDITIONAL INFORMATION THAT SHOULD BE INCLUDED	
i. **Limitations of the study, how potential sources of bias and imprecision were addressed, and caveats**	We note with concern that Annex IV includes a mention of the "limitations of the study, how potential sources of bias and imprecision were addressed, and caveats" – yet this is not included in Annex V. This information is however equally important for lay readers and for managing patients' expectations. The information could be included under "comments on the outcome", but perhaps it is better addressed under a separate heading.
ii. **Endpoints**	A description of the endpoints and rationale for their selection. This presupposes a simple explanation of what an endpoint is and what different types of endpoints mean (glossary). This could be included under the "general information".
iii. **Substantial modifications and protocol changes made along the way**	This should be included both for transparency reasons and also as an explanations for any delays. It may be intentioned to be included under the "general information" but this is not explicit in the Regulation.
iv. **Patient involvement**	If applicable, a section outlining how the patient community were engaged with in the setting of the research priorities, selecting the clinically relevant endpoints or in developing the methodologies would be welcomed. The Regulation recommends that patients should be more involved in the design of trials, and that such involvement should always be described in the protocol. Many lay patients are not likely to read the protocol, however, so a mention of this aspect in the lay summary would be helpful.

In addition EPF makes the following comments on some of the information categories:

Category of information (as described in the Regulation)	EPF comments
Name and contact details of the sponsor	Patients should be able to find information about financial and other relationships between researchers and pharmaceutical companies or other organisations. A link to the relevant section of the protocol, if the information is contained there, would be helpful.
General information about the clinical trial (including where and when the trial was conducted, the main objectives of the trial and an explanation of the reasons for conducting it	Including a description of the endpoints and rationale for their selection. Including a description of the phase/purpose of the trial. "Patients often do not realise that a phase 1 trial is the first of many stages and that the full process will take considerable time."
Investigational medicinal products used	This should include a description of the condition that the medicine, intervention or device is expected to treat,

	written from the patient perspective rather than (only) from a clinical one, and ensuring that any medical terms used are explained in the text.
Description of adverse reactions and their frequency	This should be very specific and descriptive. More specifically, it should include information about expected vs. unexpected side effects.
Overall results of the clinical trial	The key most important section for patients. This needs to be written in a way that is simple and yet comprehensive and unbiased. Ideally it should be assessed from the patient's perspective also (taking into consideration what results are a priority for patients and to what extent the trial meets them.)
Comments on the outcome of the clinical trial	Another key section for patients. This needs to be written in a way that is simple and yet unbiased. In this section, caveats and biases could be addressed.
Indication if follow up clinical trials are foreseen	Including information about the timeline foreseen, if this is known.
Indication where additional information could be found	This section could include e.g. links to other clinical trial registries; additional information available from EMA and/or national medicines agencies; scientific articles; the Cochrane database, NHS Choices, etc. Patients would like to be able to find links to similar trials either conducted in the past or currently running in other parts of the world, and their results if available.

How should information be communicated?

Information will only be understandable if it is presented in a patient-friendly language and format. Moreover, it should be relevant to patients' information needs. However, the Regulation gives no guidance as to how the information contained in the lay summary should be written. Indeed, there is relatively little research on this, although some guidance is available at least from the UK.[5] Some issues that EPF believes need to be addressed are described below.

Ensuring a summary is written for lay persons

To write a good lay summary is not simple and requires a specific skill, but this is often not recognised. A survey in 2012 by BioMed Central found that 79% of the researchers did not involve lay people, and the same percentage either would not pay or did not know whether they would consider paying for professionally written lay summaries.[6]

[5] http://www.dcc.ac.uk/resources/how-guides/write-lay-summary ; http://www.invo.org.uk/wp-content/uploads/2013/03/Improving-quality-of-plain-English-summaries-report-final.pdf ;
[6] Denegri and Faure (2013)

Patients need to have access to the information in plain language. One suggestion is that when communicating medical terminology, it is most lay-friendly to have the lay explanation of the term embedded into the text, with the medical or scientific term subsequently included in brackets. "This makes the text easier to read and prevents it from appearing intimidating."

Since the summary is meant to be short, and some scientific terms require more explanation than can be accommodated in the text, it is important to have an integrated glossary at the reader's disposal. Moreover, since the European database will be eventually translated into all EU languages, there may be quality issues to consider to ensure that the translated versions of the summary are equally reader-friendly.

Sponsors who are providing summaries should ensure these are written by professional science writers or journalists, to ensure the communication is lay-friendly. Patients play an important role by being involved in the development of the summary to ensure it truly meets their needs. This should be relatively easy when patients are closely involved in the research itself; when that is not the case, patient representatives should be involved in developing or reviewing the lay summaries.

The European Medicines Agency (EMA) already provides the European public assessment reports (EPARs). The EMA then consults with patient/consumer organisations that each summary is appropriate for a lay audience. The EMA also has an established system for patient/consumer reviews of medicines' package information leaflets. A similar system could be explored for reviews of lay summaries involving the member organisations on the Patient and Consumer Working Party (PCWP), with the caveat that this may pose capacity and support issues for the patient representatives as well as the Agency which would need to be resolved

User-friendliness of the electronic interface

The interface of the database should be structured in a user-oriented way and include guidance and including a glossary of key terms. Many words commonly used in clinical trials reporting are not understood by all patients (such as "efficacy", "endpoint", "surrogate"...). Some glossaries targeted at patients are already available, although they may not include all terms.[7] The layout of the electronic interface needs to be intuitive and user-friendly.

The EU database should have an integral glossary that is simple and easy-to-use on the electronic interface, for example by "hovering" mouse over a word. Existing patient-friendly glossaries can be used as guidance. A glossary of terms should be available on the EMA database and directly accessible through the results section: this should be as intuitive as possible, for example using pop-up text boxes, but also printable.

In an eventual public consultation, a special section should be dedicated to communication and web-design. Similarly, within the EMA stakeholders' environment (e.g. a working group) it could constitute a specific topic. Communication experts from patients' and consumers'

[7] EGAN-Roche: http://www.biomedinvo4all.com/en/research-themes/clinical-trials/clinical-trial-glossary . Clinicaltrials.gov has a glossary: http://clinicaltrials.gov/ct2/about-studies/glossary. The EU clinical trials register has a glossary in PDF format that could be reviewed: https://www.clinicaltrialsregister.eu/doc/EU_Clinical_Trials_Register_Glossary.pdf

organisations, especially experts focusing on web content and website design, could also be consulted.

Trustworthiness

Conveying scientific information, especially where the interpretation of results may depend on some quite nuanced details, into simple language that a non-medical person can understand, is not easy and can risk coming across as biased, even with the best intentions.

In addition to easy understanding, there may be concerns about the factual accuracy of summary results, given that summarising always involves simplification. Summaries will most likely be written by the pharmaceutical companies or academic institutions that conduct the research, which could risk introducing bias (even unconsciously) into the communication. However, the European Medicines Agency is not likely to have adequate resources to check every summary.

In addition to Member States' national competent authorities, medical and scientific organisations could be involved in reviewing summaries. Similarly, some (especially highly specialised) patient and consumer organisations may have the capacity to do this, but would need support.

Empowering patients through scientific health literacy

Patients will be more empowered to judge for themselves whether a summary of results is trustworthy when they know how to interpret clinical trials results. This means that patients should be able to understand the main principles and concepts of trial design and conduct, especially how to assess the evidence, and potential sources of bias.

In addition to the EMA database, patients want to know about other reliable, unbiased online sources of information on trials generally as coverage in the media about clinical trials can often highlight negative aspects and potentially undermine trust in medical research.

Some useful resources exist to make scientific concepts understandable to the general public. For example, a good guide written in simple language for lay people is *Testing Treatments* (2nd edition, 2011) available online in an interactive website format in multiple languages, as well as PDF book free of charge.[8, 9]

Patient organisations can disseminate information about the EMA database and the lay summaries available there; it would be very useful if medical professionals, too, could inform patients about this source of information.

[8] *Testing Treatments* interactive: www.testingtreatments.org; at least part of the content is also available in other languages, including French, German, Italian, Spanish, Croatian and Turkish.

[9] Other examples include www.patientslikeme.com/clinical_trials ; disease-specific sites such as European Huntington's Disease Network (http://www.euro-hd.net/html/network); HealthTalk online (http://www.healthtalk.org/peoples-experiences/medical-research/clinical-trials/topics); NHS Choices has extensive lay-friendly content on research (http://www.nhs.uk/conditions/Clinical-trials/Pages/Introduction.aspx) The James Lind Alliance and UK DUETS database address treatment uncertainties from patients' and other perspectives (http://www.library.nhs.uk/DUETS/; http://www.lindalliance.org/)

Example: "In the U-BIOPRED project [Unbiased BIOmarkers in PREDiction of respiratory disease outcomes], a Patients Input Platform (PIP) was developed to give input to the project, as well as to communicate about the results. A 'patients for patients' approach has been developed. A more general European PIP is in the process of being created (at least for allergy and respiratory diseases) and as regards examples, EFA is planning to assess this next year." (European Federation of Allergy and Airways Diseases Patients' Associations)[10]

EPF recommendations

To help foster an open, inclusive and accountable system, EPF makes the following recommendations:

1. EPF calls for **a set of guidelines to be developed at EU level**, with the involvement of patient organisations, to ensure that the lay summaries written for the EU database adhere to a common set of quality standards. The existing *core quality principles*[11] could be used as a starting point. In addition, existing guidance on lay summaries should be reviewed and used to arrive at the common set of guidelines.
2. Our members who responded to the consultation would prefer the guidelines to be drafted by a **dedicated working group hosted at the European Medicines Agency**, with a sufficient number of patient representatives an involving the European Commission, regulators and industry. This would enable in-depth discussion and ensure that patients and patient organisations are engaged with the process form the beginning. A specific topic could focus on the user-friendliness of the electronic interface.
3. Once proposals are made, an **EU-wide consultation** should follow in order to invite input from all interested parties, including patients, patient representatives and members of the wider public.
4. The possibility of establishing a system of **patient reviews of lay summaries** should be explored, similar to the existing EMA system for reviews of EPARs and patient information leaflets via the PCWP. Patient organisations should be appropriately supported to undertake such reviews.

[10] http://www.efanet.org/unbiased-biomarkers-in-prediction-of-respiratory-disease-outcomes-u-biopred/
[11] "Core quality principles for information to patients on diseases and treatment options", developed by the High-Level Pharmaceutical Forum (2008): http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/itp_quality_en.pdf

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