MULTI-REGIONAL CLINICAL TRIALS

THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

Using Data for the Public Good: Sharing Aggregate and Individual Results

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Returning Results to Research Participants
A Health Policy and Bioethics Consortium
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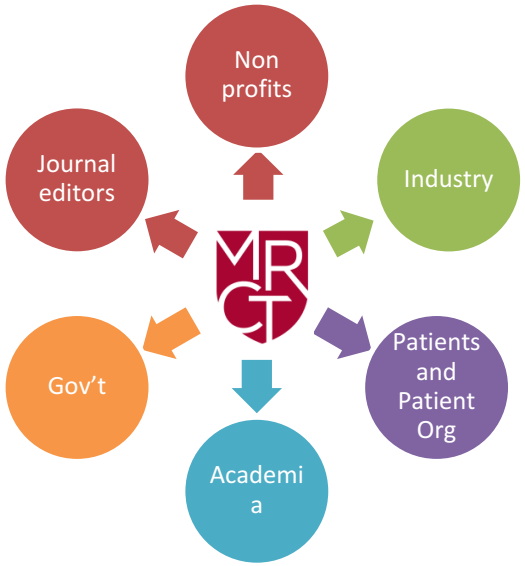
Our Mission

Engage diverse stakeholders to define emerging issues in global clinical trials and to create and implement ethical, actionable, and practical solutions.

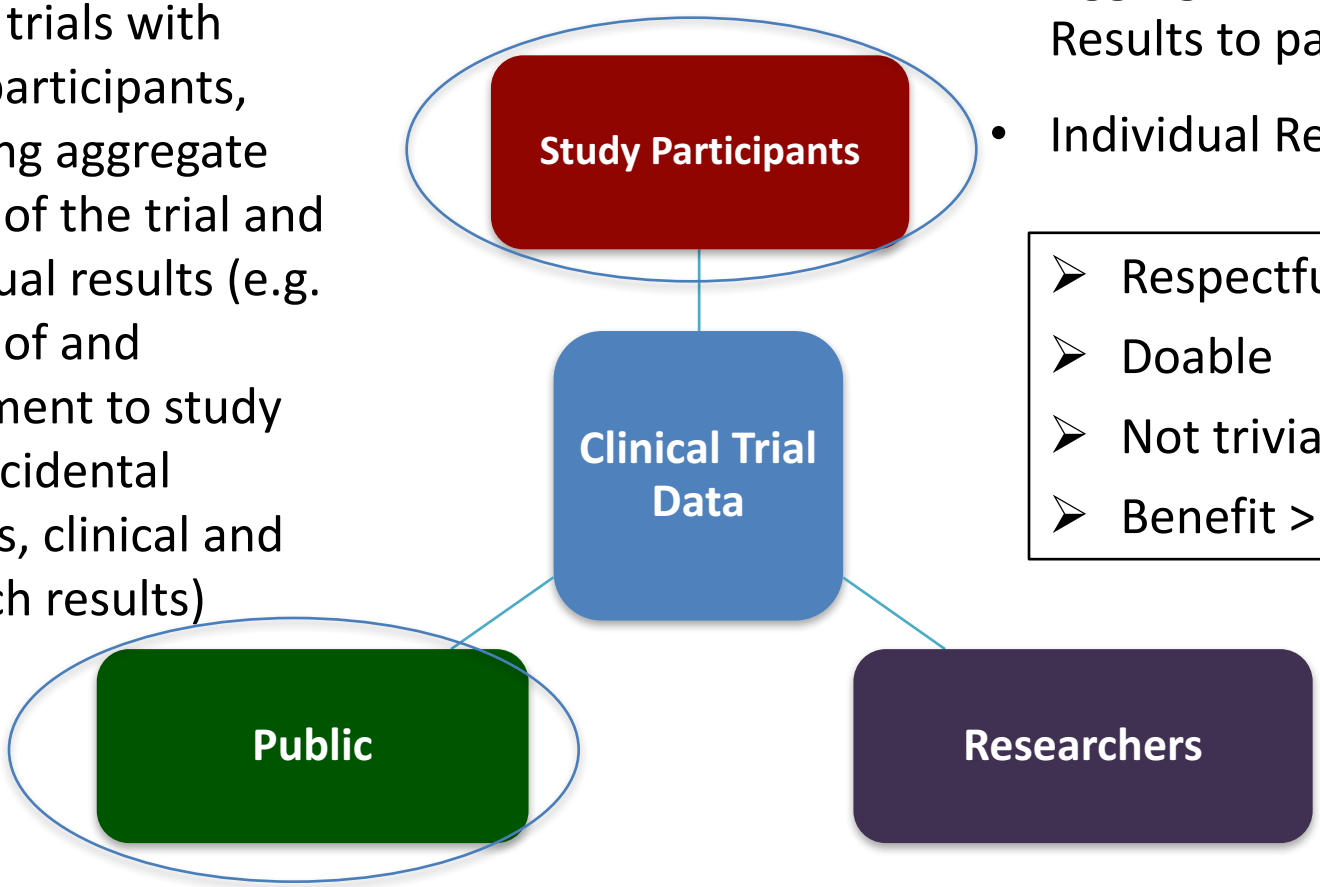


Data Sharing and Transparency

- Return of summary (aggregate) results
- Return of individual results

The various audiences of clinical trials data sharing

The sharing of research results from clinical trials with study participants, including aggregate results of the trial and individual results (e.g. results of and assignment to study arm, incidental findings, clinical and research results)



Return of

- Aggregate Research Results to participants
- Individual Results

- ➢ Respectful
- ➢ Doable
- ➢ Not trivial
- ➢ Benefit > risks

Sharing clinical trial results on a website enables public transparency and trust

Why now?

- **Declaration of Helsinki**: Paragraph 26:
  - "All medical research subjects should be given the option of being informed about the general outcome and results of the study."

    http://www.wma.net/en/30publications/10policies/b3/
- **EU Parliament**: Regulation (EU) No 536/2014 (2014):
  - Sponsor of a clinical trial must submit "a summary of the results of the clinical trial together with a summary that is understandable to a layperson, and the clinical study report, where applicable, within the defined timelines.
  - Article 37: 4. Irrespective of the outcome of a clinical trial, within one year from the end of a clinical trial in all Member States concerned, the sponsor shall submit to the EU database a summary of the results of the clinical trial. " → Required on EU portal, 2017.
- **PhRMA EFPIA Principles for Responsible Clinical Trial Data Sharing**
  - In order to help inform and educate patients about the clinical trials in which they participate, biopharmaceutical companies will work with regulators to adopt mechanisms for providing a factual summary of clinical trial results and make the summaries available to research participants.

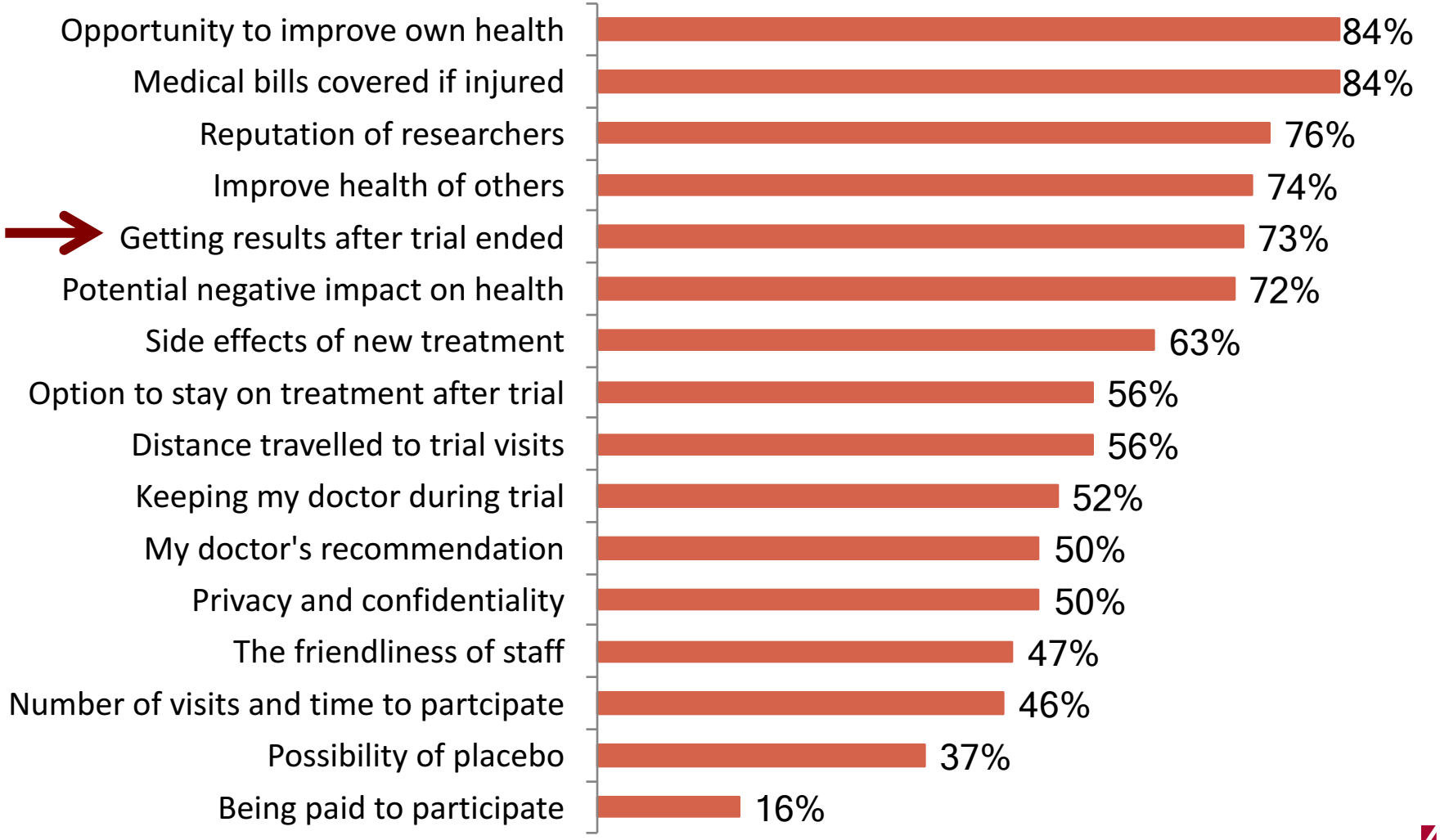
    http://www.phrma.org/sites/default/files/pdf/PhRMAPrinciplesForResponsibleClinicalTrialDataSharing.pdf

Rationale for returning aggregate results to participants: Patient/Participant Perspective in the U.S.

Patients / Study Volunteers	Research Professionals
• 90% want to know the results of their clinical trial[1] • 91% never hear back from study staff or sponsor[2] • If not informed, 68% would not participate in future trials[3]	• 98% of study staff would like to provide results to their volunteers[4] • 95% of research ethics board chairs strongly support (Canadian survey)[5]

1. Shalowitz and Miller. 2008. *PLoS Medicine.* 5:714-720.
2. Getz et al. 2012. *Expert Rev. Clin. Pharmacol.* 5(2):149-156.
3. Sood et al. 2009. *Mayo Clinic Proceedings.* 84(3):243-247.
4. Dixon-Woods et al. 2006. *BMJ.* 332:206-210.
5. MacNeil and Fernandez. 2007. *J Med Ethics.* 33:549-553.

Factors important to participants when considering research



patientslikeme®

Participants prefer frequent updates

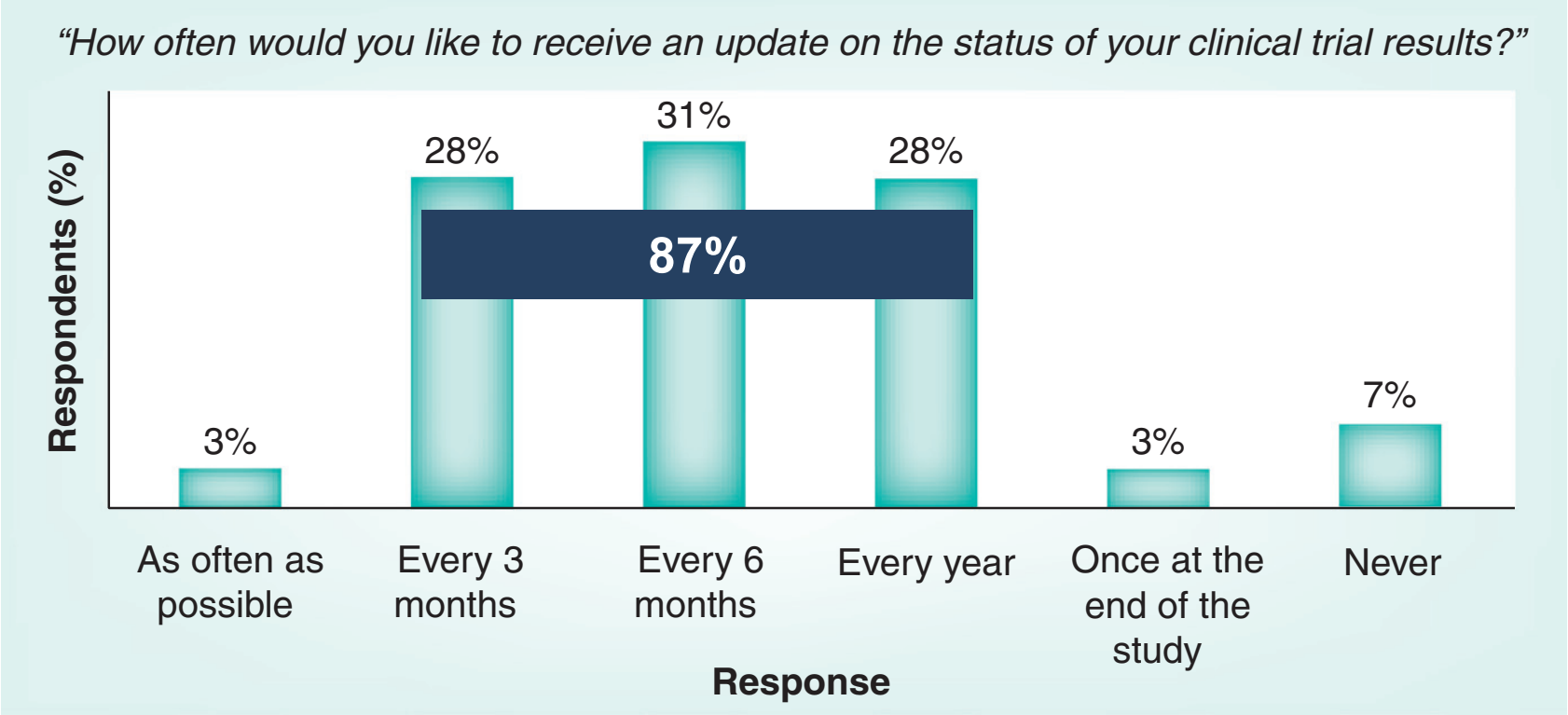


Figure 1. Volunteer preferences for update frequency (n = 29 Lyrica study volunteers).

Getz K et al. 2012. Expert Rev. Clin. Pharmacol. 5: 149-156

Data supported that understanding improved

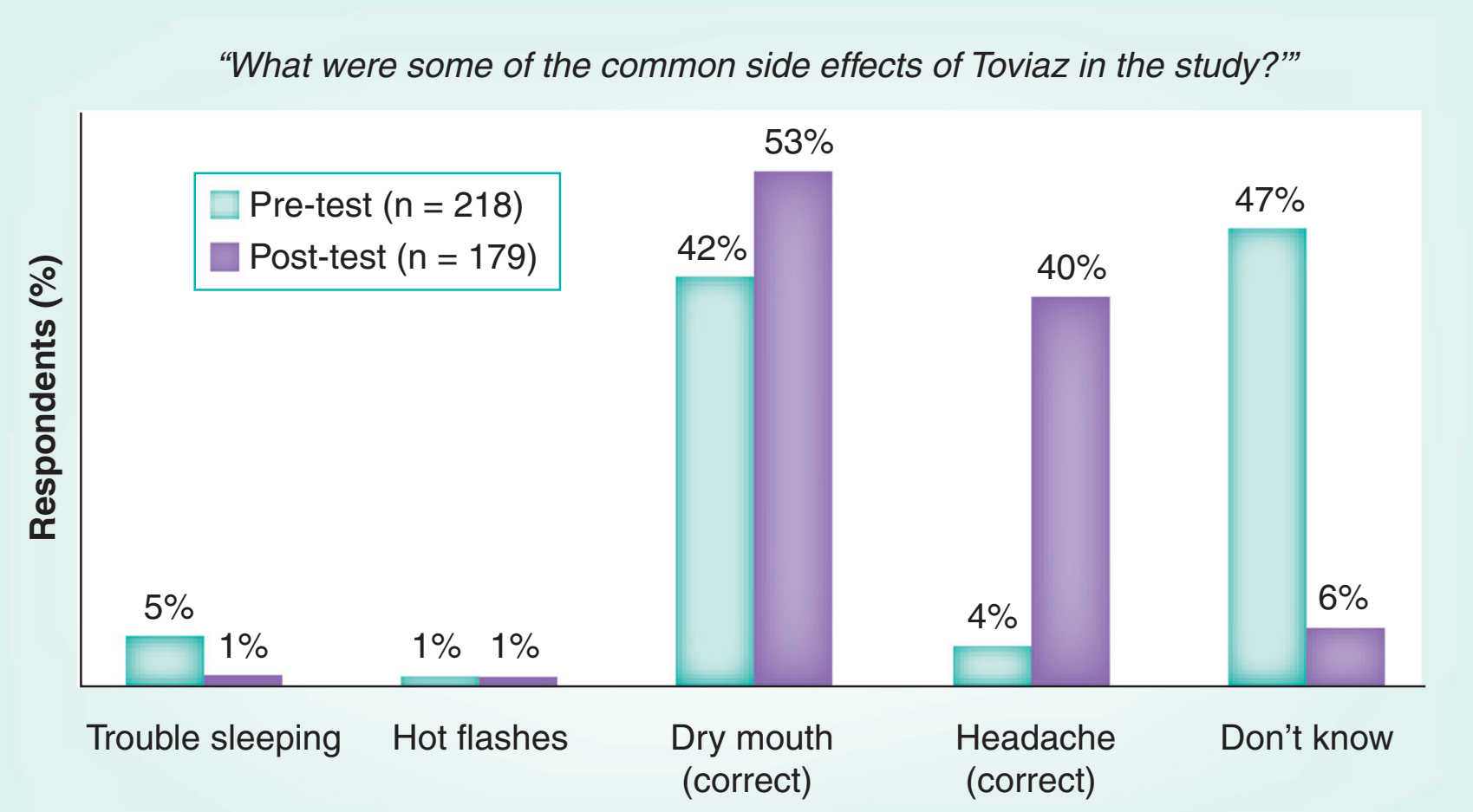


Figure 3. Volunteer pre- and post-test comprehension of Toviaz side effects.

Getz K et al. 2012. Expert Rev. Clin. Pharmacol. 5: 149-156

Goals

- **Develop standards and best practices.**
- **Ensure principles are respectful of global cultural expectations.**
- **Address perceived barriers** to widespread implementation.

Rationale:

Returning results allows sponsors and investigators to recognize and honor the essential contributions and volunteerism of clinical trial participants

Expectations of academic, industry, not-for-profit sponsors similar

Returning results is a key aspect of **improving transparency** and **increasing public trust**

Scope:

Communication and dissemination of ***summary*** research results

MRCT Center Deliverables

- Return of Results Guidance Document

  http://mrctcenter.org/wp-content/uploads/2016/07/2016-07-13-MRCT-Return-of-Results-Guidance-Document-Version-2.1.pdf

  – Process flow of returning results
  – Methods for returning results
  – Content of results summaries
  – Health and numerical literacy

- Return of Results Toolkit

  http://mrctcenter.org/wp-content/uploads/2016/07/2016-07-13-MRCT-Return-of-Results-Toolkit-Version-2.2.pdf

  – Templates for communicating study results
  – Neutral language guidance
  – Endpoint table

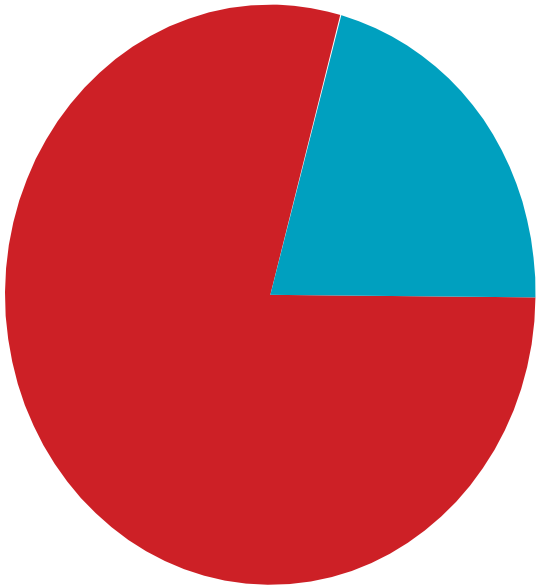
EU Clinical Trials Regulation 536/2014

http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2014.158.01.0001.01.ENG

1. Clinical trial identification
2. Name and contact details of the sponsor;
3. Main objectives
4. Population of subjects (include eligibility criteria);
5. Investigational medicinal products used;
6. Description of adverse reactions and frequency;
7. Overall results of the clinical trials;
8. Comments on the outcome of the clinical trial;
9. Indication if follow up clinical trials are foreseen;
10. Where where additional information could be found.

Fair and balanced
Not biased nor promotional

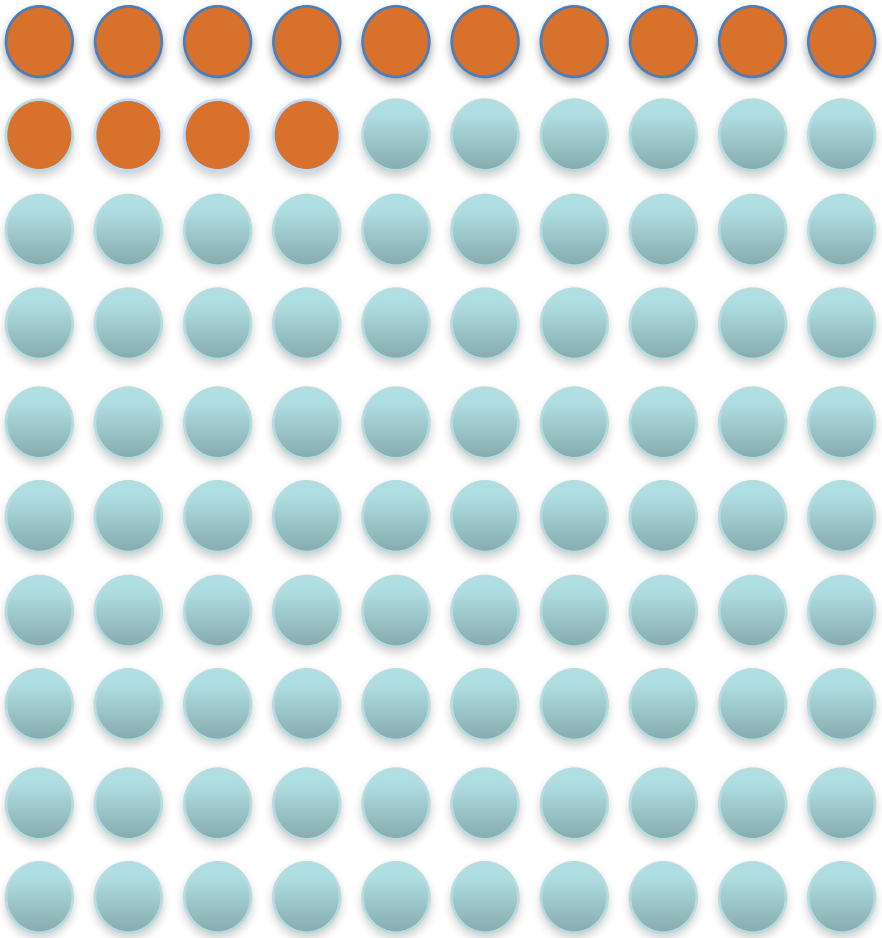
Example



In 20% (or 1 in 5) of patients, tumors got at least 30% smaller

In 80% (or 4 in 5) of patients, tumors did not get at least 30% smaller

Example

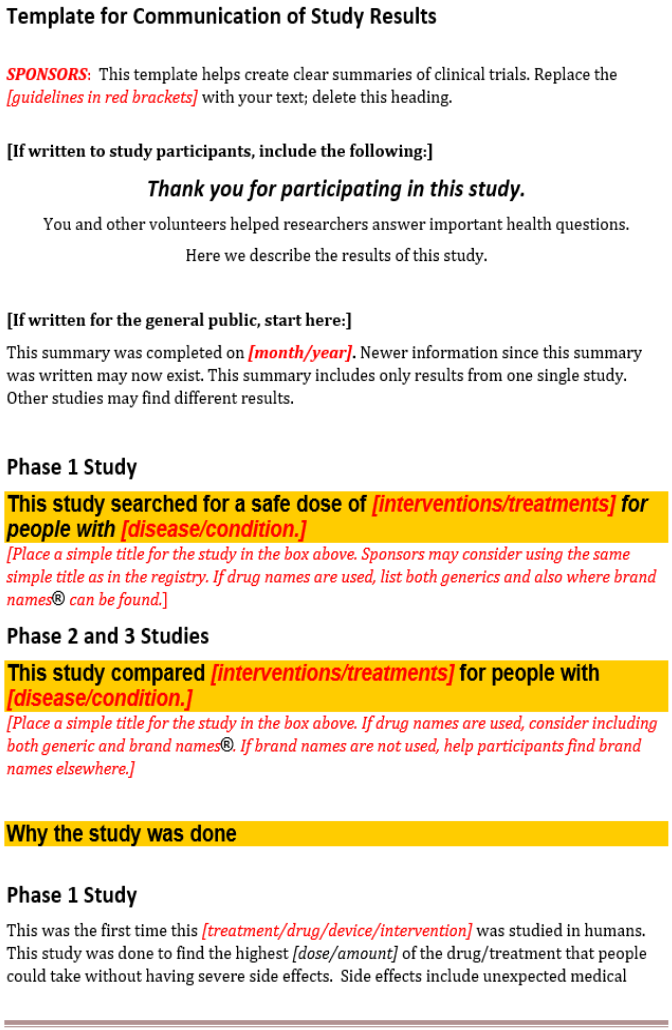


14%

Or

About 1 in 7

Return of results templates



Template for Communication of Study Results

SPONSORS: This template helps create clear summaries of clinical trials. Replace the *[guidelines in red brackets]* with your text; delete this heading.

[If written to study participants, include the following:]

Thank you for participating in this study.

You and other volunteers helped researchers answer important health questions.

Here we describe the results of this study.

[If written for the general public, start here:]

This summary was completed on ***[month/year]***. Newer information since this summary was written may now exist. This summary includes only results from one single study. Other studies may find different results.

Phase 1 Study

This study searched for a safe dose of *[interventions/treatments]* for people with *[disease/condition.]*

[Place a simple title for the study in the box above. Sponsors may consider using the same simple title as in the registry. If drug names are used, list both generics and also where brand names® can be found.]

Phase 2 and 3 Studies

This study compared *[interventions/treatments]* for people with *[disease/condition.]*

[Place a simple title for the study in the box above. If drug names are used, consider including both generic and brand names®. If brand names are not used, help participants find brand names elsewhere.]

Why the study was done

Phase 1 Study

This was the first time this *[treatment/drug/device/intervention]* was studied in humans. This study was done to find the highest *[dose/amount]* of the drug/treatment that people could take without having severe side effects. Side effects include unexpected medical

- Located in MRCT Return of Results Toolkit
- Templates for Phase 1, Phases 2 and 3, and Trials ending early
- Includes examples
- Incorporates principles of Health Literacy and Numeracy

Neutral Language Guide

Language to avoid	**Language to consider**
This study proved…	This study found that... This does not mean everyone in that group had these results.
This study proved that using <drug A> to prevent <disease/condition> is effective.	This study found that people with <disease/condition> who got <drug A> had <primary endpoint>.
This means that <Drug A> is better than <Drug B>.	In this study, people who got <drug A> had more <study endpoint> than some people who got <Drug B> with the same health conditions.
<Drug A> works better than <Drug B>, but some people didn't tolerate it as well.	In this study, more people received or were treated with <study endpoint> with <Drug A>. They also had more side effects that interfered with their daily lives, like <list specific adverse events>.

Similar principles have been suggested by TransCelerate BioPharma:
Recommendations for Drafting Non-Promotional Lay Summaries of Clinical Trial Results

Endpoint Descriptions and Examples

- Toolkit lists common clinical trial endpoints
  - Definition with a general description
  - Examples of simple, plain language for research results summaries
- Endpoints included:

- Composite Endpoint
- Dose Escalation
- Exploratory Biomarker
- Mortality / Overall Survival
- Morbidity
- Non-Inferiority
- Patient-Reported Outcomes
- Prevention / Incidence
- Progression-Free Survival
- Surrogate Endpoint

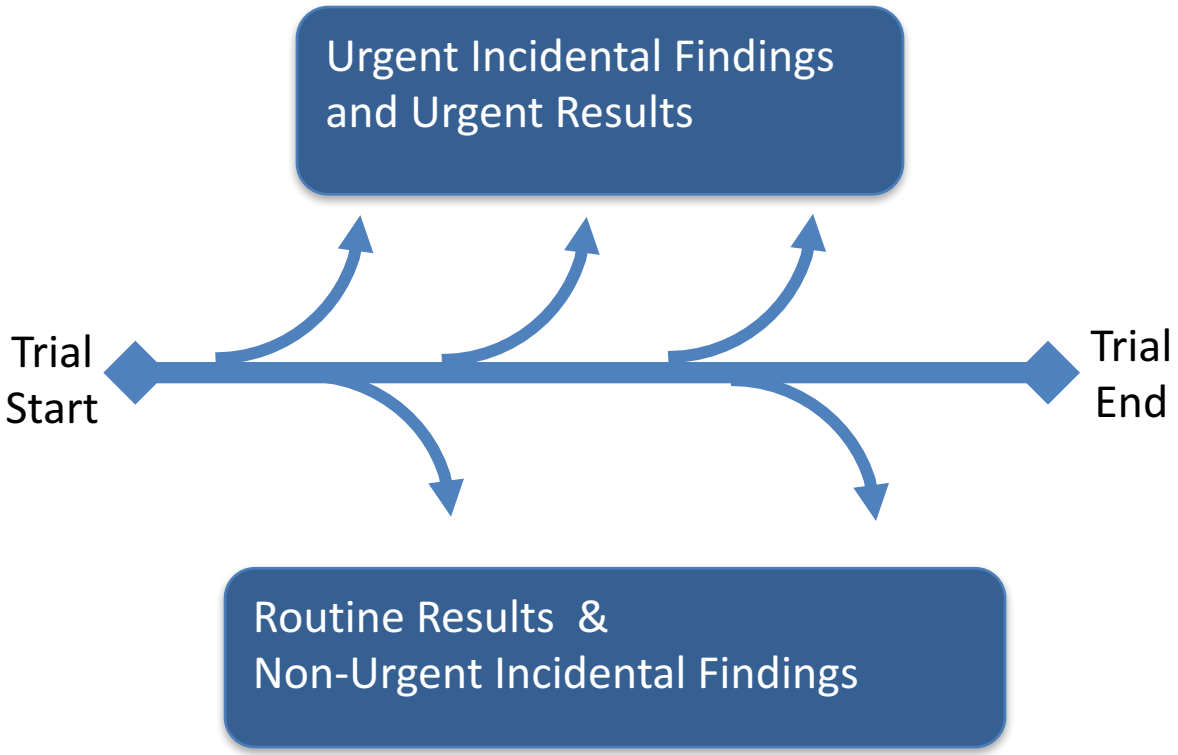
Special Considerations

- Timing
- Trials that close early
    - Futility
    - Efficacy
    - Safety
    - Low accrual
- Observational, long-term follow-up, and extension studies
- Notification of results to a 3rd party designated by the participant
- Vulnerable populations
- Legally Authorized Representatives and other designated parties
- Assent for Return of Results to Children
- Complexities of the Global Context

What about me?

Individual Return of Results (IRR)

Data Types



Individual Study Results & Study arm

Exploratory Results

Aggregate Results

Spectrum of results to return to participants:

- Aggregate research results
- Assignment to and results of study arm
- Routine clinical results performed in the course of research
  - Analytic validity: approved laboratories and processes only?
  - What is global standard for trustworthiness and does it matter?
  - Medical (e.g. clinical) and/or personal utility?
- Incidental findings discovered in the course of a clinical trial
  - Of potential clinical significance or actionable
  - Of uncertain significance (and does the patient have a right to know?)
- Research results
  - Of unknown significance
  - Particular reference to genetic/genomic results
- Other results

Easiest

Hardest

And if one commits to return, who has that obligation and for how long?

Principles and Approach: Return of Individual Study Results (1)

1. Providing individual research results responds to the **expressed interests and expectations** of many clinical trial participants that their results be communicated to them.

2. Considerations pertaining to the return of individual research results to clinical trial participants should be integrated into the clinical trial and **proactively planned**.

3. The **informed consent process** should include information about the sponsor's intention regarding the return of research results and allow for discussion of participant's preferences to receive these results.

4. The plan for the return of individual research results should be **reviewed by an independent ethics body** overseeing the research, to ensure the rights and welfare of research participants are protected.

Principles and Approach (cont.)

5. If results are offered, participants should be **able to choose** whether or not to receive their individual research results.

6. Sponsors and investigators have an obligation to return individual research results responsibly, taking into account **medical significance, analytical validity and personal utility**.

7. Individual research results should be returned in ways and at times that **maintain the integrity of the research**, insofar as the safety and welfare of the research participants are not at risk.

8. The purpose of research is **not clinical care**, and return of individual research results cannot substitute for appropriate clinical care and advice.

9. Return of individual research results should be planned and executed in **compliance** with institutional policies and local, regional, and national laws and regulations.

A look forward

- Research participants want to receive information about the clinical trial to which they participated. There is no reason not to do so. Return of results should become the expectation and practice in clinical research.

- Logistics, content, process and standard methodologies and approaches for return of aggregate results have been delineated and are designed for all sponsors and for all trials. Methods are efficient, roles and responsibilities are clear, multinational requirements have been incorporated.

- Principles for return of individual results have been outlined and each situation demands specific consideration balancing analytic validity, medical significance, personal utility, and the integrity of the research, inter alia.

- This is resource intensive. Funding for return of results should be provided as an anticipated component of human subjects research. Resource implications following return remain unclear.

- Harmonization and consistency are critically important.

Comments, questions and discussion
Thank you

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