DIA 2019
GLOBAL ANNUAL MEETING
SAN DIEGO | JUNE 23-27

Voice of the Patient – Returning Aggregate Results through Plain Language Summaries

Barbara E. Bierer, MD

Professor of Medicine, Harvard Medical School

Faculty Co-Director, the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital & Harvard

Program Director of the Regulatory Foundations, Law and Ethics Program Harvard Catalyst | the Harvard Clinical and Translational Science Center

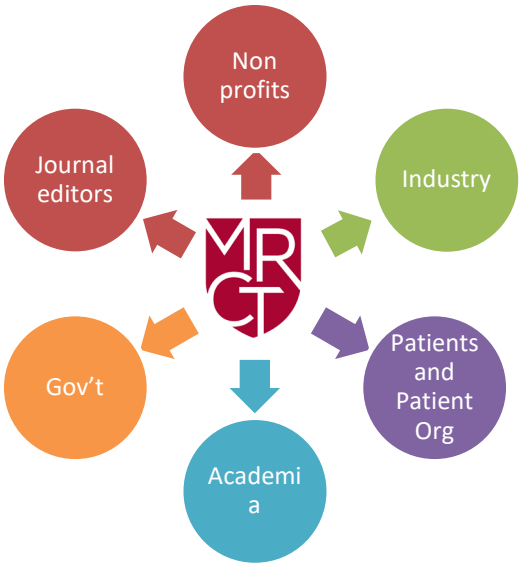
bbierer@bwh.harvard.edu

Disclaimer:

- The opinions contained herein are those of the authors and are not intended to represent the position of Brigham and Women's Hospital or Harvard University.
- The MRCT Center is supported by voluntary contributions from foundations, corporations, international organizations, academic institutions and government entities (see www.MRCTCenter.org) and well as by grants.
- We are committed to autonomy in our research and to transparency in our relationships. The MRCT Center—and its directors—retain responsibility and final control of the content of any products, results and deliverables.
- I have no personal conflicts of interests related to the content of this presentation or discussion.

Our Mission

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



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

Goals

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

Rationale:

Returning results is a key aspect of **improving transparency** and **increasing public trust,** and fundamentally, recognizes and honors the contributions of clinical trial participants.

Scope:

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

Similar expectations of academic, industry, not-for-profit sponsors

Return of results: MRCT Center workgroup

Academic/Medical Center:
Carmen Aldinger – MRCT Center
Mark Barnes - Ropes & Gray, LLP / MRCT Center
Barbara Bierer - Brigham & Women's Hospital/MRCT
Assunta De Rienzo - Brigham & Women's Hospital
Alla Digilova – MRCT Center
Rebecca H Li – MRCT Center
Holly Fernandez Lynch - Harvard Law School
Pearl O'Rourke - Partners HealthCare
Nesri Padayatchi - Univ. of KwaZulu-Natal
Amish Shah - MRCT / Harvard Law School
Zachary Shapiro – MRCT/ Harvard Law School
Patrick Taylor - Children's Hospital, Boston
Sarah White - Partners HealthCare
Elizabeth Witte – Harvard Medical School
Sabune Winkler – Harvard Medical School

Industry/Trade Associations:
Salvatore Alesci – PhRMA
Richard Bergstroem – EFPIA
Elizabeth Garofalo - Novartis Pharma AG
Laura Hagan - Merck Serano
Sandra Hayes-Licitra – Johnson & Johnson
Angelika Joos – Merck Sharp & Dohme
Barbara Kress – Merck
Sarah Larson – Biogen Idec
David Leventhal – Pfizer
Craig Lipset – Pfizer
Laurie Myers – Merck (CO-CHAIR)
Alex Nasr – AbbVie
Mary Ann Plummer – J&J (prior CO-CHAIR)
Sandy Prucka – Lilly
Ben Rotz – Lilly
Beth Roxland – Johnson & Johnson
Jessica Scott – GSK

Institutional Review Boards:
David Forster - WIRB Copernicus Group
Mary Oster – NE IRB
Jim Saunders - NE IRB

Nonprofit:
Behtash Bahador – CISCRP
Phyllis Frosst - Personalized Medicine Coalition
Zach Hallinan – CISCRP
Marc Wilenzick – International AIDS Vaccine Initiative

Patient Advocates:
Nicola Bedlington – European Patients Forum
Deborah Collyar – PAIR (CO-CHAIR)
David Haerry – European AIDS Treatment Group
Cheryl Jernigan - Susan G. Komen
Yann LeCam – EURODIS
Marcello Losso - HIV RAMOS
Jane Perlmutter – Gemini Group

Research/Consulting Firms:
Barbara Godlew - The FAIRE Company, LLC
Pierre Gervais - QT Research
Paulo Lacativa - CCBR Clinical Research
David Walling – Collaborative NeuroScience

Return of Aggregate Results — Principles

Return of Aggregate Results to Participants Principles

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) Return of Results workgroup developed a practical guidance document for *all* sponsors (e.g., industry, non-profit, government, academic) to address in detail key challenges in returning results and potential solutions. The purpose of creating and disseminating general clinical trial result summaries to clinical trial participants is to ensure that study participants are informed about the trial results, that they know that their participation is and has been respected and appreciated, and that they understand the value of their contribution to science and public health. The foundation of returning aggregate results to participants has been summarized in 8 principles:

1. **Participants or their designees should be the recipients of research results summaries.**
2. **Returning results to trial participants respects their volunteerism and their partnership in research; we recommend, therefore, that sponsors offer to provide results to study participants for *all* clinical studies.**

http://mrctcenter.org/projects/return-of-results-to-participants/

MRCT Center Deliverables

- Return of Results Guidance Document
- http://mrctcenter.org/wp-content/uploads/2017/03/2017-03-20-MRCT-Return-of-Aggregate-Results-Guidance-Document-3.0.pdf
  - Process flow
  - Methods
  - Content of results summaries
  - Health and numerical literacy
- Return of Results Toolkit
- http://mrctcenter.org/wp-content/uploads/2017/03/2017-03-13-MRCT-Return-of-Aggregate-Results-Toolkit-3.0.pdf
  - Templates for communicating study results
  - Neutral language guidance
  - Endpoint table
  - Useful checklists

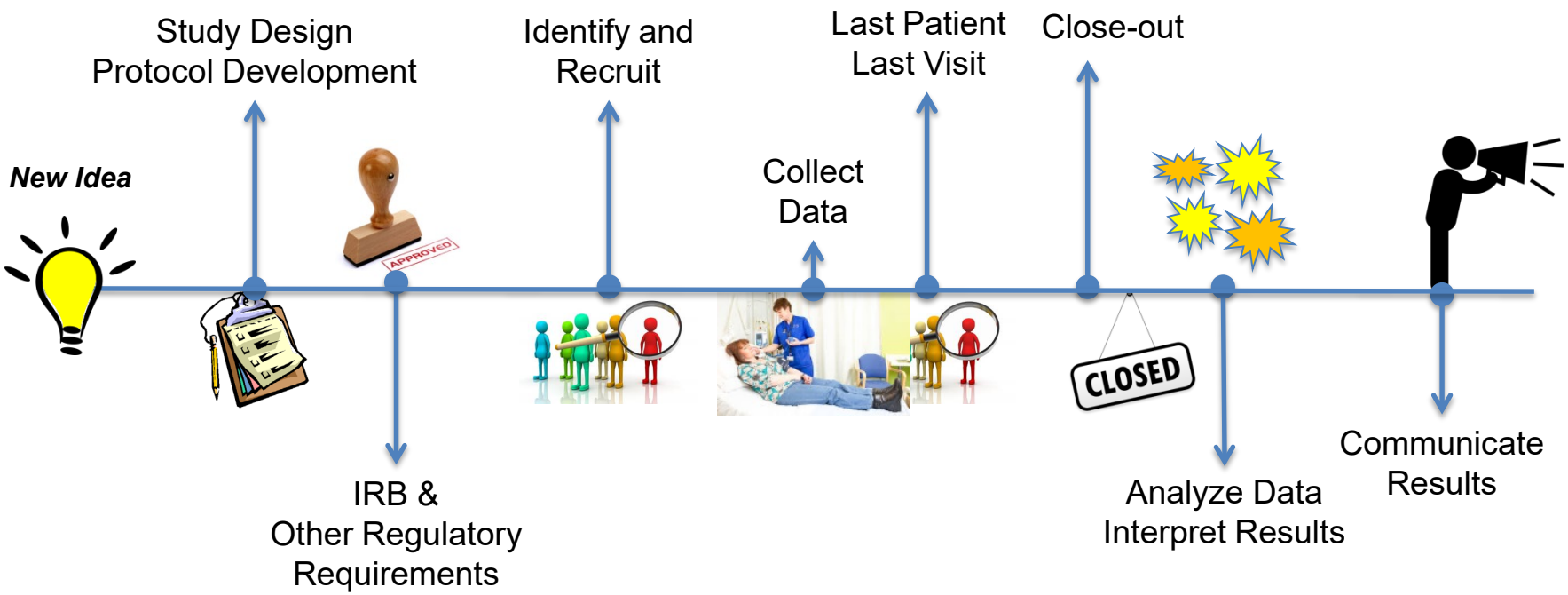
Phasing of return of results

Pre-Study preparation

Protocol Development

During study conduct

When study ends



- Organizational Preparation
- Level, timing, methodologies

- Address whether, what, when and how to return results
- IRB review and approval

- Introduce PLS
- Manage expectations
- Engage and communicate

- Prepare summary, aligned with IC, CSR, Manuscript
- Web site or individual outreach through PIs/sites
- Follow up

Methods of returning aggregate results

- **To Whom:**
  - All participants who have been enrolled and agreed to receive results

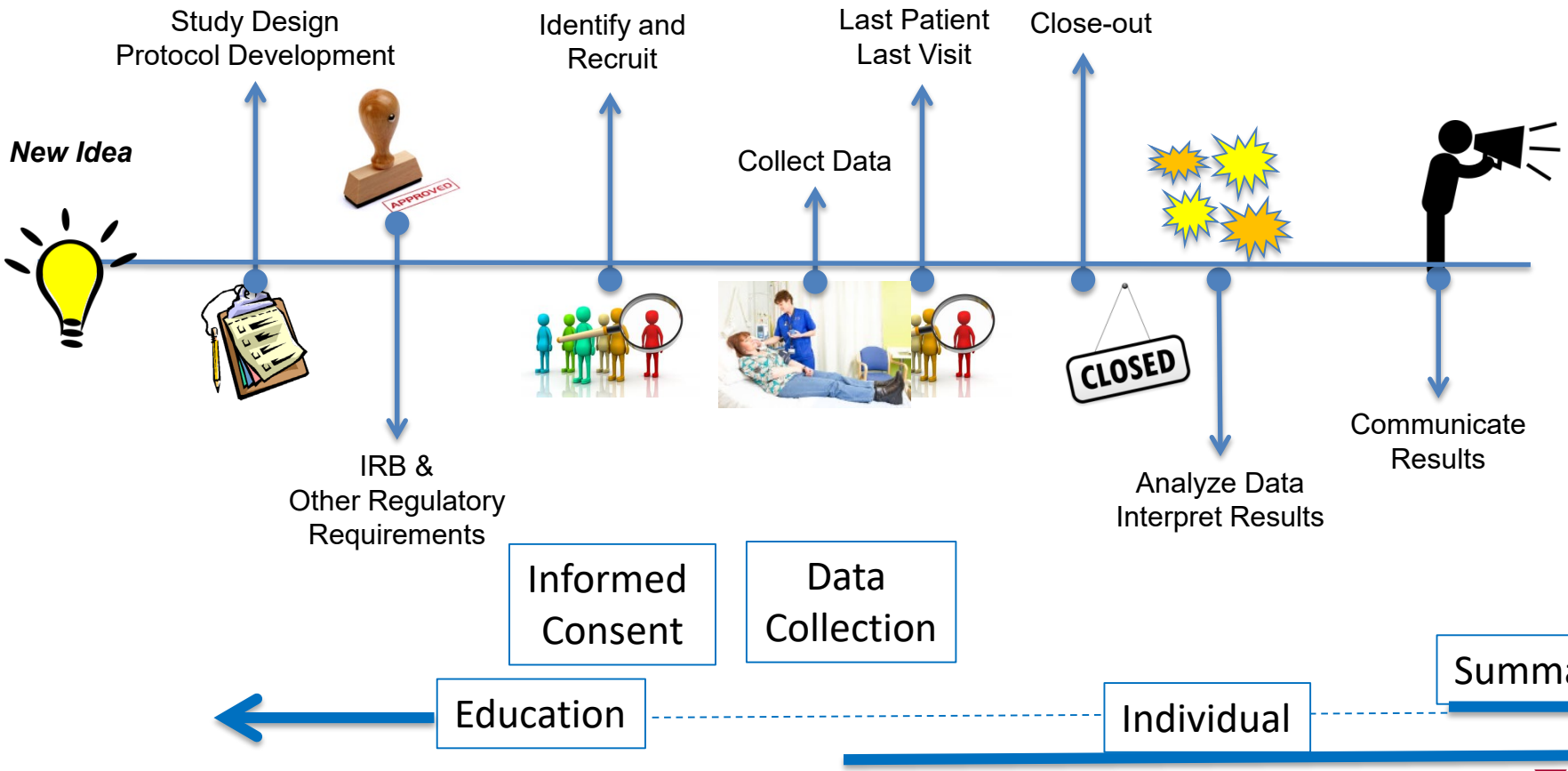
- **Several Methods of Return:**
  - Internet based methods (flexible, cost-effective, current, security may be important)
  - Interactive methods (e.g., face-to-face meeting(s), telephone call(s), two-way online meeting(s), dynamic email exchange, etc.)
  - One-way communications (e.g. video summary, automated phone message, printed materials)
- **Timing:**
  - Within 1 year of completion or 'end of study' or publication (EMA, one year from LPLV)

Participant Clinical Trial Results Summaries - Process

- Write in unbiased and non-promotional language
- Obtain review by independent, objective editor(s) and patient rep(s)
- Incorporate the patient's voice into the summary
- Translate into languages consistent with translations of informed consent
- Make available an individual from the study site or neutral informed third party to answer questions for participants
- Make provisions for vulnerable populations and other instances
- Consider as to whether to inform, and whom to inform, in the event of a participant's death
- Use plain language (sixth to eight grade reading level)
- Apply health and numeracy principles

Health Literate Communications: Summary is only one example

- Returning results in plain language allows for investigators and sponsors to honor the essential contributions and voluntarism of study participants



A systems approach

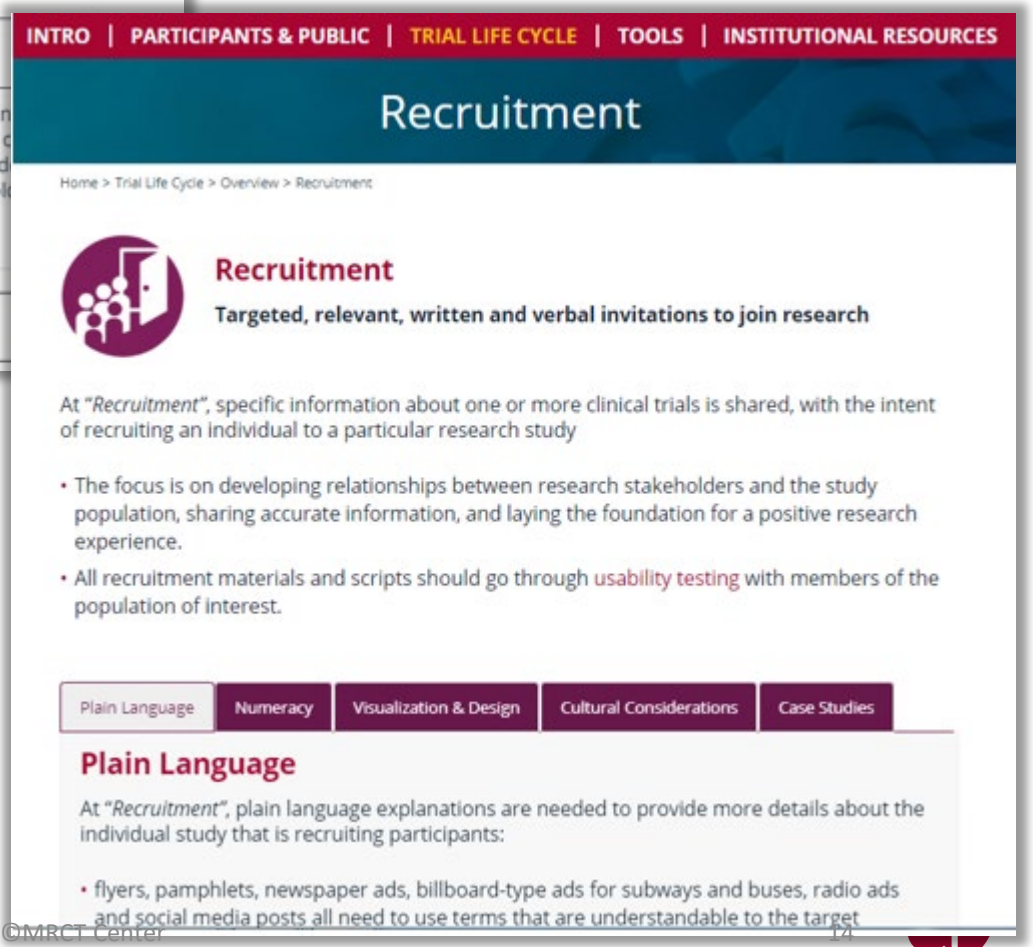
- Corporate and individual commitment to communication and, I would argue, participant engagement throughout the process
- Trials engineered to deliver results that are important to the participants and patients and their loved ones, and to society
- Process—like any other—that requires dissection, analysis, and reengineering
  - Plain language: terms, use and meaning in relevant culture
  - Design, visualization, numeracy
  - Education and training of all involved
  - Commitment to provide the resources required
  - Tools and resources to simplify where possible
  - Iterative quality improvement
  - Incentive structures for desired behaviors
  - Oversight, metrics, tracking, and transparency built as part of process


HEALTH LITERACY HOME | MRCT CENTER HEALTH LITERACY PROJECT | CONTACT
MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD
HEALTH LITERACY IN CLINICAL RESEARCH
ABOUT | PARTICIPANTS & PUBLIC | TRIAL LIFE CYCLE | TOOLS | INSTITUTIONAL RESOURCES
COMING SOON!
MRCT Center endorses the use of health literacy practices when developing clinical research information
CLINICAL TRIAL LIFECYCLE
DISCOVERY
RECRUITMENT
CONSENT
ON STUDY
END OF STUDY


INTRO | PARTICIPANTS & PUBLIC | TRIAL LIFE CYCLE | TOOLS | INSTITUTIONAL RESOURCES
Clinical Trial Life Cycle Overview
Home > Trial Life Cycle > Overview
Health literacy supports the participant through these 5 steps of the clinical trial journey.
DISCOVERY
Public awareness of, education about, and access to clinical research
RECRUITMENT
Targeted, relevant, written and verbal invitations to join research
CONSENT
Clear written and verbal conversations about informed consent to research participation
ON STUDY
Clear information about ongoing research procedures, data collection and reporting
END OF STUDY
Plain language summaries, results reports, and research publications

6/23/19


INTRO | PARTICIPANTS & PUBLIC | TRIAL LIFE CYCLE | TOOLS | INSTITUTIONAL RESOURCES
Principles of Health Literacy in Clinical Research
Home > Intro > Principles of Health Literacy in Clinical Research
These principles of health literacy provide a basis from which to adopt and integrate health literacy practices into clinical research. They are intended to support clinical research stakeholders, including sponsors and funders, investigators and study teams, and Institutional Review Boards in their communications with potential, enrolled, and past participants. Additional information on how to take action can be found here.
Principles of Health Literacy in Clinical Research
1
– Create clear clinical research communications for the target audience.
Clinical research and medical concepts can be difficult to understan
regardless of a person's educational background. Yet, individuals c
only benefit from and use information that they understand. In ord
communicate in ways that promote participant autonomy stakehol
must allow sufficient time to develop, test, modify, and confirm
understanding of health-literate research communications.
2
+ Recognize that applying health literacy principles is a shared responsibility of all clinical research stakeholders.


INTRO | PARTICIPANTS & PUBLIC | TRIAL LIFE CYCLE | TOOLS | INSTITUTIONAL RESOURCES
Recruitment
Home > Trial Life Cycle > Overview > Recruitment
Recruitment
Targeted, relevant, written and verbal invitations to join research
At "Recruitment", specific information about one or more clinical trials is shared, with the intent of recruiting an individual to a particular research study
• The focus is on developing relationships between research stakeholders and the study population, sharing accurate information, and laying the foundation for a positive research experience.
• All recruitment materials and scripts should go through usability testing with members of the population of interest.
Plain Language
Numeracy
Visualization & Design
Cultural Considerations
Case Studies
Plain Language
At "Recruitment", plain language explanations are needed to provide more details about the individual study that is recruiting participants:
• flyers, pamphlets, newspaper ads, billboard-type ads for subways and buses, radio ads and social media posts all need to use terms that are understandable to the target

Plain language is essential but not sufficient

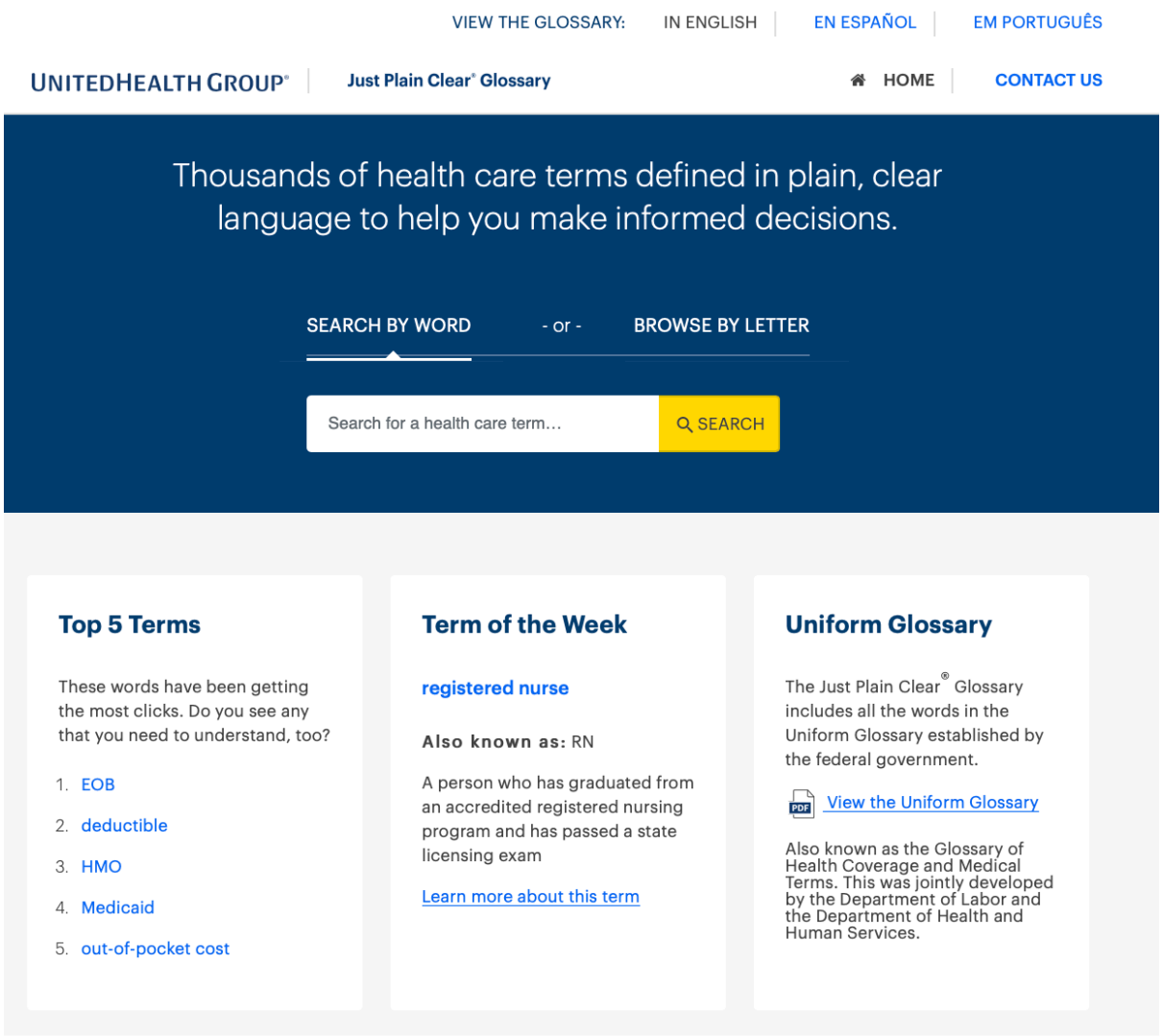
United Health Group

www.justplainclear.com

English

Spanish

Portuguese



And no need to reinvent the wheel

Less of this

Inje[illegible]on Guide for Study Drug or Placebo
[illegible]Days 1-5) and Panel B (Days 6-10)

[illegible]cebo Injection

[illegible] 1 mL of study drug or matching placebo. The volume removed from the vial determines the dose administered. The study staff will tell you how much to inject from each vial.

Important Information

- **Refrigerate kit box: Do Not Freeze.**
- **Vials should only be used one time.**
- **Only uncap the vials that you are preparing to inject.**
- **Only inject the volume instructed by study staff. Do not inject the entire contents of either vial.**
- **Always use a new site-provided syringe/needle for each injection.**

Step 1: Prepare Vials

- Remove 2 vials from the kit box and return kit box to the refrigerator.
- Allow vials to come to room temperature for at least 15 minutes.
- Vials should then be inverted a minimum of three times.
- Wash your hands with soap and water.

Step 2: Prepare Syringe

- Remove the cap from one of the vials and wipe the top of the vial with an alcohol swab.
- Open a new syringe and needle.
- By pulling back on the plunger, draw air into the syringe up to the mark of the volume to be injected and then slowly inject the air into the vial.
- Keep the needle in the vial and turn the vial upside down. Make sure that the needle tip is well below the surface of the liquid in the vial.
- With the tip of the needle in the liquid, pull slowly back on the plunger to get the right volume into the syringe.
- Check the syringe for air bubbles. If there are bubbles, hold both the vial and syringe in one hand, and tap the syringe with your other hand. The bubbles will float to the top. Push the bubbles back into the vial, then pull back to get the right volume of study drug/placebo.
- When there are no bubbles, take the syringe out of the vial. Put the syringe down carefully so the needle does not touch anything.

Step 3: Injection

- Clean an injection site that is about 2-3 inches away from your belly button on your abdomen with a new alcohol swab. Let dry thoroughly.
- Hold the syringe in the hand that you will use to inject study drug. Use the other hand to pinch a fold of skin at the cleaned injection site.
- Use the injection technique shown to you by the study staff.
- After the needle is inserted and while pinching the skin, pull the plunger back slightly. If no blood appears, steadily push the plunger all the way down until the study drug is injected. **Note:** If blood enters the syringe, remove the syringe, clean and prepare another spot on your abdomen and using the same syringe/needle, inject the product.
- Leave the syringe in place for about 6 seconds after injecting (the pinch may be released) and remove. After the needle is removed, you can apply light pressure with clean gauze or cotton ball but, do not rub the site.
- Place used syringe/needle (do not re-cap the syringe) in a sharps disposal container provided by the site.

More like this

How to give yourself the study medicine

Panel A (Days 1-5) and Panel B (Days 6-10)

Study medicine

Each bottle holds 1 mL of active drug or placebo.

The study staff will tell you how much medicine to use each time (this is called your dose). Only give yourself the dose the study staff told you. Do not use all the medicine in the bottle.

The study staff will tell you how much to inject from each bottle.

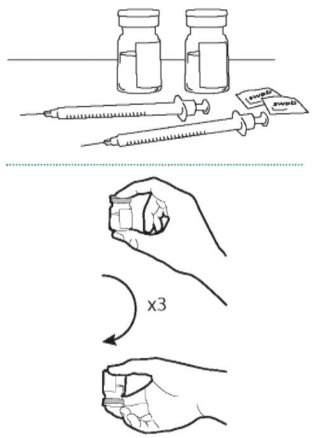
Important safety information

- Refrigerate the kit box – Do not freeze.
- Only use each bottle 1 time.
- Use a new syringe and needle each time.
- Only uncap the bottles when you use them.

Steps to give yourself the study medicine

Get ready

1. Gather your supplies:
   - 2 syringes
   - 2 bottles of medicine
   - 2 alcohol swabs
2. Take out 2 bottles from the kit box and put the kit box back in the refrigerator.
   - Let the bottles sit on the counter for at least 15 minutes to get to room temperature.
   - Turn the bottles upside down and then right side up at least 3 times.
3. Wash your hands with soap and water.



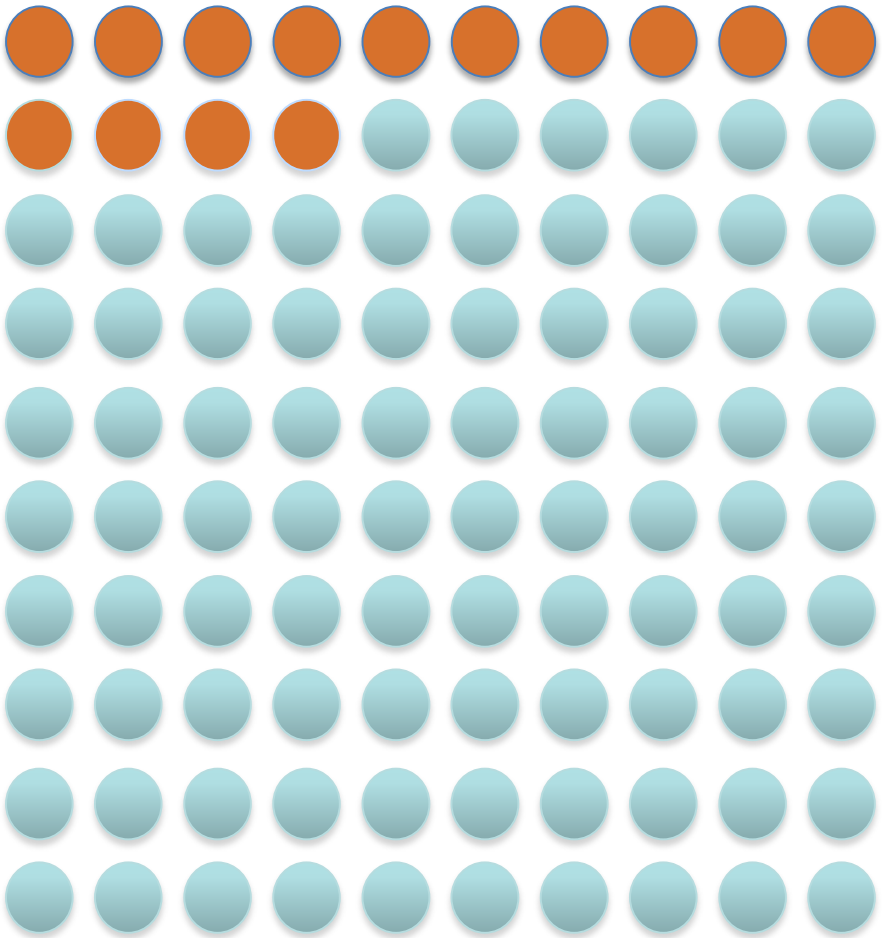
Merck & Co., Inc. example with input from Health Literacy Media

Numeracy Principles: Implementation

- Less is more – how critical are the numbers?
- Provide fewer choices – choose strategically which options to show
- Do the math – calculate or convert numbers, readers are unlikely to conduct even basic math
- Give numbers meaning and context – explain what numbers mean
- Use common terms and imaginable formats
- Use visuals
- Use whole numbers
- Use consistent denominators and timeframe
- Natural frequencies vs percentages – "1 out of 10" may be more useful than percentages because it gives context and imagery

From: "Health Literacy Missouri Best Practices for Numeracy," cited in *MRCT Return of Results Toolkit. (2016),* Appendix 4

Example

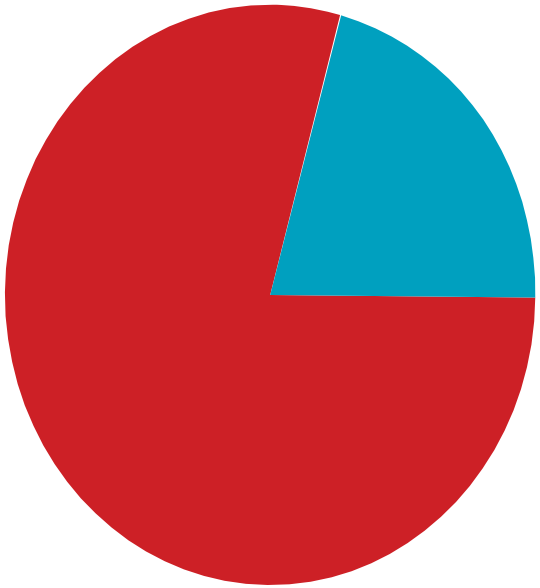


14%

Or

About 1 in 7

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

EU Clinical Trials Regulation 536/2014

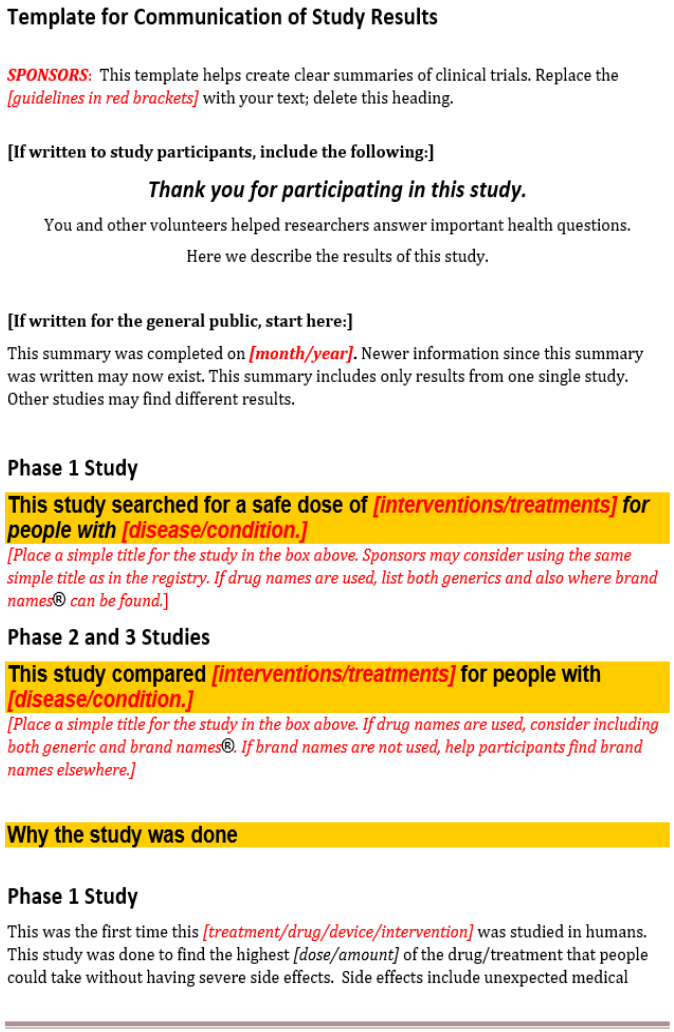
http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0536&from=EN

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

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

http://mrctcenter.org/wp-content/uploads/2017/03/2017-03-13-MRCT-Return-of-Aggregate-Results-Toolkit-3.0.pdf

Participant Clinical Trial Results Summaries - Content

Content	Example
Why the study was done (cont.)	**For clinical trials that stop early:** This study was stopped earlier than planned. This can happen for many reasons. This study stopped early because [*add one of the possible statements below, or your own **simple explanation**, to this sentence. If there is more than one reason, list all that apply.]* … too many participants had side effects (see below). … *[drug generic name]* did not improve patient results. … *[drug generic name]* was not as effective as expected *[comparator]*. … *[drug generic name]* was much more effective than expected. *[if applicable, add]* The study was stopped so all participants had a chance to take *[drug generic name]*. … not enough people joined the study. *[Include a statement about what will happen next. …* • *For side effects ..* • *For efficacy …* • *For futility …* • *Low accrual: ….]*

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> 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>.

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:

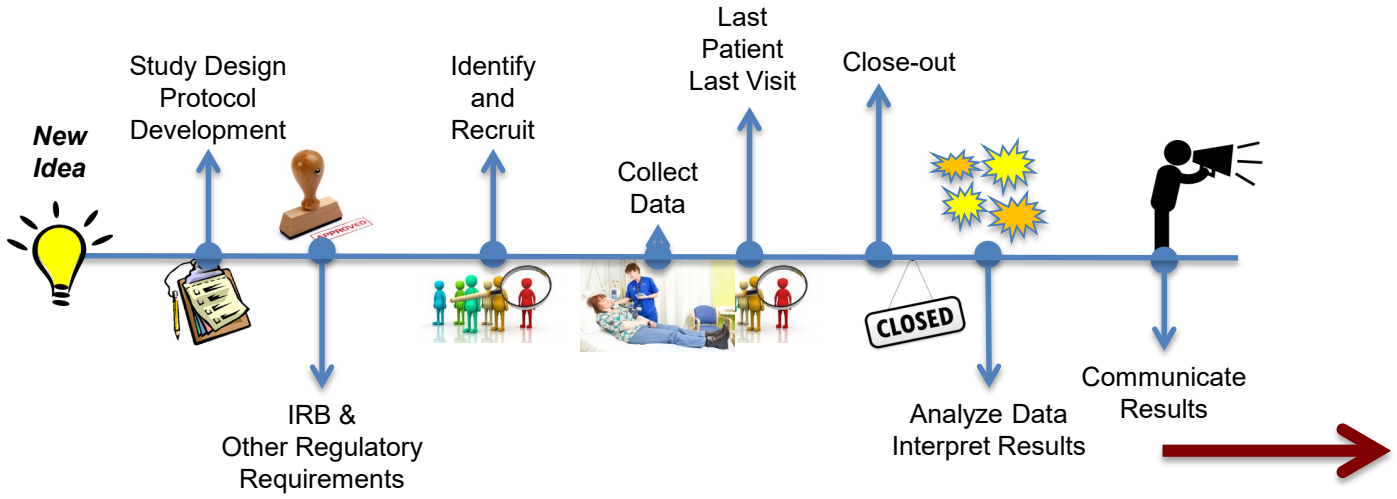
  - Composite Endpoint
  - Dose Escalation
  - Exploratory Biomarker
  - Mortality / Overall Survival
  - Morbidity
  - Non-Inferiority
  - Patient-Reported Outcomes
  - Prevention / Incidence
  - Progression-Free Survival
  - Surrogate Endpoint

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

Role of IRB / REC

- There is current no international agreement on the obligations and level of involvement of IRBs/RECs with respect to return of aggregate results.



- Results communicated after study closed: no requirement of IRB to review.
- If planned return described in study protocol, IRB/REC should review and approve overall plan to return, but not specific content.
- If plans change, or communicate during study, IRB/REC should review

Return of aggregate results

- Incorporated into the HRA (UK)
- Incorporated into the EMA guidelines
- Drafted FDA guidance
- Would be honored to work with other regulatory agencies, sponsors, and DIA

Harmonization

Global regulatory convergence

Comments, questions and discussion
Thank you

Barbara E. Bierer, MD
bbierer@bwh.harvard.edu