# *MRCT Return of Results Guidance Document*

MULTI-REGIONAL CLINICAL TRIALS

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

**Version 2.1**
**July 13, 2016**

## Research Results Summary Guidance Document

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## Contents

## Abbreviations

**BMJ**: British Medical Journal
**BIO**: Biotechnology Industry Organization
**CCI**: Commercially confidential information
**CLIA**: Clinical Laboratory Improvement Amendments
**CRO**: Clinical Research Organization
**CSR**: Clinical study report
**DIA:** Drug Information Association
**EC:** Ethics Committee
**EFPIA**: European Federation of Pharmaceutical Industries and Associations
**EMA**: European Medicines Agency
**EU CTR:** European Union Clinical Trials Register
**EudraCT**: European Clinical Trials Database
**FAQs**: Frequently asked questions
**FDA**: US Food and Drug Administration
**FDAAA:** Food and Drug Administration Amendments Act (FDAAA)
**FIP:** International Pharmaceutical Federation
**GCP**: Good Clinical Practice
**HHS:** US Health and Human Services
**HRA:** UK Health Research Authority
**IAPO**: International Alliance of Patients' Organizations
**IC**: Informed Consent
**ICF:** Informed Consent Forms
**ICMJE:** International Committee of Medical Journal Editors
**ICN**: International Council of Nurses
**IFPMA**: International Federation of Pharmaceutical Manufacturers and Associations
**IRB:** Institutional Review Board
**LAR**: legally authorized individuals
**LSLV**: last study last visit
**MRCT Center at Harvard**: Multi-Regional Clinical Trials Center at Harvard University
**NIH**: National Institutes of Health
**OHRP:** Office of Human Research Protections

**PRO:** Patient-Reported Outcomes

**QOL**: Quality of Life

**REC**: Research Ethics Committee

**ROR:** Return of Results

**RRS**: Research Results Summaries

**TEST Act**: US Trial and Experimental Studies Transparency Act

**PhRMA**: Pharmaceutical Research and Manufacturers of America

**PI**: Principal Investigator

**PLOS**: Public Library of Science

**UK**: United Kingdom

**US:** United States

**WMA**: World Medical Association

## Executive Summary

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) Return of Results workgroup is a multi-stakeholder group comprised of 53 members from industry, academia, patient advocacy and non-profit centers. We developed this resource at the request of sponsors who are currently developing processes for dissemination of non-technical summaries to trial participants. The mandate of this workgroup was to provide a practical guidance document for *all* sponsors (e.g., industry, non-profit, government, academic) that addresses in detail key challenges in returning results and potential solutions. The team initially convened in January 2014, culminated during an in-person meeting on September 17, 2014, and posted the MRCT ROR Guidance Document version 1.0 in March 2015. Version 2.0 and 2.1 are posted in response to questions and suggestions, and as a result of continued progress in the aggregate return of results.

Major changes in Version 2.1 include:

- Updates to IRB/REC section

Major changes in Version 2.0 include:

- Section on Challenges has been condensed
- Section on "Role and involvement of the IRB/REC" has been added
- Internet-based methods have been given more prominence as a method of delivery
- Section on "Responding to participant follow-up queries" has been added
- Section on how to address return of results in "Protocol development" has been shortened
- Section on "Participant end-of-study visit (last study visit)" has been expanded
- "Summary of Essential Elements for Inclusion in the RRS" has been updated
- Document has been edited and updated throughout, comments from TransCelerate BioPharma Inc. and others have been considered and integrated
- All sections have been numbered

This document describes the process flow for returning results to study participants, including:

- Pre-Study preparation
    - Organizational preparation, policies, processes
    - Establishing level/timing/delivery
    - Resource planning
- Protocol Development
    - Describing ROR as voluntary, including who what where when how
    - Informed consent form description
- During study conduct
    - Letter of appreciation
    - Last study visit of participant content
    - Intermittent engagement with participant thereafter
- When study ends
    - Content of summary document and health literacy principles
    - Adherence to global regulatory framework

It provides suggestions for the return of aggregate study results, including:

- To Whom:
    - All participants who have been enrolled and, if appropriate, randomized
- 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 earlier, and
    - Within 6 months if pediatric trial

Participant clinical trial summaries should be prepared that are:

- Unbiased and not promotional
- Reviewed by independent and objective editor(s) and patient representative(s)
- Written in plain language (sixth to eight grade reading level) and apply health literacy principles. Health and numeracy principles applied.
- Translated into additional languages consistent with translations of informed consent

- In addition, clinical trial summaries should make available:
    - An individual from the study site or neutral informed third party to answer questions for participants
    - Provisions for vulnerable populations and other instances
    - Considerations as to whether to, and whom to, inform in the event of a participant's death

Essential elements to include in Research Results Summaries:

- Thank you to study participants
- Simple title of the study
- Summary of results
- Disclaimer
- Why the study was done
- Study information
- How the study worked
- Side effects/ adverse events
- Official title of the study
- Final comments, including where to obtain further information

Highlights of the MRCT Center Return of Research Results Guidance Document include:

- Recommendations are congruent, unless otherwise noted, with the European Medicines Agency (EMA) mandate to post results on the European Clinical Trials Database (EudraCT) and the joint "Principles for Responsible Clinical Trial Data Sharing: Our

Commitment to Patients and Researchers" released by the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the Pharmaceutical Research and Manufacturers of America (PhRMA)[1]
- Best practices for how to return results to participants, recommended timing and processes for content development;
- A patient-centered approach that incorporates principles of health literacy, numeracy and cultural literacy;
- Considerations for returning results under "special circumstances" including pediatric populations and cases where the participant is no longer able to receive the results

In addition, a separate document, titled *MRCT Return of Results Toolkit* includes the following:

- Templates and examples for creating the summary
- Examples of neutral language that may be used to avoid the use of promotional language;
- A Research Ethics Committee Checklist

The ethical imperative is clear – returning results to trial participants respects their participation and recognizes participants as partners in research. Therefore, **our recommendation is that all sponsors offer to provide results to study participants for all clinical studies**.[2]
Our objective is for sponsors and investigators to utilize this guidance document and the accompanying toolkit as the basis to enact their own internal processes for returning results.

[1] http://www.phrma.org/sites/default/files/pdf/PhRMAPrinciplesForResponsibleClinicalTrialDataSharing.pdf. Accessed July 8, 2016.
[2] It is important to note that the EMA will proactively publish the clinical study reports submitted as part of marketing authorization applications for human medicines (see http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000555.jsp; accessed July 8, 2016; http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf)

# 1. Introduction

## 1.1 Purpose

The purpose of creating and disseminating general clinical trial result summaries (here termed Research Results Summaries [RRS]) to clinical trial participants is to ensure that study participants are informed about the trial results, that they know that their participation is respected and appreciated, and that they understand the value of their contribution to science and public health.

In many cases, informed consent forms in the United States (US) state that study participants will receive important information about the study, as allowed under the Food and Drug Administration Amendment Act (FDAAA) of 2007. An RRS helps to accomplish this commitment and to express appreciation for the study participant's time and effort. Returning results may help build additional participant engagement in the clinical trial process and, over time, increase public trust by creating greater transparency in the medical research enterprise. The Multi-Regional Clinical Trials Center of the Brigham and Women's Hospital and Harvard (MRCT Center) coordinated a multi-stakeholder workgroup to develop guidance for effective development and delivery of participant research summaries. This guidance covers content, process, logistics, and other considerations. In the creation of this guidance, the interdisciplinary workgroup also considered the perspective of various external stakeholders.

## 1.2 Document scope

This guidance document addresses the return of RRS to individuals who participated in research studies conducted by industry, private, academic, government and public sponsors, regardless of geographical location or phase of the trial. This RRS guidance document includes background on clinical trial disclosure, an overview of the different forms of data sharing, proposed guidance on establishing a results sharing program, detailed "how to" instructions for executing study-specific return of results, and several RRS examples. While the document considers the perspectives of the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), it is not meant to supplant or interpret any regulation or official guidance.

This document primarily addresses interventional clinical trials associated with drugs, biologics and some devices. Most trials considered here are sponsored studies involving industry, not-for-profit/academic organizations or government sponsors as well as investigator-initiated studies (where the principal investigator is the sponsor) whether funded internally or sponsored in whole or in part by an external entity.

Importantly, the best practices described herein apply to any Phase 1 – 4 clinical trial that employs a signed informed consent. By their nature, these trials involve a participant whose identity is known to the investigator or sponsor-investigator and can thus be contacted.[3] While this guidance focuses on interventional clinical trials, the best practices described herein also apply to other types of clinical research, including social and behavioral research, registries, and observational studies conducted by industry, private, academic, and public sponsors. Some studies, by their nature, will not have specific "study results" or the researcher may not know the

[3] Sponsor-investigator is defined as the person who both initiates and conducts the clinical study.

identity of the participant. Examples of such studies include tissue contributions to a biospecimen repository; some observational, social, behavioral, and long-term studies; and when the institutional review board (IRB)/research ethics committee (REC) has waived consent. Nevertheless, communication of study results is important: results derived from such studies can be posted on a public website (e.g. the website of the biorepository or registry) and notice as to the availability of these results communicated to participants. Recommendations for these types of studies are given below (see Section 5.2).

The section entitled "Special Considerations" also addresses unique situations such as clinical trials that terminate prematurely for efficacy, lack of efficacy (i.e. futility), safety, or low accrual, and situations in which a third party is designated to receive results because the participant is unable to receive the information due to impaired decision-making, death, or other circumstances.

Currently, this document does not address the return of individual research results or health data collected during the trial, results of assignment to study arm, incidental or secondary findings; general principles have previously been elucidated[4] and the MRCT Center is currently examining these aspects in detail. This guidance does mention some considerations at the time of participant end-of-study visit (last patient visit) later in this document.[5],[6]

## 1.3 How to use this document

Clinical trial sponsors and/or investigators can use this guidance document to develop and implement a process for sharing general clinical trial results with trial participants.

We note that there is no one method or approach for return of aggregate research results across all research questions and studies. The process will differ depending on the type of study, the individuals involved, and the sponsor (industry or other). For that reason, certain roles and responsibilities will be carried out by different persons and by different methods in a variety of situations. For example, a 10,000 person, multinational industry study may utilize a website to disseminate aggregate results, while an investigator conducting a proof-of-principle study for identification of biomarker relevance may opt to personally write or call the participants. Where the role of investigator or sponsor is clear, we have attempted to delineate the role; in other instances, we have commented on principles to consider in making the specific determination on a case-by-case basis.

This document:

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[4] The Presidential Commission for the Study of Bioethical Issues. Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts. Released December 2013. http://bioethics.gov/node/3183 (Accessed July 8, 2016)

[5] See also http://www.hra.nhs.uk/documents/2014/09/information-participants-end-study-guidance-researchers.pdf (accessed July 8, 2016) and http://www.hra.nhs.uk/documents/2013/08/care-after-research.pdf (accessed July 8, 2016)

[6] The MRCT Center is considering return of incidental findings, genomic results, and individual participant results currently, and will communicate recommendations at a later date.

- Provides factors to consider when designing and implementing a program to return RRS to clinical trial participants in an ethical and responsible manner
- Outlines the basic principles for responsible return of RRS
- Describes best practices for RRS content development
- Emphasizes principles of health literacy, numeracy, and cultural sensitivity in all communications
- Summarizes RRS implementation options and includes considerations for each option
- Presents a variety of special situations to consider when developing an RRS process
- Includes helpful resources such as sample language and disclaimers, guidance on applying health literacy, numeracy, and cultural principles, and examples of RRS documents

In addition, a separate document, titled *MRCT Return of Results Toolkit*[7] includes the following:

- Templates and examples for creating the summary
- Examples of neutral language that may be used to avoid the use of promotional language;
- A checklist for Institutional Review Boards (IRBs)/Research Ethics Committees (RECs), if the IRB/REC determine that review and approval is required prior to distribution
- Plain language description of endpoints that may be incorporated as needed

Note: Throughout this document, certain terms have been used deliberately such as "participant" instead of "human subject," as is the preference of clinical trial participants. Certain terms, such as "clinical trial," "study," and "research study" are used interchangably. A quick review of *Abbreviations* on page 7 and *Key Terminology*, found in Appendix 1, will aid in comprehension.

The MRCT Center encourages broad dissemination of this guidance document and suggests incorporating these practices into clinical trial operations and practices. The MRCT Center would appreciate feedback and additional contributions (addressed to MRCT@bwh.harvard.edu) so that we can continuously improve this Guidance Document and Toolkit. If these materials are used in their entirety or in part, attribution should list the "*MRCT Center Return of Results Guidance Document*" and version date.

[7] see accompanying Toolkit, provided separately

## 2. Overview of Research Results Summaries for Trial Participants

### 2.1 Background

There is growing sentiment that greater transparency and engagement with clinical trial participants will strengthen the clinical research process.[8] Individuals volunteer to participate in a clinical trial for a variety of reasons, including the desire to advance research and help others in the future, curiosity, and access to potentially disease-altering treatments available only on protocol. While motives may differ, participants expect that the knowledge gained in their study will influence future research and may impact the care of future patients and families. Returning study results to clinical trial participants is a way to meet those expectations, to provide closure and to acknowledge the valuable contributions of the participants. Further, it honors them as partners in the research process.

Patient advocacy groups and clinical trial participants have called for greater sharing of research results. The Institute of Medicine, the Patient Centered Outcomes Research Institute and the National Institutes of Health have recognized the importance of results sharing.[9] Regulatory bodies and industry groups have also recognized this need, and as a result, the mandate for greater data sharing has gained momentum in recent years.

In 2014, a 'Consensus Framework for Ethical Collaboration between sponsors, sponsor investigators, other medical professionals, and patients was established as a collaboration among the International Alliance of Patients' Organizations (IAPO), the International Council of Nurses (ICN), the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the International Pharmaceutical Federation (FIP), and the World Medical Association (WMA). The 'Consensus Framework for Ethical Collaboration' sets out common elements for interactions between industry and healthcare professionals. Importantly, it does not supersede

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[8] See example: Lunshof, J. E., Church, G. M., & Prainsack, B. (2014). Raw personal data: providing access. Science, 343(6169), 373-374. And Institute of Medicine (IOM) Committee on Strategies for Responsible Sharing of Clinical Trial Data. *IOM website.* at : http://www.nationalacademies.org/hmd/Activities/Research/SharingClinicalTrialData.aspx. 2015 (accessed July 8, 2016)

[9] Institute of Medicine (IOM) Committee on Strategies for Responsible Sharing of Clinical Trial Data. *IOM website.*http://www.iom.edu/activities/research/sharingclinicaltrialdata.aspx. 2015.; http://www.pcori.org/blog/open-science-pcoris-efforts-make-study-results-and-data-more-widely-available;http://www.pcori.org/blog/open-science-pcoris-efforts-make-study-results-and-data-more-widely-available (accessed July 8, 2016); https://www.genome.gov/Pages/PolicyEthics/Healthissues/NHGRI_Incidental_Findings_Workshop_Summary.pdf; (accessed January 22, 2016); http://epi.grants.cancer.gov/events/enrich-forum/; (accessed January 22, 2016); Fernandez CV, Ruccione K, Wells RJ, Long JB, Pelletier W, Hooke MC, Pentz RD, Noll RB, Baker JN, O'Leary M, Reaman G, Adamson PC, Joffe S; COG Return of Results Task Force. (2012). Recommendations for the return of research results to study participants and guardians: a report from the Children's Oncology Group. J Clin Oncol. 30(36):4573-9. doi: 10.1200/JCO.2012.45.2086.

the partner organizations' tailored, individual codes or guidelines - it identifies shared principles.[10] Regarding clinical trials transparency, it states: "Continuing to support the premise that both the positive and negative outcomes of research evaluating medicines, other products and services should be disclosed. Clinical research in patients and related results should be transparent while respecting patient privacy."[11]

A brief chronology of requirements and issued guidance for sharing aggregate/individual data, regulations and their impact is summarized in Table 1:

**Table 1 Key Milestones for Clinical Trial Data Sharing**

| | |
|---|---|
| 2007 | Section 801 of the US Food and Drug Administration Amendments Act (FDAAA) allowed for the possible dissemination of a "summary of the clinical trial and its results that is written in non-technical, understandable language for patients."[12] |
| 2012 | US Trial and Experimental Studies Transparency Act of 2012 (TEST Act) was introduced in the House of Representatives to amend the Public Health Service Act by "expanding the clinical trials that must be reported to the clinical trial registry data bank." The Act, however was not passed.[13] |
| 2012 | British Medical Journal (BMJ) adopted a new policy on data sharing from drug and trial devices, limiting prospective publication of trials of drugs and medical devices to those where authors agree to make the relevant anonymized patient-level data available on reasonable request.[14] |
| 2013 | AllTrials was launched to raise public awareness of clinical trials data registration and results reporting to the public. [15] |
| 2013 | Article 26 of the Declaration of Helsinki was revised to state: "All medical research subjects should be given the option of being informed about the general outcome and results of the study."[16] |

[10] Putting patients first: five global healthcare organizations sign Consensus Framework for Ethical Collaboration: IFPMA. 2014. Putting patients first: five global healthcare organizations sign Consensus Framework for Ethical Collaboration: IFPMA. [ONLINE] Available at: http://www.ifpma.org/news/news-releases/news-details/article/putting-patients-first-five-global-healthcare-org.html . [. (Accessed 10 September 2014].).

[11] Francer, J., Izquierdo, J. Z., Music, T., Narsai, K., Nikidis, C., Simmonds, H., & Woods, P. (2014.). Ethical pharmaceutical promotion and communications worldwide: codes and regulations. *Philosophy, Ethics, and Humanities in Medicine*, *9*(1), 7.

[12] H.R.3580 - 110th Congress (2007-2008): Food and Drug Administration Amendments Act of 2007 Section 801| Congress.gov | Library of Congress. 2014. *Text - H.R.3580 - 110th Congress (2007-2008): Food and Drug Administration Amendments Act of 2007 | Congress.gov | Library of Congress*. [ONLINE] Available at: https://beta.congress.gov/110/plaws/publ85/PLAW-110publ85.pdf [(Accessed 10 September 2014].).

[13] See https://beta.congress.gov/bill/113th-congress/house-bill/2031 (Accessed September 10 2014)

[14] See http://www.bmj.com/content/340/bmj.c564 (Accessed September 10 2014)

[15] See http://www.alltrials.net (Accessed December 28, 2015)

[16] See: http://www.wma.net/en/30publications/10policies/b3/ (accessed July 13, 2016)

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| 2013 | Pharmaceutical Research and Manufacturers of America (PhRMA) and the European Federation of Pharmaceutical Industries and Associations (EFPIA) jointly issued the PhRMA/EFPIA Principles for Responsible Clinical Trial Data Sharing. The principles included a commitment for sponsors to work with regulators to develop a mechanism to provide a factual summary of clinical trial results to research participants.[17] |
| 2013 | The US Presidential Commission for the Study of Bioethical Issues report entitled "Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research and Direct-to-Consumer Contexts" was published[18] |
| 2014 | The International Committee of Medical Journal Editors (ICMJE) announced that the organization is considering a policy aimed to strengthen sharing of clinical trial data requirements for journal contributors.[19] |
| 2014 | The Public Library of Science (PLOS) issued a revised Data Policy mandating all PLOS journals' authors to make fully available without restriction, with rare exception, all data underlying research findings.[20] |
| 2014 | New European Union (EU) Clinical Trial regulation introduced, "Publication and Access to Clinical-Trial Data, [Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006,]", that includes a requirement that will become effective in 2017 to post clinical study result summaries, "layperson's" summaries, study protocols, and clinical study reports to the (new) EU database.[21] |
| 2014 | The Biotechnology Industry Organization (BIO) released Principles on Clinical Trial Data Sharing affirming their commitment to "building upon the routine publication of clinical research results and ongoing collaborations with academic and government researchers in order to support additional efforts to improve public health."[22] |
| 2014 | National Institutes of Health (NIH) announced its intention to help develop procedures for registering and submitting study results, including adverse events, to ClinicalTrials.gov, helping to implement FDAAA 801. |
| 2015 | The Institute of Medicine report, "Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk," was released, concluding that adherence "to best practices and legal standards" with regard to communication of lay language summaries would increase |

[17] See http://www.phrma.org/phrmapedia/responsible-clinical-trial-data-sharing (Accessed September 10 2014)
[18] See http://bioethics.gov/node/3183 (Accessed January 9, 2015)
[19] See http://www.icmje.org/news-and-editorials/principles_data_sharing_jan2014.html (Accessed September 10 2014)
[20] http://www.plos.org/data-access-for-the-open-access-literature-ploss-data-policy (Accessed September 10 2014)
[21] 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. Available at: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0536&from=EN (Accessed January 22, 2016)
[22] See http://www.bio.org/articles/bio-principles-clinical-trial-data-sharing (Accessed September 10 2014)

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| | public trust in clinical trials and that information as to what data will be shared, how and when should occur during the informed consent process."[23] |
| 2015 | The Health Research Authority (HRA) of the National Health Service (NHS) confirms its commitment to transparency, registration and publication.[24] The HRA calls for researchers to provide all participants summary findings of the research at the end of study.[25] |
| 2016 | The National Academics of Sciences, Engineering and Medicine conducted a workshop and released a brief on "Relevance of Health Literacy to Precision Medicine"[26] |
| 2016 | The European Commission requests public consultation on their "Summary of Clinical 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" [27] |

## 2.2 Challenges

There is collective and growing interest in sharing study results with trial participants. However, the nature of the clinical research enterprise presents challenges to data sharing. Examples include:

- Confidentiality and privacy of the participant and potential compromise of the investigator-participant relationship. Commitments made in the Informed Consent Forms [ICFs] with respect to the release of participant-specific information to the sponsor or other parties must be respected.
- Numerous logistical and ethical challenges in the execution of returning RRS including local laws on data protection, maintaining accurate records regarding participant contact information over time (as the availability of results may lag behind –by years—the last contact with the participant), tracking participants' wishes as they may change their mind regarding whether or not to receive RRS, potential death of participants, assent for pediatric participants, etc. These logistical challenges are most acute when results are returned individually rather than posted on a publically available website.

[23] See http://iom.nationalacademies.org/Reports/2015/Sharing-Clinical-Trial-Data.aspx (Accessed August 11, 2015)
[24] http://www.hra.nhs.uk/resources/during-and-after-your-study/transparency-registration-and-publication (Accessed December 28, 2015)
[25] http://www.hra.nhs.uk/research-community/end-of-study-and-beyond/participants-at-the-end-of-study/ (Accessed December 28, 2015)
[26] See: http://nationalacademies.org/hmd/activities/publichealth/healthliteracy/Relevance-of-Health-Literacy-to-Precision-Medicine-SWIB.aspx and http://www.nationalacademies.org/hmd/Activities/PublicHealth/HealthLiteracy/2016-MAR-2.aspx (Accesed July 13, 2016)
[27] See: http://ec.europa.eu/health/human-use/clinical-trials/developments/index_en.htm (Accessed July 13, 2016)

- IRB/REC and regulatory oversight that may not permit data sharing with participants under certain conditions such as if, for instance, such sharing is considered potentially detrimental or harmful to the participants.
- The nature of drug development in which the results of one study may significantly impact the willingness of potential volunteers in a contemporaneous study to consent to participate and thus impact future clinical research or where sponsors chose to offer RRS after primary completion in a long term study. In the latter case, if participants know the results of the primary outcome, will they be biased for the remainder of the study?
- The timing of return of RRS, caught between the desire for timely return of information to the participants, the regulatory mandates of governmental oversight bodies (e.g. the submission of clinical study reports to the FDA, EMA, and others), and public release of information.[28]
- Resource requirements of returning RRS, often unavailable in investigator-initiated studies.
- Technology and literacy limitations, particularly in resource-poor settings, in which both access to the Internet and health literacy may be challenging.
- Local laws on data protection that must take precedence.

A number of key challenges have been cited as reasons not to return study results promptly and responsibly to participants, all of which, in our opinion, appear to be surmountable. Examples of such statements (and countering arguments) include:

- Regulatory requirements prohibit any type of communication considered "promotional" prior to FDA/EMA regulatory approval

  In the absence of official guidance from regulatory authorities regarding RRS, clinical study sponsors express caution about publicly communicating information on trials/results that might be seen as promotional.[29] Any communication about research results must be careful not to appear to claim efficacy and/or safety prematurely be construed as off-label promotion.[30]

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[28] In the US, any release of data, even to participants, may dictate certain public disclosures and filings, such as required by the Securities and Exchange Commission that monitors and enforces disclosure laws and regulations.

[29] Article 87 of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. (Retrieved from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?) uri=CELEX:32001L0083:EN:NOT) http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_cons/dir2001_83_cons_20081230_en.pdf (Accessed February 2, 2016)

[30] Title 21--Food and Drugs. Chapter I--Food and Drug Administration Department of Health and Human Services. Subchapter A—General. Part 99 -- Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices. Retrieved from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=99.101 http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=99.101 (Accessed January 22, 2015.)

- Sponsors must protect their research and development investment, and investment that might be compromised by the early communication of results

  Sponsor and organizational policies and practices safeguard commercially confidential information (CCI), particularly for novel indications. However, communicating the results of a completed trial, timed to the submission of the clinical study report (CSR) to regulatory agencies and with publication in the scientific literature, will not compromise CCI.[31] Summary results should be shared with the study participants at or about the time of study publication to the scientific community.

- Industry sponsors are unable to provide plain language summary results as they do not interact directly with trial participants

  Good Clinical Practice (GCP) guidelines as well as individual country laws and regulations include privacy and confidentiality rules, which often stipulate that the confidentiality of records that could identify study participants should be protected.[32] An industry sponsor (or a sponsor-designated clinical research organization) rarely has or retains patient identifiers or contact information, and thus cannot directly contact the participant at the end of the trial. Often, if individual contact is desired, the site investigator or a third party (e.g. a contracted service provider that will maintain confidentiality of participant identity) is called upon to return the results to participants; this raises its own logistical challenges (discussed below) as well as additional expense. Alternatives exist, such as posting plain language summaries to a publically available Internet site. Not all participants, of course, have access to the Internet, and provisions for their engagement will need to be developed (see below). Further, methods to respond to questions that participants have upon learning of the results will need to be developed if the Internet is chosen as a means to deliver RRS. Potential approaches are discussed below.

- Return of results is a resource-intensive practice

  Return of results requires time, training, staff, skill in plain language (and potential translation), communication and funding, among other considerations. Establishing a sustainable results sharing program can be a complex, lengthy, and resource-intensive process that requires multi-functional input and collaboration. Implementing this process adds additional tasks and procedures to existing sponsor study activities, beginning with study planning. Nevertheless, respect for the contributions and essential volunteerism of the participants--and the public—demand that RRS be embraced as a central and obligate component of the clinical trial enterprise. It is important to start the process, gain experience, and then adjust.

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[31] In addition, the EU has stated, starting 1 January 2015, that the clinical reports submitted as part of marketing-authorization applications for human medicines will be proactively published once the decision-making process on an application for a EU)-wide marketing authorization is complete. http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000555.jsp. (Accessed December 31, 2015).

[32] Guideline for Good Clinical Practice (E6/R1). ICH Harmonised Tripartite Guideline. 1996. Section 2.11. Retrieved from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf (Accessed February 2, 2016)

The key is how to address these challenges without creating an excessive burden either on the sponsor or on the clinical site staff while ensuring the privacy and respecting the wishes of the participants. For example, setting early expectations on the timing of data return may help address the needs of the trial participants for immediate information while also protecting stakeholder interests and meeting transparency objectives. Equally important is determining how to minimize risks that the research enterprise might face from regulatory, economic and ethical standpoints as data-sharing initiatives progress.

## 2.3 Role and Involvement of the IRB/REC

There is currently no international agreement on the obligations and level of involvement of Institutional Review Boards (IRB)s/Research Ethics Committees (REC)s. The subsequent sections are what we believe are the prevailing views of IRBs/RECs in the United States, UK and EU with the belief that a harmonized approach benefits those that have participated in clinical trials by enabling the timely return of high-level, patient-focused and non-promotional aggregate results summaries.

The IRB/REC is constituted to protect the rights, safety and well-being of individuals involved in a clinical trial. The IRB/REC reviews and approves the study protocol in advance of study initiation, and has oversight responsibilities throughout conduct of the trial.[33] In the event of return of results in the midst of a study (e.g. contemporaneous with the scientific publication of primary endpoints but the study to remain open for collection of secondary endpoints, a longitudinal observational study, etc.), the IRB/REC, throughout an open trial, has oversight responsibilities and will review planned interactions or communications with participants. If interim studies will be communicated by contacting the participants directly, the IRB/REC will review and approve the communication. If on the other hand, interim study results are communicated by public dissemination (e.g. posting results on a website), the IRB/REC does not have jurisdiction. Other than advertisements for the trial (that impact recruitment), the IRB/REC does not review many other postings such as registration with ClinicalTrials.gov. In the UK, the Health Research Authority (HRA) has explicitly stated that ethics committees need not review results summaries if the execution of the process is consistent with the plans outlined in the study protocol, even if results are returned during an open trial (e.g. longitudinal studies).[34]

At the end of a study, however, the situation changes. In the U.S. and in the EU (aside from the UK), IRBs/RECs are not required to review the plan for, or materials used in, the return of RRS to participants -- unless these plans are described in the study protocol -- *so long as* the RRS will be returned after the study has been closed by the IRB/REC.. There are three arguments in support of the position that IRBs/RECs need *not* review and approve RRS if the study has been *closed* with the IRB:

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[33] In the US, all FDA-regulated clinical research remains under IRB oversight until all research-related interactions and interventions have been completed. For HHS-regulated research, all data collection and data analysis of identifiable private information must be completed for a study to be closed. At that time, human research has been completed and the study may be closed with the IRB. Study closure itself is a change in research that requires IRB notification and approval.

[34] See http://www.hra.nhs.uk/documents/2014/09/information-participants-end-study-guidance-researchers.pdf (accessed 2 February 2015).

1. The study is closed, and thus the activity is no longer research and there are no human subjects/participants[35] involved in the activity.[36]
2. RRS are unlikely to affect the criteria for IRB approval or continued approval at continuing review (and the study is closed.) RRS does not affect participant recruitment since the post-study communications are not coercive or unduly influential as to the participant's decision to join or stay in the study. RRS does not affect equitable selection of participants, as both the design and the selection of participants are completed by this point. The communications do not affect risks or benefits as all participants have already been exposed to the physical risks and have been monitored. The communications do not adversely affect vulnerable participants.
3. Research data are often released publicly on registries such as ClinicalTrials.gov or in medical journal publications, and IRB review is not required for those activities. RRSs are a subset of the more technical result summaries described at a high-level and in a factually based non-promotional way understandable to a general audience. Some sponsors may opt to post RRS to a website or registry. Further, even when RRS are returned directly to study participants (albeit through investigators for privacy and confidentiality reasons), these same summaries are likely to be posted and publically accessible as well.

If, however, the study *protocol* describes the intent to offer return of results, the IRB/REC may not close,,or allow the investigator to close, a study until that commitment is met, as RRS may be interpreted as a "study procedure." We do not recommend, therefore, that the study protocol itself describe the intent to return research results as it may obligate IRB/REC review. The intent to return study results should, on the other hand, be described in the *informed consent document* as the participant should know when and how to anticipate the communication. When IRBs/RECs were consulted, mere mention of intent to return results in the informed consent document was not felt to necessitate IRB/REC review..

In jurisdictions in which the regulations are not clear and in which return of results is planned, it is wise to begin to educate and explain the process particularly if the intent is to harmonize the process across multiple regions. As a matter of principle, the information returned to participants should be consistent across all sites, and in all countries, without local changes. Not only would local changes create practical challenges,, but justice and fairness dictate that all participants are entitled to similar information in similar circumstances.

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[35] Note: we have replaced "subjects" with "participants" unless directly quoting regulations. This is due to feedback from patient communities.

[36] In the US, the Health and Human Services (HHS) definition of "human subject" is "an individual about whom an investigator intervenes or interacts to collect data, or about whom an investigator obtains private identifiable information." A research result communication after a study has ended involves none of these conditions. Similarly, the definition of a "human subject" under the USFDA regulations is "an individual who is or becomes a participant in research, either as a recipient of the test article or as a control." In this case, the study has ended and is closed with the IRB, so there is no longer open research and the individuals are no longer participants in the research.

## 2.4 Basic Principles

The MRCT Center RRS work team has developed a set of basic principles for the design, development, implementation, and dissemination of RRS.

For Study Sponsors[37] and Sponsor-Investigators:[38]

1. Adhere to the most current global regulatory requirements and guidance, with specific attention to the local laws and regulations where the trial was conducted.[39]
2. Assure that communications are prepared and disseminated in a manner that is non-promotional.[40]
3. Create clear, explicit and understandable research results summaries and implement a process to disseminate them in an ethical and responsible manner.
   - Adhere to health literacy principles to achieve this goal (see Appendix 3 and Appendix 4).
   - Include information for all populations included in the trial, including stating the results in culturally appropriate terms. See cultural literacy section.
4. Provide RRS in all language(s) in which participant trial materials, including the informed consent document, appear. Translation and back translation,[41] and potential review by a native speaker to ensure semantic equivalence and appropriate meaning in the native dialect, may be necessary.
5. To the extent possible, create provisions to ensure that summaries are available even if the sponsor, research site, or principal/site investigator is no longer available. The solution may entail posting the RRS on a generally accessible website and sending an appropriate communication to participants; in that case, provisions for answering follow-up questions posed by the participants will need to be considered (see below).
6. Demonstrate respect for trial participants by:
   - Acknowledging trial participant contribution to the advancement of medical science.
   - Offering participants a choice as to whether to receive trial results.
   - Creating simple and succinct content with well-defined terms that employ principles of health literacy.
   - Including information about where and/or from whom a participant can receive further information if there are outstanding questions. Sponsors should decide whether participants should be encouraged to request further information from the

[37] Or the Sponsor designee such as a contract research organization (CRO) involved in the conduct and execution of the trial.
[38] Sponsor-Investigator is defined as the person who both initiates and conducts the clinical study.
[39] In multi-center, multi-regional trials, country-specific regulations and requirements may differ. The sponsor will need to determine whether to adhere to the most stringent requirements and apply them to all countries or to tailor the RRS for each country where the trial was conducted. The latter approach introduces the complexity that multiple RRS documents may potentially be prepared, all for the same trial, based on differing regulatory requirements (see below for further discussion).
[40] *Vide supra*, footnotes 28, 29, 30, 31, 32 and *MRCT Return of Results Toolkit*.
[41] See, for instance, http://www.who.int/substance_abuse/research_tools/translation/en/ (Accessed December 31, 2015);

site Principal Investigator (PI) if available, their health care provider, or another entity as discussed further below.

For Clinical Research Sites Working with Sponsors

7. Support and participate in the dissemination of RRS to all study participants who want results. This may involve referring participants to an appropriate website or being directly involved in the communication of results.
8. Help provide information or referrals for participant questions when delivering and/or after communicating study results.
9. Investigators should convey results in a factual manner; some education to investigators may be needed to ensure that information is presented in a non-promotional manner. Some explanation of terms may be necessary (e.g., drug-related adverse events and how these are determined).

For Institutional Review Boards (IRBs)/Research Ethics Committees (RECs)

In general, if the study is open when the communication with participants is planned, or the IRB/REC chooses to execute oversight responsibility, the IRB/REC will:

- Review and, as appropriate, approve proposed plans for return of RRS to participants in the consent forms and other study documents.[42]
- Review and, as appropriate, approve any amendments to proposed plans for return of RRS to participants in consent forms and other study documents.
- See *MRCT Return of Results Toolkit* for the Ethics Committee Checklist.

[42] Much discussion has surrounded whether plans to communicate RRS should be included in the study protocol. Industry sponsors have argued that if RRS plans are included in the protocol itself, then the study cannot be closed until RRS has been completed, the requirement for RRS must be in any investigator/site contract, and compliance will be difficult to track. IRBs/RECs, on the other hand, have argued that if the plan is to communicate RRS to the participant, and that intension is a component of the informed consent document (as we recommend it should be) then the IRB/REC should be alerted to this fact and review the plans. Our recommendation is that the intention be included in the other study documents (not the sponsor's study protocol) that accompany any application from the investigator to the IRB/REC and in the informed consent document itself.

## 3. Organizational Process and Logistics

### 3.1 An organization-wide process for results sharing

All organizations conducting clinical trials should incorporate data transparency efforts into their clinical trial plans and budgets, including a robust strategy to ensure feasibility of RRS both operationally and financially. It is important to address the overall plan for RRS early in clinical trial design to ensure consistency and logistical coordination.

With the following fundamentals established, the organization can begin the process of designing an effective program. Information in this section is listed under 7 key areas:

#### 3.1.1. Level and scope of RRS

Whether an industry sponsor, not-for-profit, government agency or academic institution, organizations must decide early on what data will be shared, with whom, and how. That information should be fair, balanced, and not selective to decrease the possibility of it being interpreted as promotional, particularly in trials regulated by oversight bodies. Generally, there are different types of RRS, for different contexts:

1. Public release of study data for *scientific* audiences (e.g., posting results on ClinicalTrials.gov, journal article publication, or on a publicly available website).
2. Return of general, de-identified, and aggregate study results to *participants* in plain language. These results, intended for participants may be sent directly to the participant or posted on a web site as discussed further below.
3. Return of individual study results to participants (e.g., their specific assignment to study arm, their own clinical study data, incidental findings discovered during the course of the study, research data).[43] Individual research results are participant-specific and by their nature go beyond the study or aggregate summary results.

For the purpose of this guidance document, the MRCT Center Return of Results [ROR) workgroup has intentionally limited the discussion to the return of general study results to participants (#2 listed above).[44] The MRCT Center ROR workgroup notes, however, that even within the single goal of returning general, de-identified and aggregate study results to participants, there is a continuum of detail.

In general, RRS would include study results in a narrative summary provided to interested trial participants—and the public—after data were compiled and analyzed either after study closure or contemporaneously with a study publication (e.g. when a primary endpoint is achieved but the study remains open for secondary endpoints). Compliance with the most current regulatory requirements (see EU Clinical Trial Regulations at

[43] Such instances include secondary and discovery findings such as incidental radiographical findings on scans performed for the clinical research, DNA mutations of significance (e.g. BRAC-1), abnormal tissue pathology identified coincidentally, and abnormal laboratory tests that are independent of the study. Most organizations have policies and processes to communicate, at a minimum, actionable incidental findings in a timely fashion directly to the participant or to their health care provider. This situation is outside the scope of this document.
[44] While the actual data and communication may in fact be similar or identical between scientific audiences (setting #1) and participants or the public (setting #2), in our experience the latter requires additional logistical and other considerations.

http://ec.europa.eu/health/human-use/clinical-trials/index_en.htm) is an appropriate first step in that direction.

While organizations (e.g. sponsor, site, institution) will develop their own policies and procedures to implement the return of results to participants, greater harmonization will simplify the process, help manage expectations, and enable common education platforms.

When determining with whom the results should be shared, we recommend that, at a minimum, results should be provided to all participants (or legally authorized representatives/guardians as designated in the ICF) who were consented, regardless of whether the participant was later randomized or completed the clinical trial and who have opted to receive results. Refer to the Content section of this document for more detailed information regarding the appropriate recipients of RRS.

Sponsors should also consider providing results summaries to the general public, as will be required by the EU clinical trial regulations.

### 3.1.2. Method(s) of delivery

Next, organizations should determine the most appropriate method(s) of delivery as well as the infrastructure and resources, including cost and time, as returning results to participants can be a resource-intensive activity. Importantly, the method for delivery should be consistent with the characteristics, cultural needs and expectations coupled with an understanding of the study population. Consideration should be given to any cultural differences as well as to the need to return results in a timely manner. As a general rule, however, we recommend that any communications be targeted for a non-technical audience, using simple language and health literacy principles to the greatest extent possible. Some participants may not have access to the Internet or may require special resources to understand the content. On a practical level, the options for RRS delivery vary based on cost, resource requirements, technology, and degree of support for the participant (i.e., the opportunity for participants to ask questions). More than one delivery method may be optimal or required.

Greater flexibility and comprehension may be achieved using a variety of simultaneous delivery methods although these differing methods will differ in cost and practicality. The following questions may be helpful in planning for the method(s) of delivery:

- Does the method depend upon a face-to-face meeting at the study site, access to a telephone, or access to the Internet? Does the study population have access to a telephone or the Internet? Consider whether the method places a burden on the study site and how that may impact both the capacity of the site and potentially the participant's care decisions after the trial.
- What is the likelihood that the implications of the study results will elicit follow-on complex questions? If the likelihood is great, a face-to-face meeting at the site may be preferable to a written communication that requires participant follow-up. In this approach, there are practical implications and additional resources that may be necessary to field questions (discussed later).
- Is it likely that the study physician/investigator will have a continuing care responsibility for the participant once the trial is over? If not, who will have that responsibility and how will the caregiver or additional healthcare provider be alerted? It is important to outline the investigator and site responsibilities, to set expectations, and to ensure alignment of activities.

In this section, various RRS delivery options are categorized as (1) Internet-based; (2) interactive; and (3) one-way communication. These options are not mutually exclusive.

1. Internet-based methods. Participant and public communication can be provided through an Internet web-based portal.[45] Security considerations should be considered; no personal information (e.g. adverse event reports with protected health information) should be posted. Unlike the interactive methods that rely heavily on the research study site for RRS delivery, a study sponsor can offer and support an online portal and a highly consistent experience for the user. The quality of the user interaction will depend on the quality of the system design and testing.

   - An Internet portal provides significant flexibility for the sponsor (whether industry, not-for-profit, or individual investigator). The sponsor is able to create a landing page or site[46] for each clinical trial, giving each participant the web address. Importantly, the site—and the path to it—should be so constructed that it is not promotional.[47] The participant is then empowered to control whether to log onto the site for information and whether to give the information to a third-party designee. In fact, the sponsor can create the site (and, if password protection is desired, the password may be created before the study begins), and provide the information at the time of enrollment[48]—potentially even in the informed consent document or through an information sheet—and again at end-of-study visit. Sponsors should consider the need for a third party vendor to develop and manage a password-protected website since sponsors cannot have individual patient identifying information. Empowering the participant to exercise choice as to whether to review results respects the fact that any individual may change their mind between the time of informed consent at the beginning of the trial and study end.
   - In any Internet-based method, information on the web site should be kept current (including interim messages such as "enrollment is continuing for this study. Results are not available at this time," or "all necessary information (data) has been collected

[45] Currently only around 40% of the world population has Internet access, with far greater access in the developed world (http://www.internetworldstats.com/stats.htm; accessed January 1, 2016). While access to the Internet is a challenge for some, particularly in resource-poor settings, it is estimated that 90% of the world's population over 6 years old will have a mobile phone by the year 2020 (http://www.ericsson.com/news/1872291; accessed January 1, 2016); over time, internet connectivity through mobile technologies will increase.

[46] In most instances, a website hosting aggregate summary results will not be password-protected or private. In rare instances, particularly in the setting of follow-on and concurrent trials, sponsors may wish to consider this option. If the site is password-protected, provisions must be made to give each participant either a unique or common password.

[47] In the event that a biomedical pharmaceutical sponsors posts summary results on their own website, the path to which involves sequential landing pages with promotional content, the summary itself may be perceived as promotional.

[48] Providing the information at enrollment (even in the consent form or a participant information sheet) allows participants that have enrolled but not completed the study to access information if they choose to do so, relieving sponsors of tracking responsibilities.

and the results are currently being analyzed. We anticipate results to be available in about six months.)"

- The security of the system should be addressed. Some sponsors may wish the site to be accessible to the public. Some may wish the site to be password-protected.
- Not all participants have access to a computer or the Internet, although many have access through mobile devices. Not all participants are computer-literate or can read; and many have literacy issues. Provisions should be made utilizing alternative methods in such cases.[49] All communication should use health literacy principles, no matter what level of education is assumed (see Appendix 3 and Appendix 4).

2. Interactive methods. Interactive methods (e.g., face-to-face meeting(s), telephone call(s), two-way online meeting(s), dynamic email exchange, etc.) provide participants support and the opportunity to ask questions. However, these methods place a greater burden on the site and the investigator or their team. The consistency and quality of the interaction is difficult to monitor and is often dependent upon a staff member to facilitate the discussion. In this situation, industry sponsors will need to provide training and support materials and consider and address key issues such as staff turnover. Investigator-initiated trials may be able to standardize the communication more effectively, particularly if only a single site is involved in the study. Interactive methods can also be used in conjunction with some centralized information (e.g. Internet-based methods) to ensure participant questions can be answered and follow-up arranged, as discussed below.
    - If a biopharmaceutical company sponsors the trial and an interactive method is chosen, the sponsor should consider whether RRS is included as a requirement of study conduct in the negotiated contract with the site.

3. One-way communication methods. One-way communication methods (e.g., video summary, automated phone message(s)[50], printed materials, etc.) do not allow participants to ask questions or engage in conversation. Because these delivery methods are not interactive and can be uniform, they tend to have more consistent quality. These delivery methods tend to consume fewer research study site/sponsor resources since the site may simply notify, forward, and/or coordinate RRS delivery. Any one-way communication should be careful to avoid any information that may breach privacy (e.g. a return address on an envelope reading "Hepatitis C Study Partners").

Different situations may require one or a combination of methods. The consistency of the message is optimized in one-way personal or web-enabled communications, but comprehension and follow-up questions may require interactive methods.

[49] Alternatives that might be considered include outreach (verbal or written) by the study staff to the participant, a plan to ask the participant to visit the study site after study completion, or asking the participant to identify a trusted intermediary who could communicate the results displayed on a web site or delivered by mail.

[50] If phone-messages are chosen, participant privacy must be considered. The study team should inquire from each participant as to whether phone messages, cell (text and voice) or home, are sufficiently private to be utilized.

### 3.1.3. Responding to participant follow-up queries:

Dissemination of aggregate results of clinical trials will occasionally result in follow up questions from participants and occasionally from the public. It is advisable to make provisions for answering these questions; each plain language summary should include how to obtain further information and the method should be customized to the study population, the study itself, and the sponsor. The participant may be directed to their primary caregiver for further information, but the primary caregiver may not be familiar with the research, and the site investigator (who is often not the primary caregiver) may or may not be available as results are often available only long after a participant's last visit. Alternatively, the sponsor who is most able to answer questions about the study does not, and should not, have participant identifying information nor should participants compromise their anonymity by having to call the sponsor. Thus, there are a few options that could be considered:

- The sponsor can prepare a series of "frequently asked questions" to post with the summary results and/or to provide to site investigators (and, if known, primary caregivers).
- The sponsor could enlist a neutral third party to be the contact person(s) or entity for inquiries, a solution that might add significant cost.
- The sponsor could create a "neutral" call-in center by which anonymity could be maintained through the creation of a firewall between the center and the company records.
- With any option chosen, there is the formal possibility that participants may disclose important adverse event or other information to the contact person at the time of follow-up. Provisions should be made for appropriately recording and reporting that information to the sponsor.

Different situations may require one or a combination of methods. The consistency of the message is optimized in one-way personal or web-enabled communications, but comprehension and follow-up questions may require interactive methods.

For developers of drugs and devices, we recommend the inclusion of a results sharing plan into a product's overall clinical program development. This means that the organization must choose a delivery method, ideally during protocol development, that is feasible to fund, implement, and operate.[51]

### 4.1.4 Timing of RRS

To ensure compliance in regulated trials, we recommend RRS be returned in accordance with EU regulations for posting of summaries – these are based on strict deadlines. As of January 2015, the EMA[52] is the only regulatory body that has issued guidance on non-technical

[51] Pharmaceutical companies and device manufacturers will need to consider the operational details and planning of results reporting throughout the organization and through the clinical product development program. The internal operational details are beyond the scope of this communication.
[52] EMA Guidelines: http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1403109516539&uri=CELEX:32014R0536 and

summaries; FDAAA[53] has a provisional requirement for posting of patient summaries but a final ruling is currently pending.

To summarize, beginning in mid-2017 the EU clinical trial regulations require results be posted with the following provisions:

- 12 months from the end of a clinical trial for adult trials and 6 months for pediatric trials.
- Irrespective of the trial outcome.
- Written in a manner that is understandable to lay persons (we use the term "plain language" in this document because feedback from patient groups indicated a more positive reaction to this term as compared to "lay" summary).

Note that the RRS communication may need to be reviewed and approved by the IRB/REC of record or multiple IRBs/RECs in the event of a multi-site trial. The delay introduced by IRB/REC approval should be factored into the process.

The EU clinical trial regulations define the term "end of a clinical trial" but allows that the term may be otherwise defined in the study protocol. Other regulatory authorities have not defined whether and when summary results should be shared. While sponsors of regulated trials are required to comply with government-mandated timelines for applicable trials, many studies that are not regulated do not have defined timelines for RRS. Taken together and to mitigate confusion, we recommend consistent timing and source documents for creation of the summary in Table 2 below.

**Table 2 Suggested Timing for Returning Results**

| Trial Type | Timing | Source Document | Actions |
|---|---|---|---|
| **Regulated trials** (typically industry-sponsored, industry-initiated interventional studies, and academic trials [investigator-initiated trials] regulated by the EMA and other relevant regulatory bodies) | Within 1 year of Last Subject Last Visit (LSLV) for adult trials and within 6 months of LSLV for pediatric trials; consistent with EMA guidance[54] unless otherwise specified in protocol | Informed consent form (ICF) and study protocol, clinical study report (CSR) and/or ICHE3 synopsis (CSR synopsis) | • Return RRS to trial participants by method chosen<br>• Post non-technical summary on EU database consistent with EU regulations (anticipated mid-2017)<br>• Post on other sites as appropriate given local laws and regulations |

http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000555.jsp (accessed January 1, 2016)

[53] FDAAA Guidelines: http://clinicaltrials.gov/ct2/manage-recs/fdaaa (Accessed February 2, 2016)

[54] As noted in the EMA Appendix on disclosure rules to the functional specifications for the EU portal and database (EMA/42176/2014), Footnote p. in Table 1

| | | | |
|---|---|---|---|
| **Academic and trials not regulated by the EMA or other relevant bodies** (including most investigator-initiated industry-sponsored trials | Within 1 year of the study close by the IRB, or final data analysis, or concurrent with the release of the first study publication | Informed consent document (ICF), study protocol and publication or abstract | • Return RRS to trial participants, even for unpublished trials<br>• Post non-technical summary |
| **Longitudinal / observational /other studies** | Concurrent with the release of each major study publication | Informed consent document (ICF), study protocol and publication | • Return RRS to trial participants and after each update<br>• Post non-technical summary |

### 3.1.5 Prior Publication and Timing of RRS

The International Committee of Medical Journal Editors (ICMJE) has determined that a tabular results summary posted on ClinicalTrials.gov does not constitute prior publication, but it has not yet modified the language to reflect the upcoming changes in the EU mandate.[55] That said, prior communication of results and public awareness may decrease the novelty and priority of a proposed publication, an obvious concern for authors.

The timing of RRS should be coordinated with requirements for posting results on ClinicalTrials.gov, EudraCT, similar sites (e.g., as defined by regulatory agencies going forward), and with the potential scientific publication of the results. Most journals require novelty of the submitted study and manuscript; RRS should not contain information that trumps or inhibits appropriate publication of the study, a concern that is mitigated by the fact that a publication will contain more complete results and potentially additional endpoints. Sponsors should anticipate that participants and the public may communicate results (e.g. by social media avenues) once they have them or when results are posted on a publicly available website; there should be no assumption of corporate confidentiality once the general study

[55] "It is important to note that the ICMJE clinical trial registration policy requires prospective registration of all interventional clinical studies, but does not require results reporting for registered trials. While the ICMJE recognizes the potential problems associated with posting preliminary research results that have not yet undergone an independent peer-review process, it acknowledges that the Food and Drug Administration Amendments Act of 2007 (FDAAA; U.S. Public Law 110-85, Title VIII) mandates the posting of summary results data for certain trials in ClinicalTrials.gov. Thus, the ICMJE will not consider results data posted in the tabular format required by ClinicalTrials.gov to be prior publication. However, editors of journals that follow the ICMJE recommendations may consider posting of more detailed descriptions of trial results beyond those included in ClinicalTrials.gov to be prior publication. The ICMJE anticipates that the climate for reporting results for registered trials will change dramatically over *[sic]* coming years and the ICMJE may need to amend these recommendations as additional agencies institute other mandates related to results reporting." http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/. (Accessed January 1, 2016.)

results have been communicated.

### 3.1.6 Coordinating RRS among study sites

In a multi-site trial, RRS communications (including the guidelines and script for a verbal communication) need to be coordinated among study sites.

For industry-sponsored trials: The sponsor has the ability to generate the content for the RRS, either posting the RRS on a common web site or disseminating a common instrument to all study sites. The MRCT Center suggests, therefore, that the industry sponsor draft the RRS document (and supporting materials) and submit to the Principal Investigator (PI) or an internal lead medical doctor for review and, as appropriate, also have it reviewed by a person who is familiar with health literacy principles. The PI may dialogue with their IRB if the study is considered "open" and determine if review of the communication is necessary. For a multi-site trial, in the event that IRBs/RECs revise the RRS document, deviation from the original RRS version may occur, and harmonization will require even more time (as revised documents recirculate to other participating IRBs/RECs).[56] While there is no regulatory requirement that the RRS document be concordant across all sites, harmonization is preferred for a streamlined message and dissemination process for all trial participants.[57] Further, harmonization and consistency decreases the risk of miscommunication, the potential for subtle changes to introduce promotional content, and the promulgation of neutral and balanced content. Thus, the timing of return of results should incorporate a calculation for potential delays in multi-site research, since consistent information needs to be shared across all sites and changes may be sought.

For investigator, government, or not-for-profit sponsored trials: The MRCT Center suggests that the overall PI be involved in coordinating the RRS, similar to the PI's responsibility for the informed consent document. The PI can designate somebody with an appropriate skill set to draft the document, submit to a publications committee or other review body (if one exists) for approval in concordance with any publication, submit to the IRB/REC of record for review and approval (if required), and disseminate to the site investigators. Should the local IRB/REC, if one exists, determine that changes are necessary, these changes should be reviewed by the PI; substantive and important changes should be incorporated and re-released. It is recommended that the PI constitute or consult with a team that is familiar with principles of health literacy during the development of the document and as a review step prior to release of the RRS.

### 3.1.7 Ensuring integration and sustainability of RRS

Organizations should consider how to incorporate RRS activities and process tasks into existing workflows and checklists. Organizational policies, processes and procedures should be updated to include the intention to return results in plain language, and should utilize available clinical templates and standard documents (e.g. study protocol and ICF templates). Organizations will need to determine the type and frequency of RRS reporting and how best to monitor and incorporate feedback on participant comprehension and perceived value. Methods such as initially soliciting feedback from focus groups prior to dissemination, or

[56] This further delay is not an issue in single-site IRB review of multi-site trials.
[57] The UK HRA guidelines do not comment on the need for or benefit of dissemination of consistent information.

periodic "teach-back" interviews in sample populations may be helpful in gathering information.

Organizations have choices in establishing an infrastructure to support these new RRS functions: integrate the RRS work into an existing department, create new areas of responsibility, or outsource one or more components of the program (i.e., content development, production, or delivery/dissemination).

## 3.2 Process and logistics for study-specific results sharing

After the organizational program is developed and infrastructure is established (i.e., internal or outsourced arrangements are ready for program execution), implementation of study-level RRS can proceed. An optimal study-specific process starts before study enrollment begins and concludes when the participant receives the RRS and their questions are answered as described further below.

One target audience of the RRS is the study participant, yet there are additional stakeholders who may desire notification of RRS, including a designated third party (e.g. spouse, parent, or other caretaker of participant), study site, the participant's physician(s), institutional review boards, publications for which articles have been or will be submitted, advocacy and community organizations, and other entities as required by law or regulation. The general public is another important target audience. Any planning for communication should review and determine whether, when and how each stakeholder will be informed.

### 3.2.1 Before the study starts

Planning for RRS prior to study start can help the organization implement a smooth process. The primary pre-study activities include:

- Updating organizational policies, processes and procedures as needed.
- Updating investigator and site policies, processes and procedures as needed.
- Establishing the level/timing/delivery method of the planned RRS.
- Budgeting for RRS activities.
- Developing and incorporating the RRS information into appropriate study documents including the informed consent document, the program communication and publication plan and possibly the study protocol and investigator contract (see discussion above).
- As appropriate, developing an information sheet for participants[58]
- As appropriate, building staff capacity (e.g., conduct training) with appropriate expertise.

Additional information is listed in During Study Conduct, Participant End-of-Study-Visit, below.

[58] "Information for participants at the end of a study: Guidance for Researchers" retrieved from: http://www.hra.nhs.uk/documents/2014/09/information-participants-end-study-guidance-researchers.pdf. (Accessed February 2, 2016.) To the best of our current knowledge, only the UK HRA requires an information sheet for participants at this time; the development of an information sheet is a practice that could profitably be emulated elsewhere.

### *Protocol development*

- Anticipates the notion that participants will be given an opportunity to receive study results.
- It is recommended not to include specifics, otherwise any change in the delivery method will trigger a required amendment as well as IRB/REC review (see IRB/REC section for more detail).

### *Informed Consent Form (ICF) development*

Include a section in the ICF that explains, in simple terms, the RRS information. Very specific and detailed information will constrain sponsors and investigators, particularly as approaches evolve with experience and practice. Therefore, a more general statement may be more appropriate, such as:

- How the participant can take action to receive or opt-out of receiving an RRS (e.g., "In the future, you can decide whether or not you wish to receive the general results of the study. You do not need to decide now about this.")
- The timing and format for RRS delivery (e.g., for sponsor-investigator trials: "We anticipate that your participation will end in *[month/year],* but the study itself will continue until all participants and all sites have completed their study. Then the results must be analyzed and the researchers will need time to understand the results. That generally takes a year or so as the analysis is often complicated. Therefore, you will receive [*insert the specific contact information and next steps for the participant - for example: "a letter with a link to the general study results" "information on the website about the study only a year after the last participant has ended the trial"*]. "Please let us know if you do not have access to a computer or access to the Internet.")[59]
- For instances where the participant will be contacted directly (usually either by the investigator or third party), the ICF should emphasize the importance of the patient keeping their contact information up to date with the study site in order to provide an RRS to them as soon as it becomes available.

### *Resource Planning*

Resources and funding are addressed at this stage. Increasingly complicated study designs require accurate budget forecasting and should include RRS budgetary needs (for RRS planning, data analysis and compilation, and execution). Additionally, this is an ideal time to identify and schedule the following items:

[59] In the event that a participant does not have access to the planned method of communication (e.g. no Internet access, is illiterate, homeless and thus unable to receive a letter and no appropriate delegate to assist), the investigator should consider how to communicate with the participant—perhaps including the opportunity to return to the site for explanation—and document the difficulty and anticipated solution. The sponsor should also be notified as should the IRB/REC if this eventuality represents a deviation from the written approved protocol. If no solution can be found, the investigator should work with the sponsor and the IRB/REC to manage the consequences and amend the protocol if necessary.

- The sponsor should notify, discuss, and agree internally upon the resources responsible for RRS execution (i.e. internal departments, external vendors, investigators, and/or study sites)
- If RRS will be disseminated while the study is ongoing (e.g. longitudinal studies) and provided individually to the participants, the investigator should dialogue with their IRB/REC to determine whether and what IRB/REC review is necessary. If RRS is envisioned by posting to a public site and not returned individually to participants, IRB/REC review is not required. If the study has ended, the investigator may inform the IRB(s) of record of RRS and even provide an RRS copy to the IRB (see Role and Involvement of the IRB/REC above). In some cases, institutions may have separate review boards for RRS, especially when genetic research results are involved and can be provided.

### 3.2.2 During study conduct

The organization may choose to perform preparatory RRS activities while the study is ongoing and prior to study close-out to save time. RRS compilation can begin by selecting the pre-approved RRS template (see *MRCT Return of Results Toolkit* for examples) and populating information that will not change (i.e., from the protocol and ICF [refer to the Content section]).

Some organizations[60] (typically the investigator, study team, and/or third party) may choose to stay "connected" with the study participants[61] throughout the study, potentially ensuring continued participant engagement. Examples of communication opportunities to keep participants connected and updated include:

- A thank you letter after the ICF is signed and participant enrollment has been confirmed
- A letter of appreciation after the individual participant has finished their last follow-up visit (see Participant end-of-study visit below)
- An annual holiday card, enclosed in an envelope for privacy, detailing the stage of the study (e.g., "The study is continuing to enroll study participants. We do not anticipate analyzing the results for at least another year.")
- Periodic letters explaining the stage of the study (e.g. "The study enrollment is complete. The last person will complete their follow up visits in 18 months and we will then begin to analyze the results." Or "The data are gathered and complete. It will take approximately 6 months to analyze the data so that we know the study results.")
- When Internet posting of results is anticipated, an effective method to retain participant (and public) engagement is to ask visitors to the site to join a listserv. Such registration is, of course, elective, but it permits the site moderator to "push out" notifications of periodic

[60] It is important to remember that except in rare instances, the study sponsor does not retain any participant contact information, so direct communication (if any) becomes the responsibility of the investigator, study team, and/or a third party. Some study sponsors are developing methodologies to engage participants with appropriate consent and election (e.g. Pfizer Blue Button initiative that allows participants to download their electronic clinical data collected during the trial. See http://www.pfizer.com/news/press-release/press-release-detail/pfizer_expands_clinical_trial_data_access_policy_and_launches_data_access_portal; accessed 5 (Accessed October, 5, 2015)

[61] Of course, data privacy and data protection laws take precedence.

updates (e.g. an email stating simply "Updated results are available" and the link) that then notifies the user that there is new information posted on the website.

Communicate with those study participants who have completed or ended their active participation in the trial is encouraged, recognizing that some may wait months or years between their last study visit and the time when the RRS will become available.

Occasionally, unexpected study challenges can result in early termination of the study. Refer to the Special Considerations section for recommendations on addressing these situations.

Investigators and their study teams have an opportunity to address participant access to information about the study throughout the study conduct. Specifically:

### *Discussion of informed consent* (IC) *with participant*

At the time of IC discussion, in addition to specifics about the study, the consenting investigator may mention:

- Whether, when and where RRS will be posted to an Internet website, how that website can be accessed
- Trial participants who will receive RRS (e.g., consented and enrolled, randomized, and/or those completing study)
- The process and anticipated timing for the participant to opt-in or –out of RRS
- The anticipated timing for RRS distribution (e.g., study publication, submission to US FDA or other regulatory body, a specified time after study completion)
- Whether, and what, information will be given to participants regarding their own data during and after the study participation (see below)
- How the participants will remain in contact with the study site
- For instances where the participant will be contacted directly, the importance of keeping their contact information up to date with the study site should be emphasized to the participant to allow for re-contact.
- Whether participants would like to designate a person to receive information in the event of their incapacity or death

### *Participant end-of-study visit (last study visit)*[62]

The end of an individual's participation in a study (end-of-study visit) is an ideal time for the investigator to discuss the participant's individual data as well as the anticipated aggregate results of the study. It is a time when participants should again be thanked for their voluntarism and participation in research that will add to knowledge that may benefit future generations of patients and serve to enhance public health. In some cases, of course, return of individual or aggregate results will not be appropriate. For example, the

[62] See also http://www.hra.nhs.uk/documents/2014/09/information-participants-end-study-guidance-researchers.pdf (accessed January 1, 2016) and http://www.hra.nhs.uk/documents/2013/08/care-after-research.pdf (accessed September 15, 2014)

sponsor/investigator may not want to or be able to return results for tissue contributions to a biorepository;[63] some observational, social, behavioral, and long-term studies; or in cases where the IRB/REC has waived consent. In other types of research, discussion of return of results may be appropriate.

Since participants may not remember all the information shared at end-of-study visit, it is helpful if this information is provided in a written summary.[64] If the information is consistent with the information provided to the IRB/REC at the outset, there may not be a need for ethical review depending on the guidance of local regulatory authorities.[65] However, the IRB/REC of record may wish to review the information sheet, particularly in instances where the information is incremental to or is different from the original plan (whether included in the protocol or not). Consideration should be given to offering the following information at the end-of-study visit:

- What participants can anticipate after their participation ends and advice regarding monitoring for anticipated and unanticipated adverse events (e.g., rare, common, severe and serious). In the event of questions or adverse events, whom to contact and the appropriate contact information.
- A reminder that the participant may be contacted in the future if any adverse events are uncovered that might impact their health—and if contact information for the participant is available at that time.
- Access to any benefits or care as a consequence of participation (if offered) should be explained.
- Advice as to where to obtain further treatment and/or clinical care, particularly in the event that the participant does not have a healthcare provider.
- Any information regarding the participant's personal data compiled during the study (see below)
- Discussion as to whether the participant would or would not like to receive aggregated study results at end of study, with an opt-in or opt-out statement.[66]

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[63] Notably, some tissue banks are creating periodic newsletters to all donors, a practice that serves to express appreciation of the donation and to illuminate the benefits of tissue-based research.

[64] All information sheets should follow principles of health literacy, as discussed elsewhere in this document.

[65] Recent proposed guidance from the Health Research Authority, National Health Service, UK, definitively states that "If the end of study information sheet builds on the information provided in the original PIS and is in line with the arrangements agreed by the REC as part of their approval, then the end of study information sheet does not require ethical review…", and "There is no need to seek to REC review of the end of study information sheet simply because you did not reference the end of study information sheet in the initial documentation reviewed by the REC. Similarly, any material used for the dissemination of the study findings should not be submitted for ethical review." http://www.hra.nhs.uk/documents/2014/09/information-participants-end-study-guidance-researchers.pdf, (accessed September 12, 2014). The regulatory authorities have not harmonized guidance on this point, and sponsors and investigators are encouraged, therefore, to seek guidance from the IRB/REC of record.

[66] We note that providing the choice as to whether to receive RRS is both costly (requiring the development of IT infrastructure and complicated monitoring) and difficult to track, if the intention is to provide results in a method other than via a website (e.g. personal letter or a conversation with a caregiver, investigator, or study team member). The concept of voluntariness is incorporated into a web-enabled process whereby the participant must actively log onto a website to see results (e.g. "If you would like to view the summary results,

This information may be dependent on the method of dissemination of RRS. If an Internet website will house RRS, the participant should be reminded how to access the site, and that access is elective (e.g. "If you would like to view the summary results, you may go to the following website…"). Ensure that the participant has the ability to access the results in the format provided (e.g. literacy if the results will be written, Internet access if results will be posted).[67]

- If participant has opted to receive RRS, an approximate timeline for available information.
- Information regarding whom to contact in the event of questions regarding the content of the RRS (see Template in *MRCT Return of Results Toolkit*).
- A confirmation of the participant's contact information and an opportunity for the participant to correct it. A reminder to the participant in the future to maintain current contact information. Note that while participant contact information is necessary for RRS, it can be retained without keeping "identifiable private information" linked to the study.
- Whether the participant would like to designate a third party to receive results in the event of their incapacity or death.

The MRCT Center suggests that, prior to RRS being developed, study sponsors and/or investigators should consider providing participants with a formal "thank you" for their participation and providing further information on next steps.

### *Individual participant data[68]*

In general, individual participant information should not be posted to an Internet website unless a secure, password-protected website is employed. Individual participant data including randomization may be shared with the investigator and site or through other methodologies (e.g. the "Pfizer Blue Button Initiative"[69]) that can more reasonably ensure confidentiality and privacy. The investigator or site will then communicate with the participant.

Particular attention should be paid to what information will be given to participants regarding their own data during and after the study. If health information (e.g. Clinical

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you may go to the following website…"). This is a simpler and less costly process, although participants that do not or are unable to have web connectivity will need to be accommodated.

[67] Sometimes the method of delivery will impact the participant's desire to opt-in (e.g. participants may not wish to receive a letter at home).

[68] The MRCT Center is currently engaged in a significant project on return of individual results to participants. See http://mrctcenter.org/projects/return-of-individual-results/ (accessed January 1, 2016). We anticipate that this section will be updated in the near future.

[69] See http://www.pfizer.com/news/press-release/press-release-detail/pfizer_expands_clinical_trial_data_access_policy_and_launches_data_access_portal; (accessed January 1, 2016)

Laboratory Improvement Amendments (CLIA)-approved laboratory results or radiographic studies)[70] is derived as part of ***clinical*** care, the patients have a right to that information. However some ***research*** tests are performed for the express purpose of the research study but are nevertheless performed and interpreted in a manner identical to clinical practice. [71] In this limited setting, the MRCT Center suggests that the results should be shared with interested participants and their healthcare provider as long as they are performed under conditions identical to that performed for clinical care.[72] While the results are often, but not always, shared with the participant during the clinical trial, often there is reason to summarize these studies at the participant's last visit for their records or for the benefit of the referring caregiver.

***Experimental*** tests performed in a non-CLIA approved laboratory should not be shared or if shared, only after additional consideration and discussion. Such considerations might include whether the test was or can be repeated under CLIA-approved conditions, whether the result is actionable, or whether the result has implications for the participant's health beyond the study (e.g. finding a BRCA-1 mutation that confers an increased risk for developing breast, ovarian and other cancers). In such cases, the sponsor and investigators should consider whether and how to repeat the test in a CLIA-approved laboratory and whether and how to inform the participant and/or their provider.

Often the participant will want to know to which specific "arm" of a study they were assigned. Investigators and their study team should be prepared to explain if and why that information can or cannot be shared and when.[73] It may be helpful to anticipate and address this question in advance of the end-of-study visit (e.g. during the informed consent discussion, at intervals during study treatments). If the information will be made available, even long after the study ends, the participant should be so informed. The investigators can then in turn share specific information with the participant or healthcare provider. Any communication should follow the principles outlined here, including those of health literacy.

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[70] The Centers for Medicare & Medicaid Services regulates all laboratory testing on human samples in the U.S. through the Clinical Laboratory Improvement Amendments (CLIA). See https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/clia (accessed 2 February, 2, 2015). It does not regulate laboratory tests performed for research. Many other countries have similar, but not identical regulations and rules to ensure the quality and validity of laboratory testing.

[71] For instance, an oncology study calls for three MRI studies, one at baseline (required for clinical care) and one after the first and fourth cycle of investigational agent. The second two studies are "research" studies, and would not have been done but for the research. Nevertheless, the studies are performed in a manner identical to the first and can be relied upon for clinical decision-making. Note that this situation differs from research on specimens collected from the participant for the development of a novel biomarker or surrogate endpoint, in which there is no (or unproven) clinical validation.

[72] In the US, such conditions may require generating results in a CLIA-approved laboratory. Other situations are beyond the scope of this current document (e.g., if individual genomic results are returned, whether and how to provide for genetic counseling.)

[73] Thus, investigators and their study teams should be prepared to explain the concepts of bias and "blinding" and the necessity of maintaining the blinding until the end of study. While randomization may minimize differences between groups at assignment at the outset of the trial, it does not prevent differential treatment, outcome assessment, or analysis later in the trial. Blinding is important throughout the trial in order to prevent any bias estimate of treatment effect.

### 3.2.3 After all data for the primary endpoint has concluded and (often) after the study ends

After data analysis is complete (at least for the primary endpoint and often coincident with the end of the study), RRS should be finalized and dissemination plans made. Content preparation begins in earnest after data analysis, consolidation, and summary reporting. The RRS is developed according to template instructions (see *MRCT Return of Results Toolkit*).

The RRS may be reviewed by the clinical trial team, and, if available, a medical communications group. In addition, optimally internal and external reviewers with varied backgrounds and perspectives may be helpful, including those with legal and regulatory expertise (e.g. to ensure promotional language is not included), and those familiar with health literacy principles. For investigator-initiated trials, it may be helpful for the human research protections office or a trained research patient advocate to help review the document. Piloting the written summary with a select group of appropriate individuals that should be, but need not be, participants may help to ensure comprehension and the intended meaning of the communication.

The MRCT Center suggests considering the selection of one or more individual(s) with the following perspectives, as review by these individuals may be helpful particularly as the process is initially developed and launched. Whether and which reviewers are necessary will depend upon the study population, study specifics and complexity, location, and sponsor:

| **Perspective** | **Potential reviewers** |
|---|---|
| Primary focus and content expertise in the area studied | Principal investigator or specialty physician |
| Limited expertise in the area studied | Member of a Community Advisory Board or other community representative |
| No affiliation (personally or family member) with the institution | CRO representative, external medical writer, or cooperative group member |
| Limited experience with the condition/ disease | A person who does not have the condition/ disease studied, nor do they have a family member with the condition/disease or any relationship to the clinical trial |
| Expertise in patient-focused communications | A member of an advocacy group, an individual familiar with health literacy principles; an individual who will review for clarity, tone and objective language in the communication |
| A representative from study sponsor | Someone other than from commercial or marketing representation if a for-profit entity<br>Medical writer<br>Statistician (to ensure accuracy) |

| | |
|---|---|
| | Plain language summary review process should be consistent with the CSR. |
| Individuals with both adequate and low health literacy skills, to assure comprehension | Members of appropriately selected focus group |
| Expertise in clinical research ethics | An IRB/REC professional with no relationship to the clinical trial. A central IRB is an option. |

For FDA, EMA and other regulated studies, it is important that the RRS be concordant with the submitted clinical study report (CSR).

After completing RRS review, the next step is to identify the study participants who have agreed to receive the RRS, and notify them that the RRS is now available. (Depending on the program design, the organization may offer one final opportunity for study participants to choose whether or not to receive the RRS, either at the last study visit or when the summary becomes available).

The organization can then initiate dissemination of RRS, the execution of which will vary based on individual program design. As part of the dissemination tasks, the sponsoring organization may also be posted on websites such as ClinicalTrials.gov, EudraCT, or sponsor websites or may provide RRS copies to participating study sites, IRBs involved in the study, treating healthcare providers, and appropriate health-related community organizations.

If an interactive method of communication is chosen, all questions from the participants should be retained and reviewed. The MRCT Center workgroup also suggests that participant feedback, specifically comprehension and perceived value of the RRS, be obtained and this information incorporated into process improvement activities going forward. Such feedback can also be obtained via focus groups, longitudinal surveys, or semi-structured interviews.

## 4. Content of RRS

### 4.1 General Principles

A clear distinction exists between academic journal articles reporting technical and specific clinical study results and an RRS of general results to study participants and the general public who are not generally engaged in scientific or medical fields.

The general RRS should first be developed to ensure comprehension by a trial participant, and subsequently edited for regulatory compliance. The tone, style, language, reading level, layout, and content of each RRS should be constructed with the participant in mind while adhering to both the letter and spirit of government rules and regulations.[74] It is critical to involve a reviewer familiar in the regulations to ensure that no "promotional language" is included. It is also helpful to involve a person familiar with health literacy to facilitate the review of communications that are clear and understandable to participants.[75] Clear communication benefits all participants, regardless of their education, level of health literacy or familiarity with the clinical trial process. As has been stated, "Adopting health literacy universal precautions acknowledges that the complexity of the health care system challenges virtually everyone…And it recognizes that all patients benefit from clear, actionable information and simple patient education materials."[76]

Content in the RRS can come from different sources (e.g., the informed consent document, protocols, clinical study reports (CSR), publications, poster abstracts, ClinicalTrials.gov or other regulatory postings). All information in an RRS should be clear and simple. Context should focus on the results of the clinical trial in question. It is always important to state that the results reported in the RRS are only of a single study that may be part of a larger drug or product development program; the results of this single study may not be representative of other studies or the program as a whole. Data from the study should be reported even if it is contrary to the approved product label. The RRS should describe where to obtain further information, if available.

RRS developers should use accepted health literacy principles. Professionals (e.g., patient advocates, some medical writers) who have educated themselves on these principles can assist in simple language result summaries. Appendices 4 and 5 provide resources to help writers develop and evaluate materials using accepted health literacy principles. (There are also commercially available software programs that can assist in simplifying language, some for an annual user fee.) Critical factors of health literacy include:

- Well-organized content presented with familiar vocabulary to non-medical people, and short sentences.

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[74] Getz, Hallinan, et al. (2012); Meeting the obligation to communicate clinical trial results to study volunteers; *Expert Rev. Clin. Pharmacol.* 5(2), 149–156.
[75] Koh, H. K., Brach, C., Harris, L. M., & Parchman, M. L. (2013). A proposed 'health literate care model would constitute a systems approach to improving patients' engagement in care. *Health Affairs*, *32*(2), 357-367.
[76] *Ibid*.

- 6-8th grade reading levels. Reading level scales[77] that approximate grade levels are helpful, for health literacy (see Appendix 4 for detailed information). EU guidance, currently in draft form[78], enumerates literacy assessments by country and suggests tools that can be used to assess literacy levels for the commonly spoken languages in Europe.
- Elements designed to help improve reader comprehension such as
    - Headlines to organize information
    - Presentation of the "big picture" before the details (inverted pyramid writing style)
    - Descriptive headers and subheadings
    - Bullet points instead of paragraphs
    - Numeracy principles to describe statistics (see Appendix 4 for detailed information)
    - Limited use of tables and charts
    - Adequate "white space" (e.g. separate paragraphs and topics by one or two lines, a minimum of 12-point font)
    - Hyperlinks to summary sections, additional information, and resources for online summaries and background information
    - Where to access additional resources and other online summaries
    - Limited use of imagery (icons, logos, etc.)
    - Sufficient contrast between font and background color
    - Avoidance of text in "all caps"
    - Limited use of acronyms, abstract, medical, or multisyllabic words (e.g., "unanticipated," "hematopoietic," etc.). If such words must be used, add clear language to define them.

It is important to anticipate the questions patients may have after receiving the RRS, particularly if there is some action that the participant may need to take based on the results. Some of these questions may be addressed in a separate Frequently Asked Questions (FAQ) or Question and Answer document.

The summary information must be relayed in a way that is perceived as neutral, non-selective, balanced and simply reflect the data and findings of the study.

## 4.2 Levels of personalization for result summaries

In terms of scope, there are various levels of content that apply to study participants. In addition to the public release of study data (e.g. ClinicalTrials.gov, EudraCT, journal publication), the participant may receive (1) a general overview of study results that could also be shared with other stakeholders, (2) detail of the study arms, and potentially their assignment to study arm and their own study data, and, potentially (3) individual results for each participant. Only general guidance is given here.[79]

[77] See, for instance, the Microsoft Word tool that measures readability scores. This is one example of many.
[78] See http://ec.europa.eu/health/files/clinicaltrials/2016_06_pc_guidelines/gl_3_consult.pdf (accessed July 9, 2016)
[79] As mentioned, the MRCT Center is currently engaged in a significant project on return of individual results to participants. See http://mrctcenter.org/projects/return-of-individual-results/ (accessed January 1, 2016).

### 4.2.1. General overview of study results

The first level of summary information contains an overview of the study and presents the conclusions of the study in simple language that uses health literacy concepts. This general RRS is intended for trial participants, but may also be considered as a more public version of the summary if such uses are desired (e.g., for media, IRBs, study sites, community groups, patient advocacy organizations, future participants, etc.). The summary might also be posted on EudraCT, ClinicalTrials.gov (although the website does not currently support this function), another website, or other searchable sites.

Study participants should learn about the study results at the same time as other parties, instead of being "the last to know." All too often, participants hear about the results of a study from the media (TV, newspaper, radio) rather than from the investigator or their physician. On the other hand, in the US and other countries, companies must publicly release information that may impact their valuation and thus cannot, by securities law, let participants know study results in advance of the public. Therefore, information release to all audiences should be coordinated and planned. Sponsors and investigators should consider developing a formal communication and publication plan and a risk and contingency plan to think through specific eventualities, including timing and outreach.

### 4.2.2. Results by study arm ("Group") see 75

More detail for each study arm/treatment group can be offered to inform study participants which group(s) they were in, refer them to their treating physician (if not involved in the study), or to a specialist for more information. The templates in the *MRCT Return of Results Toolkit* give general information about each arm, and can be expanded with more detail if the sponsor chooses this option.

### 4.2.3. Study results for each individual see 75

Individual study results for each trial participant are beyond the scope of this document, due to a large number of other factors to consider when returning an individual result. The MRCT Center suggests that the decision as to whether or not to produce and distribute individual results should be made during protocol development. Additional materials that assist physicians in giving consistent, quality information to their patients are encouraged.

### 4.2.4. Incidental Findings see 75

Rarely, study results reveal incidental findings that hold immediate clinical implications for individual participant(s). The MRCT Center suggests that in this situation, the sponsor and investigators should consider how and when to advise the participant or their caregiver as to specific actions that should be taken. When the incidental finding has implications for immediate action, investigators and sponsors should inform the appropriate party as soon as reasonably possible and not wait until study termination. If unanticipated, it is good practice to inform or to request a determination from the IRB/REC in advance of disclosing the result.

## 4.3 Essential sections for Return of Results Summaries (RRS)

The MRCT Center considers the following RRS document sections essential to ensuring participant comprehension. Each section includes a description of suggested content. In addition, templates for interventional (therapeutic) phase 1 and randomized phase 2/3 clinical trials and studies closing early are available in the *MRCT Return of Results Toolkit*.

Titles for each section are provided in the left column of Table 3[80], with short explanations and/or examples. Additional information on frequently reported endpoints and non-promotional language is also available in the *MRCT Return of Results Toolkit*.

**Table 3 Summary of Essential Elements for Inclusion in the RRS[81]**

| *Essential sections* | *Description of content* |
|---|---|
| ***A thank you to study participants*** | Includes a simple thank you for the study participant's contribution to the study. This is part of the header in the template, but can also be placed in the body of a letter. |
| ***Simple title of the study*** | Describes the study in plain, simple language for study participants who may not understand medical or scientific terms. The full title is required by U.K. guidelines, with short title added, if desired, as well. |
| ***Summary of results*** | Write a one- to two-line concise summary statement with the take-home message (like an abstract to a paper). Results must be communicated in a factual manner and a simple data table presenting the primary endpoint(s) at a minimum may be helpful. Additional endpoints should be considered only to the extent they are statistically sound and can be selected in an unbiased way that increases rather than diminishes clarity and understanding of the study for a general audience. |

[80] Recently, the EU published a draft proposal for comment entitled, "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" in which they state, "It should be noted that the wording of the ten elements cannot be changed but that sponsors can, if they wish, combine categories where this makes sense… Sponsors may also decide to change the order of the headings if they feel this is appropriate and add sub-headings as required." See http://ec.europa.eu/health/files/clinicaltrials/2016_06_pc_guidelines/gl_3_consult.pdf (accessed July 9, 2016). The MRCT Guidance and Toolkit do not conform to the draft guidance proposed by the EU as we do not believe that the headings and language used comports with health literacy principles. Should the EU guidance be finalized, the MRCT Center anticipates that we will modify the materials accordingly.

[81] The EU directive at http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2014.158.01.0001.01.ENG is summarized in Annex 5, "CONTENT OF THE SUMMARY OF THE RESULTS OF THE CLINICAL TRIAL FOR LAYPERSONS" states, "The summary of the results of the clinical trial for laypersons shall contain information on the following elements: (1) Clinical trial identification (including title of the trial, protocol number, EU trial number and other identifiers); (2) Name and contact details of the sponsor; (3) 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); (4) 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); (5) Investigational medicinal products used; (6) Description of adverse reactions and their frequency; (7) Overall results of the clinical trial; (8) Comments on the outcome of the clinical trial; (9) Indication if follow up clinical trials are foreseen; and (10) Indication where additional information could be found." (accessed 2 February 2015). Note however, that the "comments" cannot be considered promotional or conclusory.

| | |
|---|---|
| ***Disclaimer*** | State that this summary includes only results from one single study. Other studies may find different results. Newer information since this summary was written may now exist. |
| ***Why the study was done*** | Includes why this study is important, purpose of the study, and why the endpoints were chosen. Consider including a brief, simple statement of what is known about the disease/condition and how it is generally treated. |
| ***Study Information*** | Includes the following<br>▪ *Start and stop dates, with explanation of early stoppage when appropriate (see Early Clinical Trial Closure template in the MRCT Return of Results Toolkit)*<br>▪ *Countries in which the study was conducted*<br>▪ *Characteristics of the study population, number enrolled, number randomized and number completing study.*<br>▪ *Date result summary was produced. If there are substantive changes, an addendum will be created. (Occasionally the first communication is updated rather than an addendum created.)*<br>• Clear description of the specific population that was studied (e.g., key eligibility criteria such as age, gender, race/ethnicity, molecular subtype of the disease under study)<br>• A clear statement that the results apply to this population, and not any other population, and under these specific conditions.<br>Explanation that other information may be available later and where such information may be found |
| ***How the study worked*** | Explain the phase of this study and the fact that this is only one study in an overall drug development process.<br><br>Provide a simple explanation and consider picture or diagram that shows the protocol flow, number of arms, treatment per arm, and other pertinent information that is helpful to understanding the results (e.g. study procedures especially if relevant to the understanding of the results). The contextual information should help to ensure comprehension of results. Avoid or minimize the use of unfamiliar acronyms and medical terms. If any medical terms are used, include a simple explanation, followed by the medical term in parentheses. *For example: "numbness and pain in hands and feet (peripheral neuropathy)."* |

| | |
|---|---|
| ***Side effects / Adverse events*** | Consider using simple terms (e.g. symptoms, side effect[82], warning signs, safety events) instead of "adverse events." Define the term used in simple language. In the EU database, adverse events or "side effects" are not currently to be listed in the RRS.<br><br>Additional information to consider in this section:<br>• For each adverse event: how common or rare; how mild or severe?<br>• Any secondary endpoint that statistically measured adverse events<br>• A description of any severe effects (if they occurred), with an explanation of short or long-term consequences, when possible<br>• Additional regulatory requirements - described in clear, simple terms<br>• Plain language should be used, not medical jargon, when describing adverse events (i.e., use "fainting" instead of "syncope"). |
| ***Official title of the study*** | Include the official title and all related study number(s). |
| ***Final Comments*** | Include wording such as "This research helps future patients and families by helping us understand more about each medicine today. If you have questions, please talk to your *[e.g. study doctor, trial designee for study specific questions, or your personal physician about your individual health care]* or contact *[list appropriate contact information and/or resources available]* about the study or your part in it."<br><br>List the official numbers *(e.g. protocol number, federal number(s), other IDs),* followed by the official title of the study, with wording such as "To learn more about this trial, visit the ClinicalTrials.gov website at *[provide URL link for this protocol here]*. More information may also be available by looking up the official number or title, or by going to *[list any websites that may have sponsor information, plain language information, non-scientific articles, etc.]*."<br><br>List additional information that will help explain the study or the disease/condition, such as "You can also find more details |

[82] Prior to regulatory approval, even anticipated risks (e.g. nausea and vomiting as a consequence of chemotherapy administration) are termed "adverse events." "Side effect" is a term usually reserved for common adverse reactions described after the safety profile of an investigational product is known and approved for use, however, by plain language principles and with the desire for participants to understand the RRS, the term "side effect" is used here. In the setting of RRS of an investigational product, the term "side effect" does not imply causality and should not be inferred to indicate liability; "side effect" is used simply to assist in plain language communication.

about this study at: *[List all applicable citations and websites that are not listed in ClinicalTrials.gov. This can include resources as well as articles]."*

List all sponsors, including companies, private foundations, public funding, donors, etc.

Thank them again.

## 4.4 Cultural Literacy

Numerous studies and articles have highlighted the under-representation of racial and ethnic minorities within clinical trials.[83] Further, studies have shown that language barriers contribute significantly to patient dissatisfaction.[84] In order to avoid furthering informational disparities among those minorities who enrolled in the research study, sponsors and investigators must take steps to ensure that their process for returning results reflects cultural literacy principles.

### 4.4.1 Translation of Research Results Summaries

Sponsors should professionally translate RRS into languages used by all trial locations, and into relevant languages if the percent of racial or ethnic minorities at an individual site exceeds a predetermined percentage (e.g., 10%). Further, translations should be read and interpreted by a native speaker to ensure appropriate connotation, and attention to dialect and local language (e.g. differences between Spanish and Hispanic languages) should be given. Additionally, translation may profit from forward-back-forward translation to ensure accuracy of information, and that the summary remains neutral, balanced, and non-selective in nature.

Certain anatomical and medical terms that are adequately defined in English may need further definition in another language. For example, in Spanish, the term *cancer del utero* is used to encompass both cervical cancer and uterine cancer. According to a 2005 study, Mexican women "rarely used or recognized the term 'cervix.'" Therefore, in a Spanish-translated RRS, further description would have to be used to distinguish between the two types of cancer.[85] In India, one translation of a "novel therapy" was interpreted to be "a book treatment," as the word "novel" was translated as a noun and not an adjective..

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[83] The Edict Project: Policy Recommendations to Eliminate Disparities in Clinical Trials. http://www.lifebeyondcancer.org/wp-content/uploads/EDICT_Project_Booklet.pdf http://nebula.wsimg.com/28471e643140476abdccd3e246a03598?AccessKeyId=4ECD43F4A65F6DBF7F21&disposition=0&alloworigin=1 (accessed February 2, 2016).

[84] David RA and Rhee M (1998): The Impact Language as a Barrier to Effective Health Care in an Underserved Urban Hispanic Community. *Mt Sinai J Med.* 65:393-7;
Wilson E, Chen A, Grumbach K, Wang F, Fernandez A(2005): Effects of Limited English Proficiency and Physician Language on Health Care Comprehension. *J Gen Intern Med.* 20:800-6.

[85] Hunter JL (2005): Cervical Cancer Educational Pamphlets: Do They Miss the Mark for Mexican Immigrant Women's Needs? *Cancer Control.* 12 Suppl 2:42-50.See:

### 4.4.2 Cultural Review of Research Results Summaries

In addition to having RRS translated, a medical professional with knowledge of the culture of the minority group (or the most prominent minority group(s) if there are multiple ethnic groups) should review the summaries to ensure that they reflect cultural norms and do not become promotional in translation. For example, a study has shown that Mexican immigrant women often lack "mother-to-daughter teaching of female anatomy, reproduction, and normal body functions."[86] A summary should take this into consideration, and provide greater background in these areas, while ensuring respectful (not patronizing) communication and avoiding any change in the interpretation or meaning of the RRS.

### 4.4.3 Cultural Review of Return Processes

Further, certain cultural norms may warrant changes to the return of result logistics of an individual site. For example, in China, it is common practice for doctors and family members not to disclose a terminal cancer diagnosis to the patient.[87] Similar cultural preferences may apply to the return of results to patients. This may necessitate a more involved consenting process that includes the patient's family, and require review and approval by the IRB/REC.

## 4.5 Templates for Research Result Summaries (RRS)

Examples of existing result summaries from a variety of contributors are included in the *MRCT Return of Results Toolkit*. They cover different types of clinical trials to offer examples.

Templates for interventional phase 1 trials, randomized phase 2/3 trials, and trials that close early are also included in the *MRCT Return of Results Toolkit* to assist efforts in creating general study result summaries.

We thank each contributor who provided examples in the *MRCT Return of Results Toolkit*.

http://www.ncbi.nlm.nih.gov/pubmed/16327750http://www.ncbi.nlm.nih.gov/pubmed/16327750 (accessed February 2, 2016).

[86] Id.

[87] Jiang Y, Liu C, Li J-Y, et al (2007): Different attitudes of Chinese Patients and their families toward truth telling of different stages of cancer. *Psycho-Oncology*. 16: 928-936.

## 5. Special Considerations

Sometimes, circumstances occur that may affect the normal RRS process. This section lists some of these special considerations with recommendations.

### 5.1. Trials that close early

When a trial is discontinued, terminated, or stopped early, investigators should discuss this event with each study participant and include the reason for study closure (e.g., evidence of or lack of efficacy, safety events, low accrual, etc.).

- Participants who have participated remain interested in the outcome of the study, even if the study closed early. Depending on the situation, additional specific information to share may include:
    - Reasons for early study closure, i.e.:
        - Safety events: to whom participants should report ongoing adverse events or issues, and where to obtain further information, treatment, or prevention, if appropriate.
        - Efficacy: anticipated next steps for the compound/device or indication and with whom participant should discuss potential access to the compound or alternative therapies.
        - Futility: a clear interpretation for participants explaining that the compound/device was not likely to be more effective than the comparator with reasonable certainty.
        - Low accrual: potential reasons for low accrual, if evident.
    - Where participants can obtain further information or answers if questions arise.

An Early Clinical Trial Closure template is available in the *MRCT Return of Results Toolkit* for more information.

### 5.2 Observational, long-term follow-up, registry, and extension studies

There are many forms of human clinical research and clinical trials, and only a minority of clinical studies involves randomized controlled trials (RCTs) that compare at least one method of treatment to another.

Observational, long-term follow-up, extension, and registry studies do not always have a finite "end of study" or termination. Nevertheless, it is important to consider whether, when, and how often to communicate with participants regarding the study and how to inform participants of interim study results.

Sometimes an annual letter or periodic update is sufficient. Sometimes a simple communication through a website (made available with the ICF) where participants can obtain further information is adequate.

Any proposed publication (e.g., abstract, submitted manuscript, news report) should trigger the sponsor and investigator to consider whether it would be appropriate and/or timely to communicate with participants. There is no script to determine how this should be done: studies differ and specifics will always inform the choices made. Addressing RRS early in the design and conduct of the trial will help to frame appropriate management.

Long-term or registry studies and research emanating from biospecimen repositories can satisfy the obligation to return results by creating a publically available website that posts results in plain language. Participants and biospecimen donors can be directed to the website for information.

## 5.3 Studies that may not warrant return of results

For some types of research, the results may not be informative or the benefit of returning the results may not justify the administrative burden and expense. Examples might include:

- Biospecimen (e.g., tissue and blood) studies that are exploratory or identify clinical correlations if the informed consents clearly state that no results will be given. This includes those specified for future use.
- Pilot studies that are intended to determine whether further investigation is warranted.

In these types of studies, the results will often be indeterminate or of limited interest to participants. In other studies, it may be impossible to provide results because the study is not powered to deliver "results". Some minimal risk studies may be of insufficient scientific rigor to justify the return of results, such as research required of students in order to graduate.

In addition, other possible exceptions to return of results include:

- Tissue banking and bio banking activities. Studies that confirm or validate specific biomarkers, however, should be included in the RRS process.
- Exploratory research results
- Research conducted under a waiver of consent
- Exempt studies
- Cluster randomized studies
- Pragmatic clinical trials

In studies of illegal or socially unacceptable behavior such as illegal drug use, domestic abuse or prostitution, providing results to participants may create the potential for a breach of confidentiality and subsequent harm. Studies with certificates of confidentiality should be scrutinized to assure that returning results will not jeopardize confidentiality or the terms of the certificate.

Finally, extremely small studies with limited numbers of participants (e.g. rare diseases) may increase the potential for participants to identify themselves and other participants, thus offsetting the value of disclosure of the general results. Risks of this sort should be covered in informed consent forms; if results are to be given to the participants, additional steps to ensure privacy should be considered.

## 5.4 Notification of results to a third party who was designated by the participant

Individuals often wish to discuss not only their medical care, but also their participation in clinical research with another person (e.g., a family member, friend, third party). Participants should have the option to share the study results with a designated third party. Any concerns about protections and liabilities are arguably less severe in the setting of RRS because personally identifiable information will not be shared. Notwithstanding the absence of legal protections or regulations, the MRCT Center suggests that participants be offered the opportunity to designate

an additional party(s) to receive the information. A sample form for release of this information – though not required – is included in the *MRCT Return of Results Toolkit*.

## 5.5 Vulnerable populations

Vulnerable individuals (e.g., children, prisoners, pregnant women, individuals who have impaired decision-making ability or impaired capacity to consent) are uniquely vulnerable to exploitation and susceptible to research-related harm. However, progress in diagnosis, treatment, and pathobiology of certain diseases require participation of vulnerable individuals in clinical research.

Provisions and extra protections are afforded vulnerable populations to permit the inclusion of these individuals in an ethical and considerate manner and special IRB/REC oversight is required. If vulnerable participants are included in the research, these individuals (depending on the individual capacity to understand) or the legally authorized representative are entitled to the general results of the study. The sponsor, investigator, and IRB/REC, if involved, should consider whether the return of results presents any specific or additional risks (e.g., psychological, behavioral, social, or legal) to the individual. The research participants should be involved to the extent that they are able, with assent as appropriate.

## 5.6 Legally Authorized Representatives and other designated parties

Laws and practices vary with respect to the definition of legally authorized individuals (LARs) and guardians. In the US, state law defines hierarchies for appointment of an LAR for healthcare decisions. Legally appointed LARs are permitted to make decisions for clinical research participation. In the event that an individual has an LAR, the LAR may serve as the proxy for RRS communications.

However, LARs are often not familiar with clinical research generally or the wishes of the participant specifically and, often, LARs are not legally appointed. In these circumstances, guardians or next-of-kin, or the individual appointed as a healthcare proxy may serve in the capacity to receive RRS communications. Again, the sponsor, investigator and IRB/REC (if involved) should consider whether the RRS presents any specific or additional risks (e.g., psychological, behavioral, social, or legal) to the individual if delivered to the LAR or other designated party.

## 5.7 Return of Results in the event of participant death

The death of a participant presents particular challenges in planning for RRS; indeed, general recommendations are difficult as the situation is often informed by the specific facts of death. Death can be anticipated (e.g., an endpoint of the trial) or likely (e.g., salvage chemotherapy for cancer); death can be a consequence of known and anticipated (e.g., infection and sepsis secondary to chemotherapy-induced neutropenia, stem cell transplant) or unanticipated (e.g., anaphylactic or idiosyncratic reaction) adverse events.

Each of these situations will demand different responses as to whether and when the next-of-kin or designated third party should receive general research results. If possible, similar to a healthcare proxy, this eventuality should be anticipated and discussed with the participant as early as possible.

It may be useful to consider asking the study participant if they would like to have a family member receive the RRS in the event that they are unavailable, die or are incapacitated. This, again, is dependent on the trial and on the participant's situation. If the organization decides that

this is useful, it should be done early in their participation. Care should be given to be respectful and sensitive in discussing their possible death.

### 5.8 Assent for Return of Results to Children

In general, if a child is of an age when assent is possible, then the child should be involved in the decision as to whether to receive the general study results. When there is concordance between the child and parent(s) in the decision, no conflict arises. However, difficulty does arise when the child and parent(s) disagree, or when the parent(s) would like to know the results of the study, but not permit the child to receive the information. These specific situations have not been addressed in the literature (to our knowledge). The parent(s) or legal guardian has the authority to make the decision, and thus for young children (e.g. ≤ 13 years of age or so), it seems reasonable to ask the parent(s) or legal guardian first, and subsequently approach the child for assent only with and after the agreement of the parent or legal guardian. In the case of a teenager, both parent and child should be asked. If a disagreement arises, the study team should explore the basis of the disagreement. In the event no resolution can be attained, the teenager should be informed that they have an independent right to the information, if they so desire, when they turn 18 years of age.

## 6. Future Directions

#### The necessity of empirical research

Very little is known regarding participant response to receiving aggregate results of trials in which they have participated.[88] What is known is that the participants overwhelmingly desire such results and expect to be informed. Research is needed not only to understand whether and how participants understand the information that is delivered, but also to delineate the nature of the content as well as the ideal methodology for delivering and communicating this information. Public and private resources should be expended to support empirical research; based on data and experience, recommendations for return of RRS will be modified and expanded.

#### A call for global harmonization

It is critical to coordinate efforts to return aggregate results globally and to harmonize regulations across all agencies within a government, and across governments internationally. Most clinical trials are multi-centered, multi-national, and often global. Different regulatory expectations and requirements will hamper and complicate well-intentioned efforts to communicate with and engage participants and the public. International guidelines and specific tactical and logistical recommendations should be coordinated and adopted. The MRCT Center is collaborating with international entities (i.e. EMA, EFPIA, PhRMA, TransCelerate Biopharma Inc.) to promote these necessary collaborations.

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[88] Dixon-Woods M, Jacson C, Windridge K, Kenyon S. Receiving a summary of the results of a trial: qualitative study of participant views. *Br. Med. J.* 332, 206–210 (2006);

Sood A, Prasad K, Chhatwani L et al. 2009. Patients' Attitudes and Preferences about Participation and Recruitment Strategies in Clinical Trials. *Mayo Clinic Proceedings.* 84(3): 243-247.

## 7. Conclusions

A significant change in the evolution of clinical research, as with clinical care, is the increased attention to, and respect for, the partnership with participants and patients. In addition, the direct involvement of participants and patients in all aspects of the design, conduct and reporting of results is welcomed. With the same overarching goal of strengthening these partnerships and increasing transparency, ensuring that participants are informed of the results of studies in which they participate is both appropriate and respectful. Finally, a commitment to inclusion and transparency may increase trust in and understanding of the clinical trial enterprise with the general public.

In most situations, return of aggregate results is feasible, practical, considerate and responsive to participant wishes. There are very limited situations in which return of RRS is not possible or beneficial, as outlined in this document; these should be considered carefully.

While return of results may be resource intensive, methods are available that are relatively low cost, practicable, and straightforward. At a minimum, employing these utilitarian methods –even if not ideal in all populations and in all locations—will respect participant privacy and individual choice. Returning research results may invigorate greater public engagement and trust in the research enterprise.

## 8. Appendices

8.1 - Key Terminology in this Document

8.2 - Timing of Return of Results

8.3 - Health Literacy Principles

8.4 - Health Literacy Missouri Best Practices for Numeracy

## 1 - Key Terminology in this Document

- **Alliance (Alliance for Clinical Trials in Oncology)**: One of the US National Cancer Institute (NCI) groups that make up the National Clinical Trial Network (NCTN). Sample summaries and templates are included from the Alliance Public Study Result Summary initiative.

- **Clinicaltrials.gov**: A registry and results database of publicly and privately supported clinical studies of human participants conducted around the world, hosted by the United States government.

- **EFPIA (European Federation of Pharmaceutical Industries and Associations)**: A trade group that represents pharmaceutical companies in the European Union (EU) and the European counter-part to PhRMA.

- **EMA (European Medicines Agency):** The EU agency responsible for the evaluation of medicinal products and the EU counterpart to the FDA.

- **EudraCT**: European Clinical Trials Database that makes summary clinical trial results publicly available, hosted by the European Medicines Agency.

- **FDA (Food and Drug Administration):** An agency of the United States Department of Health and Human Services responsible for regulation and supervision of medical products. The FDA's mandate is to protect and promote public health.

- **Health Literacy (US)**: The degree to which individuals have the capacity to obtain, process and understand basic health information and services needed to make appropriate decisions. (Note: Low health literacy can affect people of all ages, races, incomes, and education levels). Although health literacy is commonly defined as an individual trait, it does not depend on the skills of individuals alone. Health literacy is the product of the interaction between individuals' capacities and the health literacy-related demands and complexities of the health care system.[89]

- **Health Literacy (Europe):** The capacity to make sound health decisions in the context of everyday life – at home, in the community, at the workplace, in the healthcare system, in the market place, and in the political arena.[90]

- **Informed Consent (IC) or Informed Consent Form (ICF):** A document that has been reviewed and approved by the IRB/REC that is signed by the consenting investigator and research participant delineating potential risks and costs associated with the clinical trial.

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[89] U.S. Department of Health and Human Services (HHS). Office of Disease Prevention and Health Promotion. (2010). *National Action Plan to Improve Health Literacy.* Washington, DC: Author. 2010.
[90]Kickbusch et al, (2005) European Patients Forum. Health Literacy. Retrieved from http://www.eu-patient.eu/whatwedo/Policy/Health-Literacy/ (Accessed February 2, 2016).

- **Institutional Review Board (IRB)**: A formally designated committee to monitor, review and approve biomedical and behavior research involving human participants. Also termed a research ethics committee (REC).

- **Investigational new drug application (IND):** A request for authorization from the FDA to administer an investigational drug or biological product to humans.

- **Investigator**: (see Sponsor-Investigator)

- **Lay Summary**: A term typically used by researchers to describe a non-scientific summary of a clinical trial. This document substitutes the terms "general," "simple," and "plain language" summary to more accurately reflect the non-scientific summary and to avoid terms that appear to diminish the importance of non-scientists who contribute to research.

- **Numeracy:** The ability to use basic probability and mathematical concepts to explain mathematical and statistical terms. Numeracy principles in health literacy focus on simple explanations, instead of using complex fractions, percentages or statistical terms.

- **Office for Human Research Protections (OHRP)**: An office within the U.S. Department of Health and Human Services that helps protect the rights, welfare, and wellbeing of participants involved in research conducted or supported by the U.S.

- **Participant**: A person who enrolls in a clinical trial, and is used throughout this document. Regulatory language and other documents refer to participants as "human subjects" or simply "subjects."

- **Participant result summary**: Also called general study summary, lay summary, and plain language summary. This document contains a summary of the study results; see definition of Trial results below.

- **Pharmaceutical Research and Manufacturers of America (PhRMA)**: A trade group that represents pharmaceutical research and biopharmaceutical companies in the United States.

- **REC (Research Ethics Committee)**: A formally designated committee to monitor, review and approve biomedical and behavior research involving human participants. REC (and sometimes simply Ethics Committee [EC]) is often the preferred term in Europe and Asia. Also termed an IRB.

- **ROR (Return of Results):** The act of a sponsor returning clinical trial data to clinical trial participants.

- **RRS (Research Result Summaries)**: General study results in a narrative summary, provided to interested trial participants after study closure and after all data were compiled and analyzed.

- **Sponsor investigator**: Also called the Principal Investigator (PI) who holds the Investigational new drug application (IND). Sponsor-investigator is also defined as the person who both initiates and conducts the clinical study.

- **Subject**: A term used in US regulations to indicate a human participant in a clinical trial. In this document, the term "participant" is used to more accurately state the relationship between those who create and conduct research, and those who enroll in clinical trials.

- **Trial participant**: Also called study participant, research subject, study participant, and clinical trial participant. This is the individual who participates in the clinical trial.

- **Trial results**: For the purpose of this document, trial results encompass a description of summary trial results, by study arm, study arm information, clinical plan or milestone information that is relevant to participants

- **Universal Precautions (Health Literacy)**: Assuming that everyone may have difficulty understanding health information, creating an environment where participants of all literacy levels can comprehend and participate appropriately in their health and healthcare.

## 2 - Timing of Return of Results

Timing: To determine when the study results will be returned to trial participants.

**FDAAA &EU requirements for posting summary results - based on calendar**

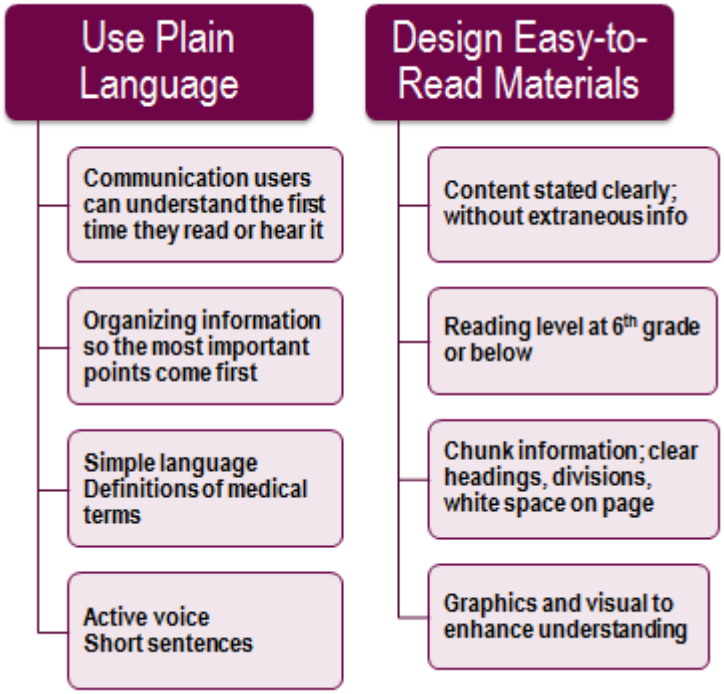
| Circumstances: | FDAAA Guidelines: Law Result Posting Requirement: | EMA Results posting requirements: |
|---|---|---|
| **Completed study** | 12 Months after the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome in a marketed product | 12 Months from the end of a clinical trial (defined as LSLV), and 6 months from the end of a study authorized to include pediatric participants[91] unless otherwise defined in the protocol for a non-marketed or marketed product |
| **If it is not possible to submit within one year (for scientifically valid reasons, detailed in protocol)** | FDAAA Law allows for an extension to delay the posting of results on ClinicalTrials.gov. This could impact the timing of returning results to patients | EMA law does not allow a delay in posting most results to the EudraCT CT website. For Phase I studies, requests may be submitted for an extension of up to 18 months. |
| **The trial reached its Completion Date before the drug, biologic, or device is initially approved, licensed, or cleared by FDA for any use** | Not later than 30 days after the drug or device is approved, licensed or cleared by the FDA…Marketed in the US.<br>If a trial has reached its conclusion, but has not been approved for marketing in the US, a Sponsor does not have to post results to ClinicalTrials.gov. Often Sponsors withhold posting results until marketing approval in the US. Once the drug is approved for the indication, the Sponsor has 30 days to post results of completed trials. | EMA requires the posting of results regardless of marketing status. |
| **The trial studies a new use of an FDA-approved drug, biologic, or device (that is, a use not included in the labeling) for which the manufacturer of a drug, biologic, or device is the sponsor of** | (1) The earliest date that is 30 days after the date that:<br>• New use of the drug or device is approved, licensed, or cleared by FDA<br>• FDA issues a letter for the new use of the drug or device, such as a complete response letter | N/A |

[91] As noted in the EMA Appendix on disclosure rules to the functional specifications for the EU portal and database (EMA/42176/2014), Footnote p. in Table 1

| | | |
|---|---|---|
| **the trial and has filed or will file within 1 year an application to FDA for approval or clearance of that use** | • The application or premarket notification for the new use is withdrawn without resubmission for no less than 210 days;<br>• Or (2) two years after the date a certification is submitted, if none of the events listed above has occurred.<br>• In essence, a sponsor does not have to post results for a product that is marketed, but for which it is seeking a new indication for- until that indication is approved by the FDA | |

FDAAA Guidelines: http://clinicaltrials.gov/ct2/manage-recs/fdaaa (accessed February 2, 2016)
EMA Guidelines: http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1403109516539&uri=CELEX:32014R0536 (accessed February 2, 2016)

## 3 - Health Literacy Principles




### Health Literacy

Communications for clinical study participants should be developed using the lessons from health literacy research. Extensive studies into health literacy conducted since 1960s indicate that health materials tend to be written at a level of complexity that exceeds the reading skills of an average high school graduate. Poor organization, unfamiliar vocabulary, long sentences and didactic writing style are a few examples of common issues that hinder broader access to health information by the general population.[92]

The writers of study results summaries should carefully consider their target audience and use clear and comprehensible content to facilitate understanding.

### Target audience

Understanding the target audience is the key to writing a clear summary.

- At a general level, content development of results summaries should be guided by the cross-cultural nature of communication (from medical culture to everyday-person culture). Well-written study results summaries will reflect good organization and style that make information more easily understood by the reader.

[92] Rudd, R. E. (2010). Improving Americans' health literacy. *N Engl J Med*, 363(24), 2283-5.

- At the study-specific level, the particular characteristics of the study population, including age, gender, race/ethnicity, location, beliefs, culture, literacy levels and behaviors, should be determined so the content can be adjusted to serve the target audience.[93]

**Organization**

Study results summaries should be written in a way that makes key messages clear to the study participants.

- To facilitate understanding, the most important information should be given first, followed by an explanation of what this information means to the study participants. [94]
- Similar ideas should be grouped together, delineated by informative headings and topic sentences that explain the purpose of each section.
- Incorporate design elements that improve readability, examples include: use of bullets instead of paragraphs; ensuring adequate "white space" in the document; limiting the use of complex tables and charts; and ensuring sufficient contrast between font and background color.

**Writing style**

Communications distributed to the study participants should be written in simple prose to ensure ease of reading:

- Avoid complex sentences that include many clauses as these are difficult to comprehend
- The use of simpler vocabulary is recommended:
    - Avoid jargon, technical or scientific language (e.g. "high blood pressure" vs. "hypertension"). [95]
    - Eliminate unnecessarily complex words (e.g. "use" vs. "utilize").
    - Be consistent in the use of terms/words throughout the document, and define them.[96]
    - Ensure that the target audience will understand the underlying idea for words that represent complex concepts (e.g. "risk" vs. "absolute probability"). Where necessary, explain the underlying concept.
    - Avoid ambiguous words and phrases (e.g. "felt badly").
- Active voice is preferred; use passive voice sparingly.
    - Active voice: Researchers studied the effect of tamoxifen on breast cancer.
    - Passive voice: The effect of tamoxifen on breast cancer was studied by researchers.

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[93] US Department of Health and Human Services. (2010). *Simply Put: A Guide for Creating Easy-to Understand Materials*. Retrieved from: http://www.cdc.gov/healthliteracy/pdf/simply_put.pdf
[94] Ibid.
[95] Ibid.
[96] Ibid.

- Using Microsoft Word, writers can test the readability of writing by using the Flesch Reading Ease Test or the Flesch-Kincaid Grade Level Test.[97] The Flesch Reading Ease Test assesses readability on a scale from 1 to 100. Larger numbers are a sign of higher readability, and indicate that a document is easier to understand. The Flesch-Kincaid Grade Level Test employs an algorithm that factors in both number of syllables per word, as well as average sentence length. It uses these data to assign a grade reading level to any document, based on the U.S. school grading system.

For more information:

- www.plainlanguage.gov
- www.nap.edu/catalog/10883.html
- The CDC has developed extensive health literacy resources.
    - Overview: http://www.cdc.gov/healthliteracy/
        - This page includes links to free online training.
    - Assessment tool: www.cdc.gov/healthcommunication/ClearCommunicationIndex/

**Numeracy**

Study results summaries are likely to include a variety of numerical data. It is important that these numeric concepts be conveyed to the study participant in an easily understandable fashion.[98] See Appendix 4 for additional detail on how to apply principles of numeracy.

**Visuals**

Well-chosen and clearly designed visual aids can help enhance understanding of text.[99] Where used, visuals should present one message per image and be clearly labeled with captions. Overly complex images, such as graphs demonstrating several relationships, can be easily misinterpreted and should be avoided. Visuals should be placed near the text they attempt to illustrate. For depictions of internal body parts or small objects, use realistic images that provide readers with context.[100] Creative solutions to ensure comprehension include videos, cartoons, and you-tube postings.

**Testing for readability**

Consider testing the readability of an initial version of the study results summary with a subset of the target population before releasing the summary to the study participants. Use the feedback and suggestions from this type of pilot review to finalize a summary that study participants will understand.

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[97] See http://www.ehow.com/how_8276984_check-reading-level-microsoft-word.html
[98] IOM. (2014). Health Literacy and Numeracy - Workshop Summary. Retrieved from: http://www.iom.edu/Reports/2014/Health-Literacy-and-Numeracy.aspx
[99] Ibid.
[100] US Department of Health and Human Services. (2010). Simply Put: A Guide for Creating Easy-to Understand Materials. Retrieved from: http://www.cdc.gov/healthliteracy/pdf/simply_put.pdf

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www.iom.edu/healthliteracyguidance
A synthesis of health literacy principles used to create health information that is better aligned with the skills and abilities of those using that information.

Jacobson, Kara L., and Ruth M. Parker. (2014) "Health Literacy Principles Checklist." *Center for Health Guidance*: Center for Health Guidance, 2014. http://centerforhealthguidance.org/health-literacy-principles-checklist.pdf
A user-friendly checklist to apply health literacy principles.

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## 4 - Health Literacy Missouri Best Practices for Numeracy

# Health Literacy Missouri Best Practices for Numeracy

We rely on these guidelines to write clear numbers.
Best practices are still evolving.

### Introduction

Numeracy (also called "Quantitative Literacy") has been defined in several ways:
*"The ability to use basic probability and mathematical concepts." -Peters et al., 2006*

*"The degree to which individuals can obtain, process, and understand the basic [quantitative] health information and services they need to make appropriate health decisions." -Ratzan & Parker, 2000*

*"A constellation of skills necessary to function effectively in the health care environment and act appropriately on health care information." - Berkman et al. 2011*

### Consider when to include numbers—don't ignore them!

- It's about giving people the information they need to make their own choices.
- Providing necessary numbers can increase comprehension and patient willingness to take medicines. When numbers are omitted, and only qualitative labels are provided, patients may misinterpret or overestimate risk.
- For example, "low risk" and "common" mean different things to different people. Providing numbers can help make these labels more concrete.
- And "rare" or "common" may cause a patient to overestimate their chance of something occurring.

### Less is more

- How critical are the numbers? Consider how useful the numbers are to your readers and how closely they are tied to the purpose of the message.
- Omitting unrelated numbers can lead to improved comprehension and higher quality choices.
- The depth of necessary data will differ according to the issue at hand.
    - For example, a cancer patient choosing a treatment type will need data regarding effectiveness and survival rates, where a patient wanting to learn how to use an inhaler does not need data on asthma prevalence.
- Highlight only essential or the most important numbers (such as through symbols)—when nonessential information is also highlighted, it may lead to worse health choices.
    - In other words, "give the right tool at the right time".

**Provide fewer choices**

- Some research suggests that providing fewer choices and less information can lead to increased knowledge and more informed decision-making. Too much choice can lead to less motivation, an inability to choose, decision-related anxiety, dissatisfaction, and regret.
- Choose strategically which options to show based on the more and less critical elements of a decision—that is, how options compare on important dimensions, how common an option actually is for the audience, etc.

**Do the math**

- Calculate or convert numbers. Readers are unlikely to conduct even basic math. Instead of "Lose 5% of your body weight," do the math for the reader, or show a few examples.
- Provide estimates for longer time periods. Cumulative or long-term risks often require readers to extrapolate information from one time period to another.
    - For example, if a patient knows the annual risk of taking a medicine, but intends to take it for many years, they must understand how the risk might change over a longer period of time. Do the math to help readers understand risk over time.

**Give numbers meaning and context**

- People have trouble extracting meaning from numbers, so always explain what the numbers mean—interpret the meaning of numbers for the reader. This can affect health judgments and choices.
    - For example, "This number means your blood pressure could be hurting your heart".
- Use evaluative labels and captions (such as "poor, fair, good, and excellent"). Combining these labels with numbers can result in greater use of the information in judgments, and changes in risk perception and behavioral intentions. But use them carefully and consider potential misinterpretations.
- Present numbers in context by using comparisons — this gives readers a reference point. Use a framework to compare choices and explain and highlight differences.
    - Show numbers as "high" or "low".
    - Compare numbers across ages or groups.
      Use a "harm anchor," which means to show patients where they are on a continuum in relation to a harmful or healthy state.
    - Give common equivalents, such as "about the size of your fist" or "about the chance of getting struck by lightning".

**Use common terms and imaginable formats**

- Present numbers that your audience understands, in common terms. People often struggle with very large and also very small numbers and measurements, such as "5 million" or "5 milligrams".

- Readers don't always understand qualitative words like "increased," "frequent," or "low risk". Use more common words, such as "higher," "happens more than once a day," or "a low chance," respectively.
- Use numerals vs. words appropriately—always use numerals for numbers over 10. Some experts prefer numerals at all times.
- Choose scenarios and examples that are easy to imagine and common among readers.
    - For example, life expectancy may be easier to envision than changes in disease risk. One study found that the consequences of risky behaviors were better recalled when framed as months of life lost or gained as opposed to risks of a disease.
    - One study showed a behavioral effect: customers changed their menu item choices when calorie information was presented as "minutes of brisk walking needed to burn calories" for an item versus just calorie count for an item.

**Use visuals**

- Combine numbers with text or visuals. People understand probability better when it's presented in combination with text or a visual. These can reduce biases, such as denominator neglect, framing effect and relying on anecdotes over statistics.
- Consider simple pictographs, line graphs, bar graphs, pie charts, tables, and flow charts.
- Use bar graphs for comparison across group.
- Use line graphs for trends over time.
- Icon arrays are increasingly being used to show risk probability. Research supports these best practices:
    - Arrange them in blocks, as opposed to scattered randomly.
    - Best for when the outcome is less than 100/1000. But for more common outcomes (greater than 100/1000), bar graphs may be preferred.
    - Shading in icon arrays is not fully understood. Single arrays have been tested, but we don't yet know the effect of comparing multiple arrays. This may disadvantage less numerate groups.
- Beware of using color to indicate important messages. Some readers may have difficulty assigning meaning to various colors.
- Use graphic images or text for emotional appeal when persuasion is acceptable. Affective reactions can influence risk perception and thoughts about behavioral change. Graphic images have been shown to create negative affect and encourage readers to consider behavioral change—especially among less educated and less numerate populations.
- Draw attention to important numbers through larger or bolder font, which can impact judgment, increase sensitivity to risk, and change decisions.

**Present numbers in the expected direction**

- Put numbers in the direction consistent with readers' expectations. This can increase comprehension and better decisions. When numbers require interpretation or conversion it requires more cognitive effort.

- For example, if on a scale of 0-100, "100" was the worst score. Flip this to be more consistent with the common scale of "100" meaning best, since a higher number usually means "better".

**Use whole numbers**

- Readers often ignore or misunderstand decimal points and the numbers that follow. In addition, these numbers are often inconsequential.
- For example, instead of a temperature of "100.4," simply say "100".

**Use consistent denominators and time frame**

- When communicating fractions or ratios, compare risks out of the same number—do not change the base number. This makes it much easier to compare numbers at a glance.
    - For example, compare: "1 out of 100" to "40 out of 100".
- Comparing options with different base numbers is hard or may trick readers.
    - For example, it's hard to compare "7 out of 35" with "3 out of 10". But, we can fix this by using 20 out of 100 (the same ratio as 7 of 35) and 30 out of 100 (same ratio as 3 of 10).
    - And when comparing "1 in 100, 1 in 1,000, and 1 in 10", readers may think that the middle one (1 in 1,000) is the "biggest" risk, since 1,000 is "bigger" than the other numbers.
- Use consistent time frames.
    - For example, consistently provide annual costs or monthly costs—don't require readers to convert time spans in order to compare.

**Be aware of framing**

- Use positive and negative framing. For example, "1 out of 10 women who take this medicine have adverse events. This means that 9 out of 10 women do not."
- Consider whether positive or negative framing is most useful. Research suggests that when communicating risk, negative framing ("You have a 1 in 10 chance of dying from this surgery") can result in a desired behavior. On the other hand when promoting healthy preventive behaviors, positive framing ("seat belts lower your chance of getting hurt in an accident") may be more effective.

**Natural frequencies vs. Percentages?**

- Natural frequencies (1 out of 10) may be more useful than percentages because they give context and imagery, where percentages are somewhat abstract numbers.
- Research suggests that less literate readers may interpret numbers as more risky when in frequency form (1 out of 10) versus percentage form (10%). This could be because frequencies elicit emotional imagery, where percentages are more abstract or meaningless.

- Be careful with this choice — test it with readers and use the best option based on the audience and a material's purpose.

**Risks and Benefits**

- Explain the nature of the risk—tell the audience what the actual threat or harm is and how they will be affected.
- State the cause and effect connection between the risk and the effects of being at risk.
- Provide enough information so that audiences can evaluate what the risk means to them and how they might be affected. For example,
    - Will they feel a minor, temporary inconvenience or a life-changing event or long-term effects?
    - What will happen if they don't take the recommended actions?
    - Could they get sick or die as a result?
    - Will the same thing happen if they do a risky behavior once vs. repeatedly?
- Explain both the risks *and* benefits of a behavior. To make informed decisions, people need to understand the risks and benefits of behaviors, treatments, and preventive measures.
- Provide absolute risks, not just relative risks. Research shows that when only relative risk is presented, patients may view risks as larger or treatments as worse. Providing absolute risk information does the math for the reader, making the choices more concrete and requiring less cognitive effort and room for error.
    - *Relative risk* tells how much more or less likely something is compared to something else. This compares 2 risks—it tells you nothing about the actual risk.
    - *Absolute risk* tells the likelihood of something happening at all—it's the risk itself. The higher the absolute risk, the more likely it is that something will happen.
        - For example, "People who eat bacon are 10 times more likely to get cancer than those who don't." This may lead readers to ask—"more likely than what?" or "10 times what?" Readers need to know the underlying risks (absolute) in order to compare. If the absolute risk is very small, even a large increase may not make a big difference. But if the absolute risk is large, even a small increase can make a big difference.

(For more about relative vs. absolute risks: http://scienceblog.cancerresearchuk.org/2013/03/15/absolute-versus-relative-risk-making-sense-of-media-stories/)

- Combine numbers, words and visuals to explain risk statements. Risk statements that solely rely on numbers may be difficult for audiences to understand. People better

understand probabilities when they are presented with words and visuals that reinforce the meaning of the numbers than when numbers are presented alone.[101]

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