

MRCT Return of Results Guidance Document



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Research Results Summary Guidance Document

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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 Harvard Multi-Regional Clinical Trials Center (MRCT Center) Return of Results workgroup is a multi-stakeholder group comprised of 54 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 convened in January 2014 and culminated during an in-person meeting on September 17, 2014.

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

- Recommendations that are congruent with the European Medicines Agency (EMA) mandate to post results on the European Clinical Trials Database (EudraCT); the European Federation of Pharmaceutical Industries and Associations (EFPIA); and Pharmaceutical Research and Manufacturers of America (PhRMA)
- 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;
- An 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.¹

Our objective for this document is for sponsors and investigators to utilize this as the basis to enact their own internal processes for returning results.

¹ It is important to note that the EMA mandate does not require the posting of either device trials or Phase I trials to EudraCT if the latter are Phase I trials conducted solely on adults and are not part of a preapproved Pediatric Investigation Plan. See: https://www.clinicaltrialsregister.eu/doc/EU_CTR_FAQ.pdf

Introduction

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, and that they understand the value of their contribution.

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 (MRCT) Center at Harvard University 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.

Document scope

This guidance document addresses the return of Research Results Summaries [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. The 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 useful RRS examples. Currently, this document does not address the return of secondary and discovery findings² (individual research results) in detail, nor the return of incidental findings discovered during performance of a clinical trial. 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 organizations or government sponsors. However, the principles in this document should also be applied to investigator-initiated studies 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

² 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 January 9, 2015)

identity is known to the investigator or sponsor-investigator and can thus be contacted.³ The best practices also apply to other types of clinical research, including behavioral or lifestyle interventions, treatment, Patient-Reported Outcomes (PROs), registries, healthcare delivery, and observational studies conducted by industry, private, academic, and public sponsors. Some studies, by their nature, will not have specific “study results.” Examples of such studies include tissue contributions to a bio-repository; some observational, social, behavioral, and long-term studies; and when the IRB/REC has waived consent.

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.

This guidance does not address returning incidental findings to participant, nor does it directly address return of individual participant health data collected during the trial. It does mention some considerations at the time of participant end-of-study visit (last patient visit) later in this document.⁴

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 different situations. For example, a 10,000 person, multinational industry study may utilize a password-protected 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.

This document:

- 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

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

⁴ See also <http://www.hra.nhs.uk/documents/2014/09/information-participants-end-study-guidance-researchers.pdf> (accessed September 12, 2014) and <http://www.hra.nhs.uk/documents/2013/08/care-after-research.pdf> (accessed September 15, 2014)

- 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*](#)⁵ 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 Ethics Committees
- Plain language description of endpoints

Note: Throughout this document, terms have been deliberately used in specific ways such as “participant” instead of “human subject.” Certain terms, such as “clinical trial,” “study,” and “research study” are also used interchangeably. 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. We would appreciate feedback and additional contributions (addressed to MRCT@harvard.edu) so that we can continuously improve this Guidance Document. 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.

⁵ see accompanying Toolkit, provided separately

Overview of Research Results Summaries for Trial Participants

Background

There is growing sentiment that greater transparency and engagement with clinical trial participants will strengthen the clinical research process.⁶ 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, acknowledge the valuable contributions of the participants, provide closure, and honor participants' roles as partners in the research process.

Patient advocacy groups and clinical trial participants have called for greater sharing of information. Regulatory bodies and industry groups have 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 the partner organizations' tailored, individual codes or guidelines - it identifies shared principles.⁷ 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."⁸

⁶ See example: Lunshof, J. E., Church, G. M., & Prainsack, B. (2014). Raw personal data: providing access. *Science*, 343(6169), 373-374.

⁷ 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].

⁸ 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.

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 Regulatory Milestones for Clinical Study 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.” ⁹
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.” - but the Act was not enacted. ¹⁰
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. ¹¹
2013	AllTrials was launched to raise public awareness of clinical trials data public reporting
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.” http://www.wma.net/en/30publications/10policies/b3/
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. ¹²
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 ¹³
2014	The International Committee of Medical Journal Editors (ICMJE) announced that the organization is considering policy aimed to strengthen sharing of clinical trial data requirements for journal contributors. ¹⁴
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

⁹ 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].

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

¹¹ See <http://www.bmj.com/content/340/bmj.c564> (Accessed September 10 2014)

¹² See <http://www.phrma.org/phrmapedia/responsible-clinical-trial-data-sharing> (Accessed September 10 2014)

¹³ See <http://bioethics.gov/node/3183> (Accessed January 9, 2015)

¹⁴ See http://www.icmje.org/news-and-editorials/principles_data_sharing_jan2014.html (Accessed September 10 2014)

	data underlying research findings. ¹⁵
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 2016 to post clinical study result summaries, “layperson’s” summaries, study protocols, and clinical study reports to the (new) EU database. ¹⁶
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.” ¹⁷
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.
2014	The Institute of Medicine report <i>Sharing Clinical Trial Data</i> was released

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 the investigator-participant relationship and participant safeguards (i.e., commitments made in the Informed Consent Forms [ICFs], including any commitment not to release participant-specific information to the sponsor)
- Institutional review board (IRB) and regulatory [oversight](#) that may not permit data sharing with participants if, for instance, such sharing is considered potentially detrimental or harmful to the participants
- The proprietary nature of drug development where the results of one study may significantly impact future clinical research
- Resource requirements of returning RRS, often unavailable in investigator-initiated studies
- Technology limitations, particularly in resource-poor settings
- Time from consent to study completion that may create challenges in follow-up

¹⁵ <http://www.plos.org/data-access-for-the-open-access-literature-ploss-data-policy> (Accessed September 10 2014)

¹⁶ 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>

¹⁷ See <http://www.bio.org/articles/bio-principles-clinical-trial-data-sharing> (Accessed September 10 2014)

Key challenges that may hinder efforts to return study results promptly and responsibly to participants include:

- Regulatory requirements that prohibit any type of promotional communication prior to FDA/EMA/marketing or 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, particularly for trials that are testing an approved drug/agent for a new indication.¹⁸ For test articles not yet reviewed and approved by regulatory agencies, sponsors have expressed concerns that communication may also be perceived as prematurely claiming efficacy and/or safety. Even after approval, communication may be construed as off-label promotion.¹⁹ FDA does provide some information that may be used to guide sponsors on language.²⁰ This document and the accompanying [MRCT Return of Results Toolkit](#), also covers possible solutions.

- Balancing sponsors' needs to protect their research and development investment with participants' interest in results

Sponsor and organizational policies and practices safeguard commercially confidential information (CCI), particularly for novel indications. Arguably, not sharing general study results individually at the end of a study but rather at the end of an entire research development program may aid in safeguarding confidential research and proprietary information. Clinical trial participants are interested, however, in receiving clinical trial results as soon as the trial concludes. Traditional disclosure practices from sponsor organizations often do not involve immediate or proximate sharing of the information. A compromise becomes even more challenging when a series of studies on a particular agent are being conducted, especially if the results may impact the ultimate conclusions. EU regulations effective mid-2016 will mitigate this challenge by requiring release of technical (and plain language) results for all interventional trials testing investigational medicinal products, regardless of approval status.

- In industry-sponsored research, industry sponsors have the study results data but, in most circumstances, cannot and will not directly interact 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

¹⁸ 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>]

¹⁹ 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>]

²⁰ The Bad Ad Program and Prescription Drug Promotion. [Retrieved from: <http://fdabadad.sigmatech.com/courses/index.htm>].

records that could identify study participants should be protected.²¹ Because direct contact does not occur between the industry sponsor (or a sponsor-designated clinical research organization) and trial participant, disseminating information in a way that does not allow direct interaction but yet permits participants to ask questions (during and after the information sharing process) is challenging. It must be handled via an indirect path, most likely through the investigator or some other third party (e.g. a contracted service provider that will maintain confidentiality of participant identity).

- Return of results is a resource-intensive practice

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. The actual delivery of results requires time, plain language skills, training, staff, and funding.

None of these challenges are insurmountable. 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.

Basic Principles

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

For Study Sponsors and Sponsor-Investigators:²²

- Adhere to the most current global regulatory requirements and guidance, with specific attention to the local laws and regulations where the trial was conducted.²³
- Assure that communications are prepared and disseminated in a manner that is strictly non-promotional.

²¹ 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

²² Sponsor-Investigator is defined as the person who both initiates and conducts the clinical study.

²³ 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 RSS for each country where the trial was conducted. The latter approach introduces the complexity that multiple RSS documents may potentially be prepared, all for the same trial, based on differing regulatory requirements (see below for further discussion).

- 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 culturally appropriate results. [See cultural literacy section](#).
 - Integrate participant support to address questions when study results are delivered.
- Provide RRS in all language(s) in which participant trial materials, including the informed consent document, appear.
- 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.
- 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

For Clinical Research Sites Working with Sponsors

- Support and participate in the dissemination of RRS to all study participants who want results.
- Help provide information or referrals for participant questions when delivering, and after communicating, study results

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

- Review and, as appropriate, approve proposed plans for return of RRS to participants in the study protocol, consent forms and other study documents.
- Review and, as appropriate, approve any amendments to proposed plans for return of RRS to participants in protocol, consent forms and other study documents.
- Depending on country-specific regulations, review proposed communications with participants that are made while the study is open with the IRB/REC.
- It is important to note that IRBs are not required to review the plan for, or materials used in, the return of RRS to participants *if* the activity is implemented after the study has been closed by the IRB. There are three arguments for the position that research results communications do not need IRB review if the study has been closed with the IRB:

1. The activity is no longer research and there are no human subjects/participants²⁴ in the activity. 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. RRS are unlikely to affect the criteria for IRB approval. RRS does not affect participant recruitment since the 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 human safety monitoring, as all participants have already been exposed to the physical risks and have been monitored. The communications do not adversely affect vulnerable participants. However, RRS does enhance the consent process to the extent that more information is shared after the study has ended.
3. Research data are often released publicly on ClinicalTrials.gov or in medical journal publications, and IRB review is not required for those activities. The only difference in the case of RSS is that these results are sent directly to the participants (who also have access to ClinicalTrials.gov and the medical literature). In countries other than the US, similar arguments may be made. In the UK, for instance, 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).²⁵

- See [MRCT ROR Toolkit](#) for the Ethics Committee Checklist.

²⁴ Note: we have replaced “subjects” with “participants” unless directly quoting regulations. This is due to feedback from patient communities.

²⁵ See <http://www.hra.nhs.uk/documents/2014/09/information-participants-end-study-guidance-researchers.pdf> (accessed 2 February 2015).

Organizational Process and Logistics

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 Chapter is listed under 6 key areas:

1. Consider the 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. Generally, different types of RRS present a continuum of increasing transparency and specificity:

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
3. Return of [individual study results to participants](#) (e.g., their specific assignment to study arm, their own study data)
4. Return of secondary and discovery findings (individual research results) identified during study participation, but not the results of the study itself, to participants²⁶

For the purpose of this guidance document, the MRCT Center ROR workgroup has intentionally limited the discussion to the return of general study results to participants at the end-of-study (number 2 listed above). 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.

The most “basic” RRS would be general study results in a narrative summary provided to interested trial participants after study closure and after all data were compiled and analyzed. This type of RRS would be sufficient to comply with most current regulatory requirements (e.g., EU Clinical Trial Regulations at http://ec.europa.eu/health/human-use/clinical-trials/index_en.htm) but may not necessarily be sufficient to the trial participants themselves.

Beyond such basic RRS, sponsors and investigators may wish to return additional information and/or be in contact with participants more frequently. Participants may

²⁶ 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 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.

become interested in topics such as when they will hear from the sponsor, results by study arm, and rare, common, severe and serious adverse events identified during the study. Each organization (e.g. sponsor, site, institution) must develop their own policy to implement the return of results to participants. The process should be delineated from protocol development through the distribution of results for each clinical trial.

When determining with whom the results should be shared, a more inclusive approach is recommended. Sponsors should consider providing RRS to interested participants (or legally authorized representatives/guardians as designated in the ICF) who were consented, regardless of enrollment, randomization or completion the clinical trial. Refer to the Content section of this document for more detailed information regarding the appropriate recipients of RRS.

2. Determine the method(s) of delivery

Next, organizations should determine the most appropriate method(s) of delivery as well as the infrastructure and resources required for implementation. Importantly, the method for delivery should be consistent with the characteristics, cultural characteristics, and understanding of the study population; as a general rule, however, we recommend that any communications be targeted for a non-technical audience, using as simple language as 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. The following questions may be helpful in planning for the method(s) of delivery during the protocol development stage:

- Does the method depend upon a face-to-face meeting at the study site, access to a telephone, or access to the Internet for web meetings? Consider whether the method places a greater burden on the study site and how that may impact both the capacity of the site and the participant's care decisions after the trial.
- What is the likelihood that the implications of the study results will elicit 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. Additional resources may also be necessary to field questions.
- 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 and how will the caregiver or additional healthcare provider be alerted?

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

- 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 also 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.

- Internet-based methods. Virtual participant communication can be provided through an Internet web-based portal and portable mobile devices that can be accessed at the study participant's convenience. Security considerations should be considered. 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. Computer-based programming offers a highly consistent experience for the user. The quality of the user interaction will depend on the quality of the system design and testing. Questions from participants can be addressed via online chat and interactive help features, while maintaining relative anonymity. It should be noted that this method could be supplemented with follow-up contact (if participants opt-in to contact).
 - An Internet portal provides significant flexibility for the sponsor (whether industry, not-for-profit, or individual investigator). The sponsor would be able to create a site, either password-protected or not, for each clinical trial, giving each participant the web address and either a unique or a common password. 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 (see below). In fact, the sponsor can create the site and password before the study begins, and provide the information at the time of enrollment²⁷, and again at end-of-study visit.
 - 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.")
 - The security of the system should be addressed. Some sponsors (e.g. government-sponsored cooperative research groups) may wish the site to be completely open and 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. All communication should use health literacy principles, no matter what level of education is assumed (see [Appendix 3](#) and [Appendix 4](#)).
- One-way communication methods: One-way communication methods (e.g., video summary, automated phone message(s)²⁸, printed materials, etc.) do not allow

²⁷ 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.

²⁸ If phone-messages are chosen, participant privacy must be considered. The study team should inquire as to whether phone messages, cell (text and voice) or home, are sufficiently private to be utilized.

participants to ask questions or engage in conversation. Because these delivery methods are not interactive, they tend to have more consistent quality and some are less expensive. These delivery methods tend to consume fewer research study site resources since the site may simply notify, forward, and/or coordinate RRS delivery. The one-way communication might be supplemented with follow-up contact if each participant chooses to opt-in.

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.

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, which is feasible to fund, implement, and operate.

3. Consider the timing of RRS

To ensure compliance in regulated trials, we recommend RRS be returned in accordance with EMA regulations for posting of summaries – these are based on strict deadlines. As of January 2015, the EMA²⁹ is the only regulatory body that has issued guidance on non-technical summaries; FDAAA³⁰ has a provisional requirement for posting of patient summaries but a final ruling is currently pending.

To summarize, the EMA regulations require results be posted on EudraCT with the following provisions:

- 12 months from the end of a clinical trial
- Irrespective of the trial outcome
- Written in a manner that is understandable to lay persons (we use the term “plain language” in this document)
- Not required for results of Phase I non-pediatric trials.

Since the EMA term “end of a clinical trial” may be open to interpretation, we recommend consistent timing and source documents for creation of the summary in Table 2 below. While sponsors of regulated trials are required to comply with government-mandated timelines for applicable trials, many studies do not have defined timelines for RRS.

²⁹ EMA Guidelines: <http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1403109516539&uri=CELEX:32014R0536>

³⁰ FDAAA Guidelines: <http://clinicaltrials.gov/ct2/manage-recs/fdaaa>

Table 2 Suggested Timing for Returning Results

Trial Type	Timing	Source Document	Action
Regulated trials (typically industry sponsored interventional studies)	Within 1 year of Last Subject Last Visit (LSLV); consistent with EMA guidance unless otherwise specified in protocol	Clinical study report (CSR) or ICHE3 synopsis (CSR synopsis)	<ul style="list-style-type: none"> • Post non-technical summary on EudraCT (not currently a requirement) • Return RRS to trial participants
Academic / non-regulated trials	Within 1 year of the study close by the IRB, <u>or</u> final data analysis, <u>or</u> concurrent with the release of the first study publication	Protocol with informed consent <u>and</u> publication or abstract	<ul style="list-style-type: none"> • Return RRS to trial participants, even for unpublished trials
Longitudinal / observational studies	Concurrent with the release of each major study publication	Publication	<ul style="list-style-type: none"> • Return RRS to trial participants <u>and</u> after each update

4. Consider 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.³¹

These factors should be taken into consideration in finalizing the organization's processes. The timing of RRS should be coordinated with requirements for posting results on

³¹ “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 9 2015

ClinicalTrials.gov, EudraCT, similar sites (e.g., as defined by regulatory agencies going forward), and with potential 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. Furthermore, there should be an expectation that participants may communicate results once they have them or when results are posted on a publicly available website. Thus, there should also be no assumption of corporate confidentiality once the general study results have been communicated. Results that may impact US Securities Exchange Commission or similar securities filings should be timed appropriately.

5. Coordinate RRS among study sites

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

In an industry sponsored trial: 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) for review and, as appropriate, for dissemination. The PI may dialogue with their IRB if the study is considered “open” and determine if review is necessary. For a multi-site trial, in the event that a single IRB/REC revises the RRS document, deviation from the original RRS version may occur. There is no regulatory requirement that the RRS document be concordant across all sites; however, concordance and harmonization is preferred for a streamlined message and dissemination process for all trial participants.

For investigator, government, or not-for-profit sponsored trials: The MRCT Center suggests that the overall PI take responsibility for coordinating the RRS, similar to the PI’s responsibility for the informed consent document. The PI or designee can draft the document, submit to a publications committee or other review body (if one exists) for approval in concordance with any publication, 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.

6. Ensure 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, and should utilize available clinical templates and standard documents (i.e., 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 of RRS.

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).

The same kind of privacy procedures included in the ICF should be applied and respected in any aggregate summary results documents.

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 efficient study-specific process starts before study enrollment begins and concludes when the participant receives the RRS and their questions are answered.

The primary recipient 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. Any planning for communication should review and determine whether, when and how each stakeholder will be informed.

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
- Establishing the level/timing/delivery method of the planned RRS
- Budgeting for RRS activities
- Developing and incorporating the RRS information in the protocol and the informed consent form
- Developing an information sheet for participants

The MRCT Center suggests that prior to RRS being distributed to patients, study sponsors and/or investigators should consider providing participants with an information sheet thanking them for their participation and providing further information on next steps³². The information sheet should include:

1. What participants can anticipate after their participation ends, including where to obtain treatment and follow-up requirements for, and advice regarding monitoring of both, anticipated and unanticipated adverse events. Some of this information may be covered within the ICF and can be repeated. Referrals for further health information should also be included.
2. Detailed 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. This information may be dependent on the method of dissemination of RRS.
3. If participant has opted to receive RRS, how to access the information and an approximate timeline for available information should be included.
4. Contact information for the sponsor/investigator, if appropriate.

³² This is also consistent with UK HRA guidance at: <http://www.hra.nhs.uk/documents/2014/09/information-participants-end-study-guidance-researchers.pdf> (accessed September 12, 2014)

5. A confirmation of the participant's contact information and an opportunity for the participant to correct it.

Additional information is listed in [During Study Conduct, Participant End-of-Study-Visit](#) below.

Protocol development

- Include a section in the protocol that describes that the RRS is voluntary and each participant has a choice to receive this information. Also explain how and when the RRS is created and distributed, including:
 - What and how identifiable participant information will be retained after study closure
 - Which trial participants will receive RRS (e.g., those enrolled, randomized, and/or those completing follow-up phase, etc.)
 - The process and timing for the participant to consent to accept or reject RRS (a simple, manageable process is recommended)
 - The basis for RRS distribution (e.g., based on study milestones, set dates after study close, etc.)
 - What action will be taken if there are changes to the study protocol or to the RRS process
 - The due diligence steps that will be done to locate a participant in instances where the participant has relocated residences, if appropriate
 - The process that will occur in the event of the death or incapacity of a participant (e.g., no notification, notification of next of kin, notification of designated third party)

Informed Consent Form (ICF) development

Include a section in the ICF that explains, in simple terms, the RRS information that is outlined in the protocol. Additionally, include specific information about:

- How the participant can take action to receive or opt-out of receiving an RRS (e.g., "At the last study visit, you can decide whether or not you wish to receive the general results of the study. You will be given a choice at that time. You do not need to decide now about this.")
- The timing and format for RRS delivery (e.g., for sponsor-investigator trials: "The study is scheduled to end in November 2015. The researchers will need time to understand the results. In about a year, 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"]. "Please let us know if you do not have access to a computer or the Internet.")
- For instances where the participant will be contacted directly, 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 RSS 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:

- 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), advise the IRBs and arrange for necessary reviews. If the study has ended, the organization may inform the IRB(s) of RRS and even provide an RRS copy to the IRB. In some cases, institutions have separate review boards for RRS, especially when genetic research results are involved and can be provided (genetic research is often exploratory and therefore researchers may not be able to provide these preliminary findings even in aggregate form). In certain circumstances, the IRB of record may require review of the RRS document and process even if the study has closed.

During study conduct

The organization may choose to perform early RRS preparation activities while the study is ongoing to save study team time prior to study close-out activities. Those responsible for RRS compilation can select the pre-approved RRS template (see [MRCT Center Return of Results Tool Kit](#) for examples) and begin populating information that will not change (i.e., from the protocol and ICF [[refer to the Content section](#)]).

Some organizations may choose to stay “connected” with the study participants throughout the study, potentially ensuring continued participant engagement. Communication examples could include:

- A thank you letter after the ICF is signed and 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.”)

It is encouraged to communicate even with those study participants who have completed or ended their active participation in the trial, 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.

Specific participant interactions should be planned throughout the course of their participation with regard to study results. Specifically:

Discussion of informed consent (IC) with participant

Investigators and their study teams have an opportunity to address participant access to information about the study throughout the study conduct. At the time of IC discussion, in addition to specifics about the study, the consenting investigator may mention:

- Whether, and which, trial participants 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 FDA, 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)³³

The end of an individual's participation in a study (end-of-study visit) is an ideal time to discuss their own 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 sponsor/investigator may not want to return results for tissue contributions to a biorepository³⁴, 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 is 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.³⁵ If the information is consistent with the information provided to the IRB/REC at the outset, there may not be a need for

³³ See also <http://www.hra.nhs.uk/documents/2014/09/information-participants-end-study-guidance-researchers.pdf> (accessed September 12, 2014) and <http://www.hra.nhs.uk/documents/2013/08/care-after-research.pdf> (accessed September 15, 2014)

³⁴ 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.

³⁵ All information sheets should follow principles of health literacy, as discussed elsewhere in this document.

ethical review depending on the guidance of local regulatory authorities.³⁶ 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 protocol. 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 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.
- 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)
- Whether the participant would or would not like to receive aggregated study results at end of study
- If the participant has opted to receive RRS, how to access the information and when to anticipate the information. 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).³⁷
- Contact information for the participant, if appropriate.
- Whether the participant would like to designate a third party to receive results in the event of their incapacity or death.

Individual participant data

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 Laboratory Improvement Amendments (CLIA)-approved laboratory results or radiographic

³⁶ 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.

³⁷ Sometimes the method of delivery will impact the participant desire to opt-in (e.g. participants may not wish to receive a letter at home).

studies)³⁸ 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. In that event, the MRCT Center suggests that the results should be shared with interested participants and their healthcare provider as long as they are performed in a CLIA-approved laboratory, under conditions identical to that performed for clinical care.³⁹

Experimental tests performed in a non-CLIA approved laboratory should not be shared or if shared, only with 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/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 shared⁴⁰. 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 and advised as to the anticipated delay. If specific assignment information will be shared, the sponsor should consider providing information on each arm of the study to investigators and their study teams to ensure consistent communication. Further, this information should follow the principles outlined here, including those of health literacy.

IRB oversight (US-only)

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 is a change in research that requires IRB notification and approval. The IRB/REC may choose to remain involved until RRS is completed, and that

³⁸ 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 2015). It does not regulate laboratory tests performed for research. Other countries have similar, but not identical regulations and rules to ensure the quality and validity of laboratory testing.

³⁹ Of course, if individual genomic results are returned, additional consideration should be given to offering genetic counseling.

⁴⁰ 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.

likelihood may increase if the plan for RRS is written into the protocol at study start. While participant contact information is necessary for RRS, it can be retained without keeping “identifiable private information” linked to the study. Nevertheless, some IRBs/RECs will wish to retain oversight. Whether the IRB/REC should or must be involved in the process for RRS currently remains at the discretion of the IRB/REC of record. Results can be communicated earlier than after study close if available.

After the study ends

This is the time to complete, finalize and disseminate the RRS. Content preparation begins in earnest after data analysis, consolidation, and summary reporting. The RRS is developed based on the data that becomes available after the trial closes, the data have been analyzed, and the template is populated according to template instructions (see [MRCT Center Return of Results Tool Kit](#)).

The RRS should be reviewed by the clinical trial team, medical communications group, if available, a review team comprised of internal and external individuals with varied backgrounds and perspectives, including those with both adequate and low health literacy. 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. Further, it may be helpful to pilot the written summary with a select group of appropriate individuals that should be, but need not be, participants. The MRCT Center suggests considering the selection of individuals with the following perspectives, as review by these individuals may be helpful:

Perspective	Example and Considerations
Primary focus and content expertise is in the area studied	Principle 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	No members of commercial or marketing; a statistician or medical writer
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 professional with no relationship to the clinical trial
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For FDA, EMA and other regulated studies, it is important that it 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 can provide RRS copies to participating study sites, IRBs involved in the study, treating healthcare providers, and appropriate health-related community organizations. An appropriate summary may also be posted on websites such as ClinicalTrials.gov, EudraCT, or sponsor websites.

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. This feedback can also be obtained via focus groups, longitudinal surveys, or semi-structured interviews.

Content of RRS

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 who are not in general engaged in scientific or medical fields.

The general RRS should first be developed from the point of view of 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.⁴¹ It is critical to involve a reviewer familiar in the regulations, so that they are a partner in development to ensure that no “promotional language” is included. It is helpful to involve a person familiar with health literacy to facilitate the review of communications that are clear and understandable to participants.⁴² All text should follow these health literacy principles so that all study participants benefit from clear presentation of study results. 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.”⁴³

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) and should always be consistent with any approved product information labeling. All information in an RRS should be clear and simple. Context could include a simple explanation of other completed trials, although we recommend focusing the RRS results content primarily on the results of the clinical trial in question.

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, 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.

⁴¹ Getz, Hallinan, et al. (2012); Meeting the obligation to communicate clinical trial results to study volunteers; *Expert Rev. Clin. Pharmacol.* 5(2), 149–156.

⁴² 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.

⁴³ *Ibid.*

- 6-8th grade reading levels. Reading level scales approximate grade levels, but should not be the sole source of review. (e.g., a Microsoft Word tool measures readability scores – see [Appendix 4](#) for detailed information.)
- 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
 - Search capabilities for additional resources and 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.

Consider what questions the patient may have after receiving the RRS, particularly if there is some action that the participant may need to take based on the results. It may be possible to answer some of these questions in the RRS, thus eliminating some additional steps that might be needed.

The summary information must be relayed using non-promotional language without any claims of safety or efficacy being made.

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. The results of an individual participant in the study are beyond the scope of these recommendations.

1. General overview of study results

The first level of summary information contains a general 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 ClinicalTrials.gov (although the website does not currently support this function), EudraCT, the sponsor’s 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.

2. Results by study arm (“Group”)

More detail for each study arm/treatment group can also 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 ROR Toolkit](#) give general information about each arm, and can be expanded with more detail if the sponsor desires.

3. Study results for each individual

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. And if a study drug has a safety signal, the participants should be advised regarding monitoring or follow-up actions.

4. Incidental Findings

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. It is also possible to request a determination from an IRB/Ethics Board in some cases.

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 ROR Toolkit](#).

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

Table 3 Summary of Essential Elements for Inclusion in the RRS⁴⁴

<i>Essential sections</i>	<i>Description of content</i>
<i>A thank you to study participants</i>	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.
<i>Simple title of the study</i>	Describes the study in plain, simple language for study participants who may not understand medical or scientific terms.
<i>Summary of results</i>	<p>Clear statement that the results described were achieved for this population, and not any other population, and under these specific conditions</p> <p>Write a clear, concise summary statement of study results in language that maximizes comprehension for study participants, especially for those who may be unfamiliar with numerical or statistical descriptions.</p> <ul style="list-style-type: none"> • Describe objectives and outcomes (whether positive or negative) that were measured statistically, using bullets. Some of these include: • Primary endpoint(s) and results by study arm using numeracy (x out of xx people [xx%]) and plain language principles • Description of each clinical study arm, including agent names (generic and brand) • Impactful and completed secondary endpoints and results by study arm using numeracy and plain language principles • Other key statistics using numeracy principles

⁴⁴ 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)

	<ul style="list-style-type: none"> • Key adverse events (see information below) • Any corollary or quality of life (QOL) components that have statistically measurable clinical outcomes ▪ Conclusion of results, potentially to include how they compare to standard practice, relevant differences by race/ethnicity, gender, age, etc. if non-promotional and no claims to safety and efficacy <p>The implications of the results if clear and need for future research</p>
<i>Why the study was done</i>	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.
<i>Study Information</i>	<p>Includes the following</p> <ul style="list-style-type: none"> ▪ <i>Start and stop dates, with explanation of early stoppage when appropriate (see Early Clinical Trial Closure template in the MRCT ROR Toolkit)</i> ▪ <i>Countries in which the study was conducted</i> ▪ <i>Characteristics of the study population, and number enrolled</i> ▪ <i>Date result summary was produced</i> • Clear description of the specific population that was studied (e.g., key eligibility criteria such as age, gender, race/ethnicity, molecular subtype) • A clear statement that the results apply to this population, and not any other population, and under these specific conditions.
<i>How the study worked</i>	<p>Explain the phase of this study and the fact that this is only one study in an overall drug development process.</p> <p>Provide a simple explanation and consider picture or diagram that shows the protocol flow, number of arms, treatment per arm, and other pertinent information. 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.</p> <p><i>For example: “numbness and pain in hands and feet (peripheral neuropathy).”</i></p>

<i>Safety Events</i>	<p>Consider using simple terms (e.g. symptoms, side effect⁴⁵, warning signs, safety events) instead of “adverse events.” Define the term used in simple language.</p> <p>Plainly state any objectives or statistically valid endpoints that dealt directly with safety events.</p> <p>Additional information to consider in this section:</p> <ul style="list-style-type: none"> • For each adverse event: how common or rare; how mild or severe? • Any secondary endpoint that statistically measured adverse events • A description of any severe effects, with an explanation of short or long-term consequences, when possible • Additional regulatory requirements - described in clear, simple terms • Plain language should be used, not medical jargon, when describing adverse events (i.e., use “fainting” instead of “syncope”).
<i>Official title of the study</i>	<p>Include the official title and all related study number(s).</p>
<i>Final Comments</i>	<p>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, your personal physician] or contact [list appropriate contact information and/or resources available] about the study or your part in it.”</p> <p>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.].”</p> <p>List additional information that will help explain the study or the disease/condition, such as “You can also find more details about this study at: [List all applicable citations and websites that are not listed in ClinicalTrials.gov. This can include</p>

⁴⁵ “Side effect” is a term reserved for common adverse reactions described after the safety profile of a drug known and the drug is approved for use. Prior to regulatory approval, even anticipated risks (e.g. nausea and vomiting as a consequence of chemotherapy administration) are termed “adverse events.”

resources as well as articles].”

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

Thank them again.

Additional inclusions for Return of Results Summaries (RRS)

Rarely, study results reveal immediate clinical implications for individual participant(s). Harvard MRCT suggests that in this situation, the sponsor and investigators should consider how and when to advise the participant as to specific actions that should be taken. If a study drug has safety implications, for instance, the participants might be advised to be monitored for specific adverse events or lab abnormalities.

Additional information to consider listing in RRS include:

- General information about sponsor and study agent. Links to this information may be included in the “Final Comments” section.
- Applicable patient foundations or advocacy organizations for the disease/condition.
- Any prior publications/articles, including a link to clinicaltrials.gov and EudraCT for the CSR
- List of study sites.
- Reference to any ancillary studies (e.g., quality of life, biomarkers, patient-reported outcomes).
- How to attain additional information on study arms or individual results.

Cultural Literacy

Numerous studies and articles have highlighted the under-representation of racial and ethnic minorities within clinical trials.⁴⁶ Further, studies have shown that language barriers contribute significantly to patient dissatisfaction.⁴⁷ 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.

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

⁴⁶ The Edict Project: Policy Recommendations to Eliminate Disparities in Clinical Trials.
http://www.lifebeyondcancer.org/wp-content/uploads/EDICT_Project_Booklet.pdf

⁴⁷ Rand A. David and Michelle Rhee (1998): The Impact Language as a Barrier to Effective Health Care in an Underserved Urban Hispanic Community.

Elizabeth Wilson, Alice Chen, Kevin Grumbah, Frances Wang, Alicia Fernandez (2005): Effects of Limited English Proficiency and Physician Language on Health Care Comprehension.

exceeds a predetermined percentage (e.g., 10%). Further, translations should be read and interpreted by a native speaker to ensure appropriate connotation.

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, the 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.⁴⁸

Cultural Review of Research Results Summaries

In addition to having RRS translated, a medical professional with knowledge of the culture of the minority group should review the summaries to ensure that they reflect cultural norms. For example, a study has shown that Mexican immigrant women often lack “mother-to-daughter teaching of female anatomy, reproduction, and normal body functions.”⁴⁹ A summary should take this into consideration, and provide greater background in these areas.

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.⁵⁰ 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.

Templates for Research Result Summaries (RRS)

Examples of existing result summaries from a variety of contributors are included in the [MRCT ROR 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 ROR Toolkit](#) to assist efforts in creating general study result summaries.

We thank each contributor who provided examples in the *MRCT ROR Toolkit*.

⁴⁸ Jennifer L. Hunter (2005): Cervical Cancer Educational Pamphlets: Do They Miss the Mark for Mexican Immigrant Women’s Needs? <http://www.ncbi.nlm.nih.gov/pubmed/16327750>

⁴⁹ Id.

⁵⁰ Yu Jiang, Chang Liu, Jun-Ying Li (2007): Different attitudes of Chinese Patients and their families toward truth telling of different stages of cancer.

Special Considerations

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

Trials that close early

When a trial is discontinued, terminated, or stopped early, investigators should discuss this 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 ROR Toolkit](#) for more information.

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.

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 limited in 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.

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 ROR Toolkit](#).

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.

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.

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.

Assent for Return of Results

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.

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.⁵¹ 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 has initiated discussions with international entities (i.e. EMA, EFPIA, PhRMA, Transcelerate) to begin these necessary collaborations.

⁵¹ 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 et al. 2009. *Mayo Clinic Proceedings*. 84(3): 243-247

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.

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.

Appendices

- 1 - Key Terminology in this Document
- 2 - Timing of Return of Results
- 3 - Health Literacy Principles
- 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 which 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.⁵²
- **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.⁵³
- **Informed Consent (IC) or Informed Consent Form (ICF):** A legal document signed by the study sponsor and research participant delineating potential risks and costs associated with the clinical trial.

⁵² 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.

⁵³ Kickbusch et al, 2005) from <http://www.eu-patient.eu/whatwedo/Policy/Health-Literacy/>

- **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 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 will 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

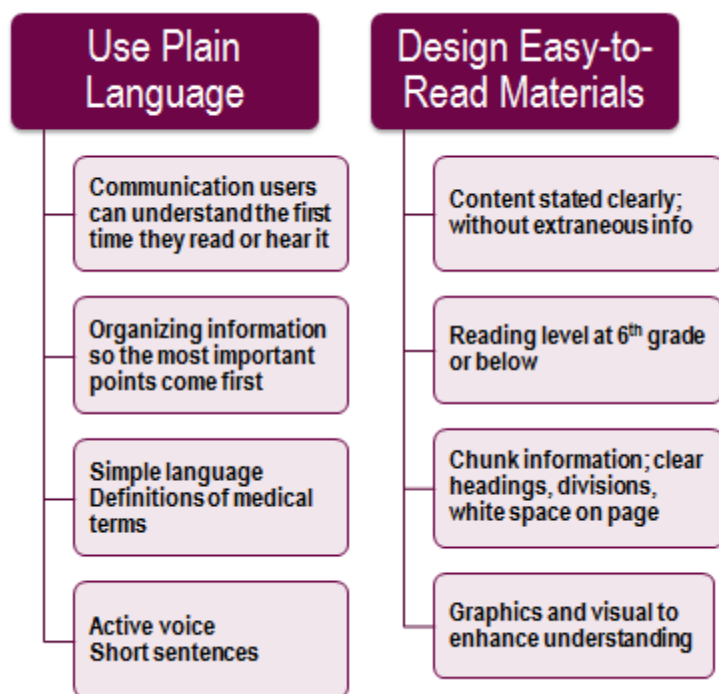
Circumstances:	FDAAA Guidelines: Law Result Posting Requirement:	EMA Results posting requirements:
Completed study	12 Months after the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome in a marketed product	12 Months from the end of a clinical trial (defined as LSLV) 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 results to the EudraCT CT website.
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. 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 the trial and has filed or will file within 1 year an application to FDA for approval or clearance of that use	(1) the earliest date that is 30 days after the date that: <ul style="list-style-type: none"> • New use of the drug or device is approved, licensed, or cleared by FDA • FDA issues a letter for the new use of the drug or device, such as a complete response letter • The application or premarket notification for the new use is withdrawn without resubmission for no less than 210 days; • Or (2) two years after the date a certification is submitted, if none of the events listed above has occurred. • In essence, a sponsor does not have to post results for a product that is marketed, but for which it is 	N/A

	seeking a new indication for-until that indication is approved by the FDA	
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FDAAA Guidelines: <http://clinicaltrials.gov/ct2/manage-recs/fdaaa>

EMA Guidelines: <http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1403109516539&uri=CELEX:32014R0536>

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.⁵⁴

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.

⁵⁴ 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.⁵⁵

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.⁵⁶
- 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”).⁵⁷
 - Eliminate unnecessarily complex words (e.g. “use” vs. “utilize”).
 - Be consistent in the use of terms/words throughout the document, and define them.⁵⁸
 - 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.

⁵⁵ 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/simple_put.pdf

⁵⁶ Ibid.

⁵⁷ Ibid.

⁵⁸ 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.⁵⁹ 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.⁶⁰ 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.⁶¹ 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.⁶² 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

⁵⁹ See http://www.ehow.com/how_8276984_check-reading-level-microsoft-word.html

⁶⁰ IOM. (2014). Health Literacy and Numeracy - Workshop Summary. Retrieved from: <http://www.iom.edu/Reports/2014/Health-Literacy-and-Numeracy.aspx>

⁶¹ Ibid.

⁶² 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

suggestions from this type of pilot review to finalize a summary that study participants will understand.

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Jacobson, Kara L., and Ruth M. Parker. (2014) "Health Literacy Principles: Guidance for Making Information Understandable, Useful, and Navigable." *Institute of Medicine of the National Academies*: Institute of Medicine of the National Academies, 22 Dec. 2014. 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.

Nielsen-Bohlman, L., Panzer, A., & Kindig, D., Eds. (2004). *Health literacy: a prescription to end confusion*. Washington, DC: The National Academies Press. http://www.peh-med.com/content/9/1/7?utm_campaign=12_06_14_PhotonSens_ArticleMailing_EMB_PA_REG_BMC_UP&utm_content=12708049532&utm_medium=BMCemail&utm_source=Emailvision

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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 1 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.⁶³

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