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MULTI-REGIONAL CLINICAL TRIALS

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

Return of Individual Results to Participants — From Theory to Practice

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September 25, 2018 CBI 2018 Philadelphia, PA

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- The opinions contained herein are those of the authors and are not intended to represent the position of Brigham and Women's Hospital or Harvard University.
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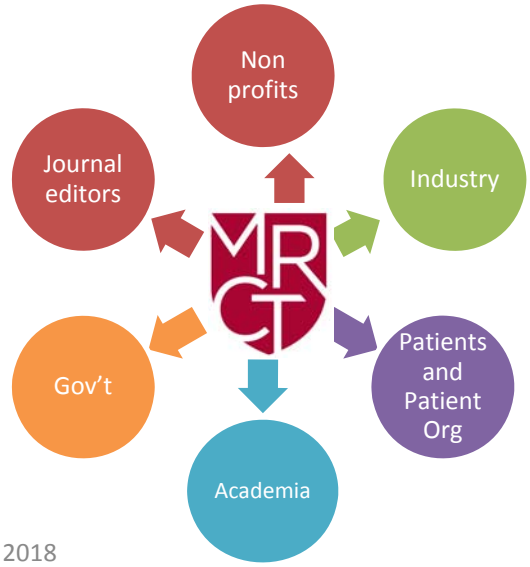
- We are committed to autonomy in our research and to transparency in our relationships. The MRCT Center—and its directors—retain responsibility and final control of the content of any products, results and deliverables.

Learning Objectives and Outline

- Review the MRCT Center's guidelines for returning individual results to participants
- Discuss the special case of genetic/genomic results that illuminate the complexity
- Consider challenges to effective communication in this setting

Our Mission

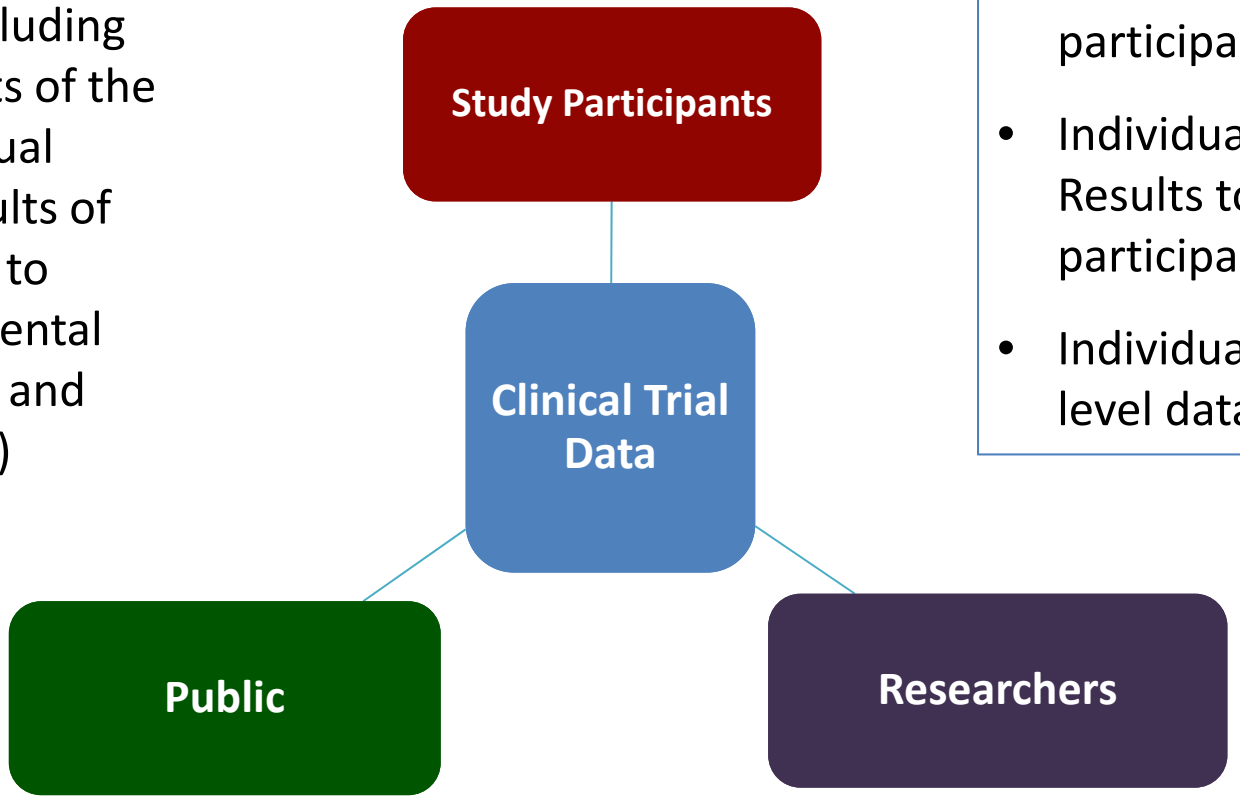
Engage diverse stakeholders to define emerging issues in global clinical trials and to create and implement ethical, actionable, and practical solutions.



- Academic credibility
- Trusted collaborator
- Independent convener

The various audiences of clinical trials data sharing

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

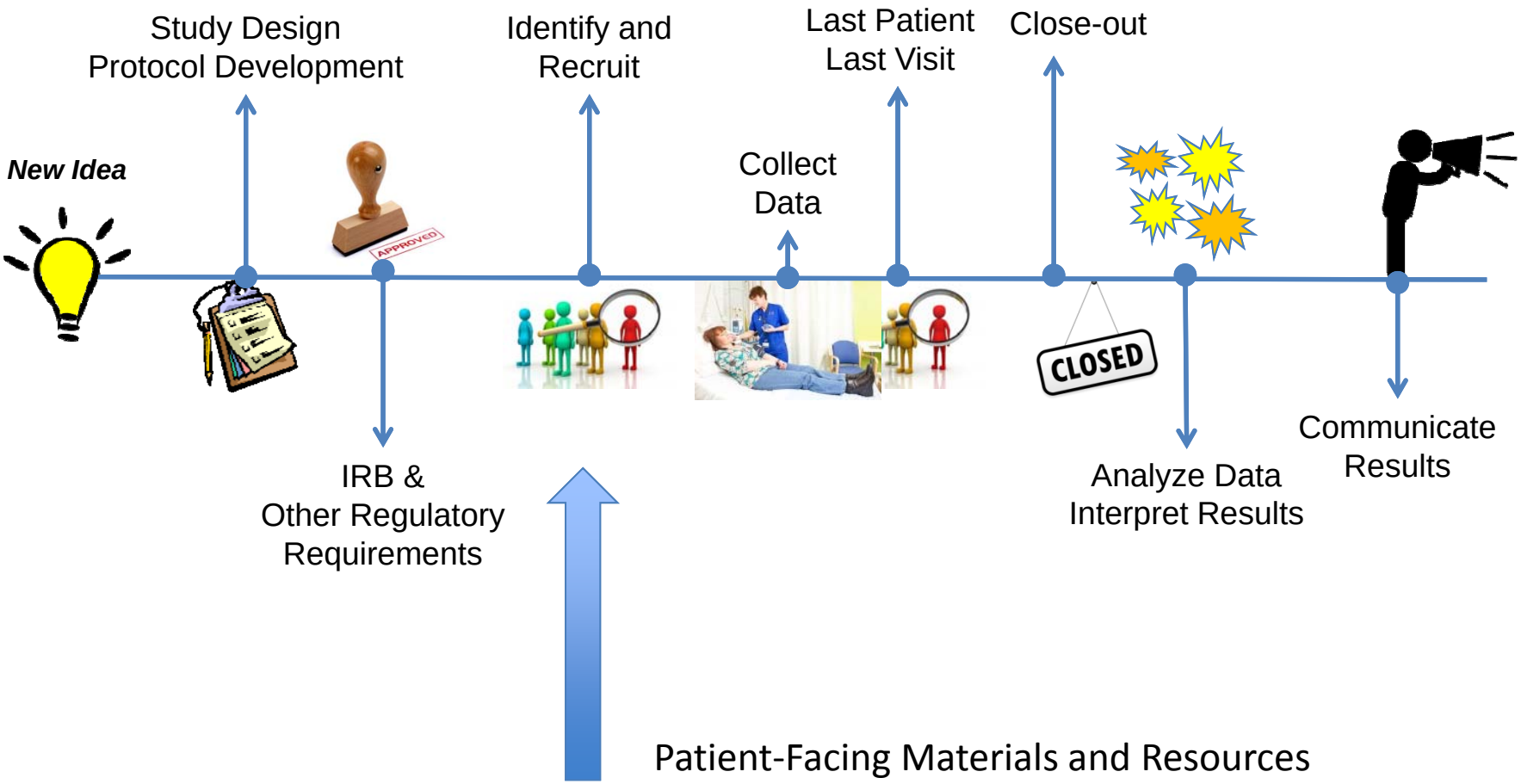


Sharing of

- Aggregate Research Results to participants
- Individual Research Results to participants
- Individual Participant level data (IPD)

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

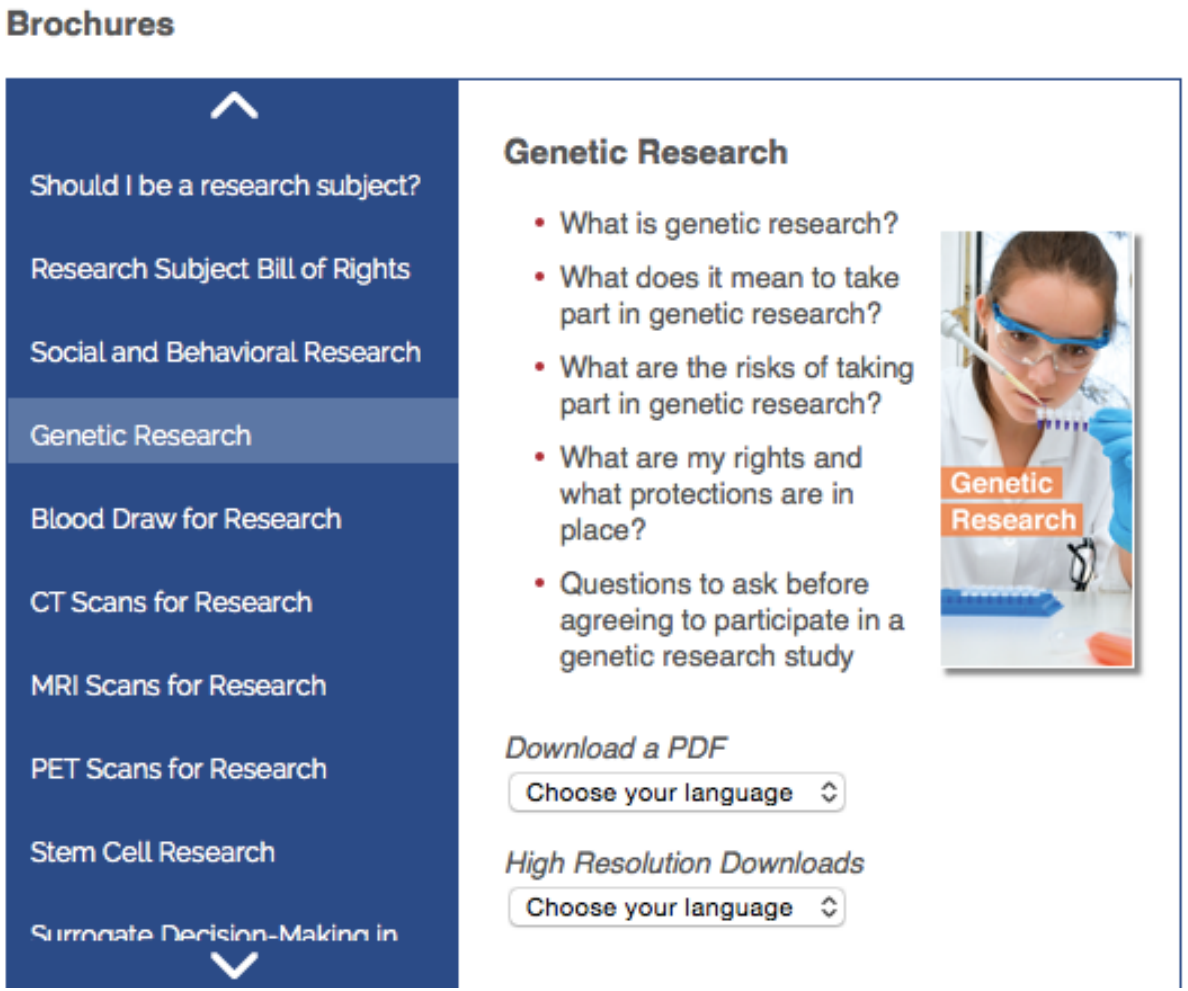
Participant journey



Informational Materials for Prospective Participants

Available in

- English
- Albanian
- Portuguese
- Arabic
- Italian
- Russian
- Cape Verdean
- Khmer/Cambodian
- Spanish
- French
- Korean
- Chinese
- Greek
- Polish
- Vietnamese



https://catalyst.harvard.edu/services/rsa/

Projects advancing global directives

Why Volunteer in Clini

- The development of new medic cures would be impossible with participation of research volun
- By volunteering in a study, you contributing to medical researc
- You could also help researchers disease or condition.
- In some cases, you can try a nev it is available outside of researc these new drugs, procedures, o not be more effective than the available.

10 Questions to Ask Bef in a Study:

- Why is the research being don
- What is expected of me if I agr the research?
- How will I benefit from the re
- Could the research hurt me?
- What will the researcher do wi
- Will the research cost me anyt
- Who pays if I'm unexpectedly
- How long will the study last?
- What happens if I decide to le
- Who should I call if I have a qu research?

This material is the work of the New England Researc Group, with contributions from the affiliated universi centers of member institutions. For more informatio regulatory/language.pdf. Funded by the NIH Nationa Sciences (CTSA) Program UL1 TR001102.

임상 연구에 자발적인 참여가 필요한 이유가 무엇입니까?

- 여러분들의 자발적인 참여 없이는 새로운 진료 기술이나 치료법의 개발이 불가능합니다.
- 여러분들이 임상 연구에 자발적으로 참여하게 되면, 의료 연구에 기여함으로써 다른 사람들에게 도움이 될 수 있습니다.
- 연구자들이 질병이나 질환을 연구하는 데에 큰 도움이 됩니다.
- 간혹 외부에서는 이용할 수 없는 연구 중인 새로운 치료법을 본인이 사용해 볼 수도 있습니다. 하지만 이러한 새로운 의약품이나 시술, 의료기기 등은 기존의 것보다 더 효과적일 수도, 혹은 효과적이지 못할 수도 있습니다.

연구 참여에 등록하기 전에 알아봐야 할 질문:

- 왜 이 연구가 실시되고 있습니까?
- 연구에 참여한다고 동의를 하게 되면, 이후에 어떻게 됩니까?
- 이 연구를 통해 제가 받는 혜택은 무엇입니까?
- 이 연구가 저에게 해를 끼칠 수 있습니까?
- 연구진이 저의 정보를 가지고 무엇을 합니까?
- 이 연구에 참여하는 데 제가 지불해야 하는 비용이 있습니까?
- 연구에 참여하다가 예기치 않게 제가 신체적 손상을 입으면 누가 그 비용을 부담합니까?
- 연구 기간은 얼마나 됩니까?
- 연구 참여를 도중에 포기하기로 결정하면 어떻게 됩니까?
- 이 연구에 대한 질문이 있는 경우 누구에게 전화를 해야 합니까?
- 제 세포 조직으로부터 만들어진 조직이나 세포주가 다른 사람에게 이식이 되지는 않습니까?

연구 대상자의 권리

연구 대상자는 다음과 같은 권리를 가집니다.

- 친절하고 공손한 치료를 받을 권리
- 연구로 알아 내고자 하는 것이 무엇인지에 관해 알 권리
- 연구 대상자에게 어떤 일이 일어날 것인지, 시술이나 의약품, 의료기기 등이 기존 것들과 어떻게 다른지에 관해 알 권리
- 연구 기간 동안 있을 수 있는 부작용이나 불편에 관해 알 권리
- 연구에서 혜택을 기대할 수 있는지, 기대할 수 있다면, 어떠한 혜택을 기대할 수 있는지에 관해 알 권리
- 연구 대상자가 선택할 수 있는 다른 방법이 있는지, 방법이 연구에서 사용되는 다른 방법보다 더 좋은지 (혹은 나쁜지)에 관해 알 권리
- 만약 의료 문제가 발생하면 어떤 종류의 치료가 가능한지에 관해 알 권리
- 연구에 참여하기로 동의하기 전, 또는 연구가 진행되는 도중 언제라도 연구에 관해 질문할 수 있는 권리
- 연구에 참여할 것인지 여부를 결정할 때 심리적 압박을 받지 않을 권리
- 연구 진행 도중, 연구 대상자의 안전에 영향을 미치거나 계속 연구에 참여할 의사에 영향을 미칠 수 있는 새로운 정보가 있을 경우 이에 관해 알 권리
- 연구에 참여하지 않을 권리, 또는 연구가 시작된 후에 이 연구 참여에 관한 마음을 바꿀 수 있는 권리 (이러한 결정은 연구 대상자가 병원에서 받는 진료에 영향을 미치지는 않습니다.)
- 연구 대상자 본인이 서명한 동의서 사본을 요청할 수 있는 권리

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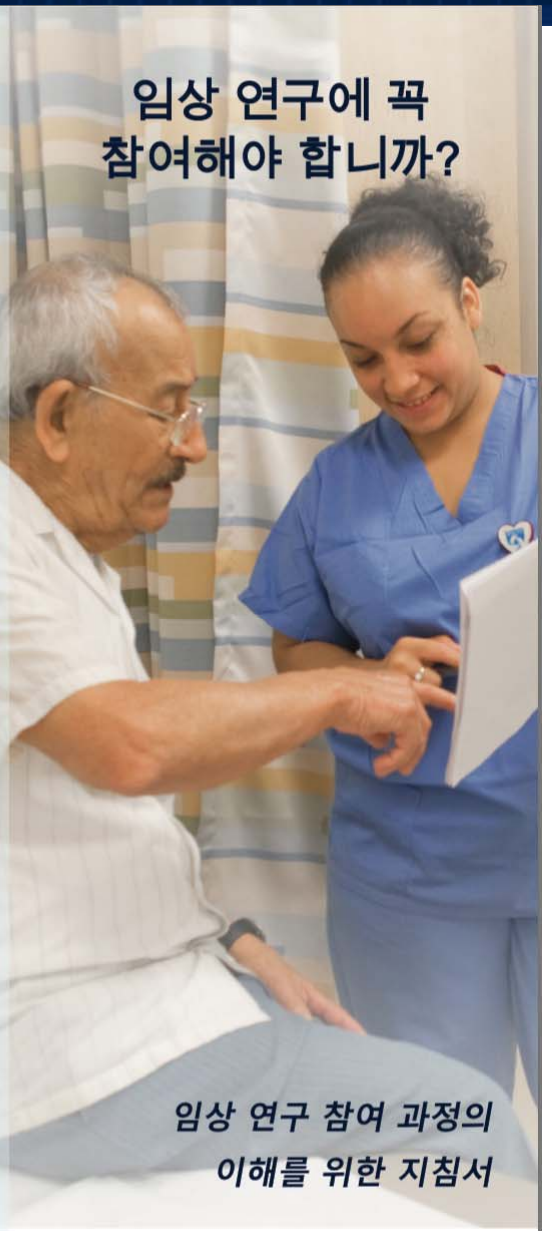
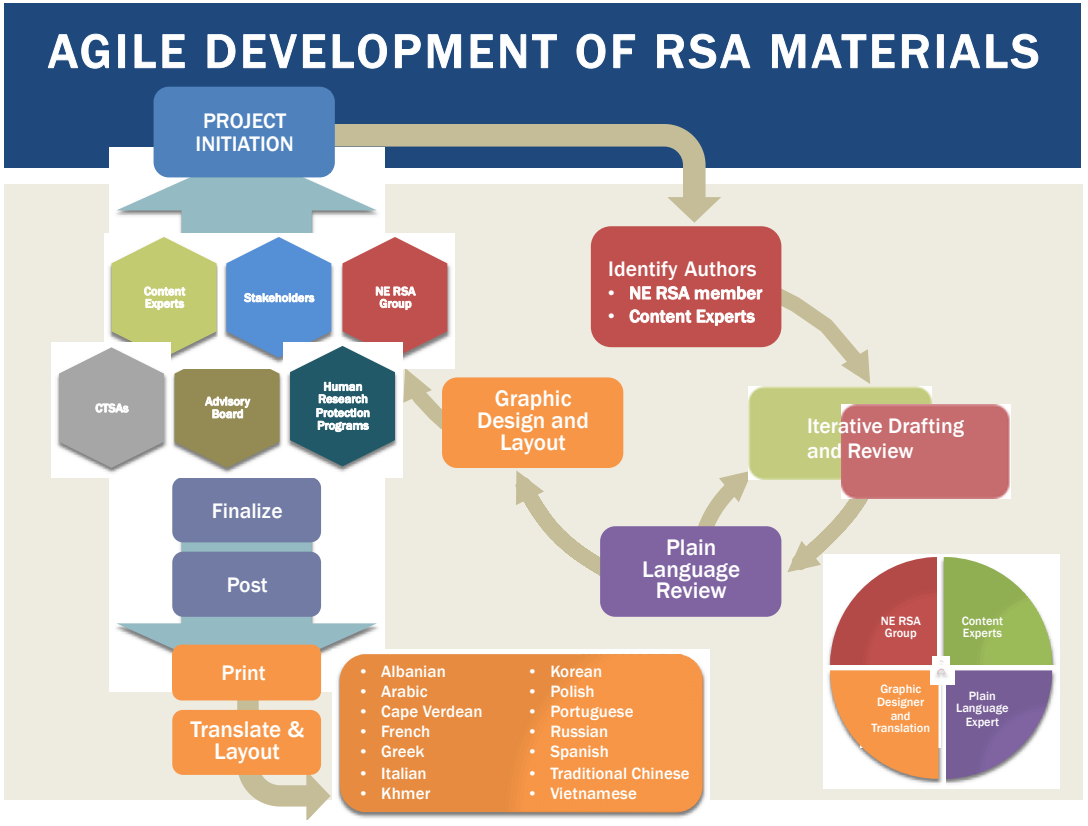


Projects advancing global directives

- **Informational Materials for Prospective Participants:**
  - **23** brochures developed
  - **15** languages available
  - **173,627+** downloads (as of June 2018)

- **Process**

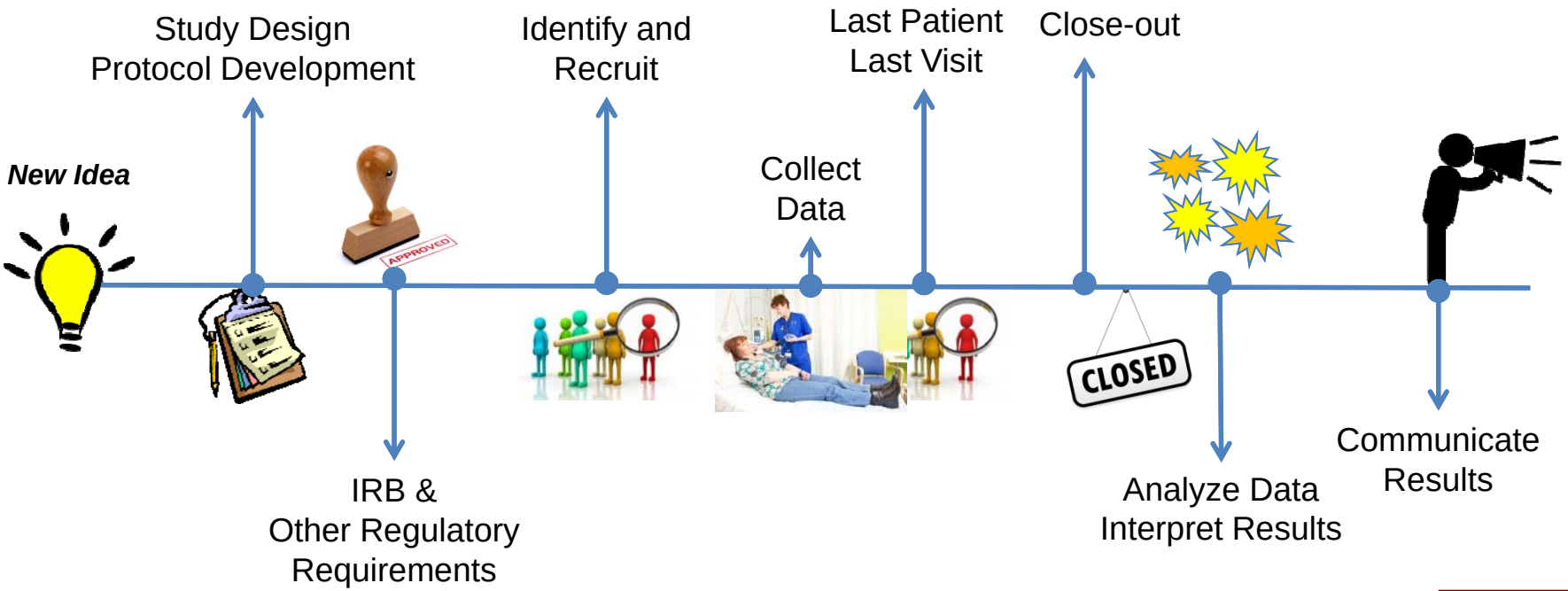


Brochure (Publication Year)	# of Downloads
Should I Be a Research Subject? (2011)	4,673
Bill of Rights (2012)	601
Social and Behavioral Research (2014)	4,376
Blood Draw for Research (2014)	3,444
CT Scans for Research (2014)	1,082
MRI Scans for Research (2014)	1,666
PET Scans for Research (2014)	1,595
Genetics Research (2014)	5,133
Incidental Findings (2014)	1,346
Surrogate Decision Making (2014)	979
Stem Cell Research (2015)	13,615
Research Data (2016)	500

Brochure (Publication Year)	# of Downloads
Research Registry (2016)	344
Participating in a Survey (2016)	1,401
Giving Samples for Research (2016)	834
Health Research vs. Health Care (2016)	1,579
Drug Research (2016)	1,678
Meet the Research Team (2016)	680
Using Telemedicine in a Research Study (2016)	875
tES for Research (2017)	859
TMS for Research (2017)	1,099
What is a Clinical Trial? (2017)	2,121
COI in Research (2017)	946

Total Downloads thru June 2018: 41,598
Total Downloads 2011-2018: 173,627

Phasing of return of results: Aggregate study results



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

- Introduce PLS
- Manage expectations
- Engage and communicate

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

MRCT Center Principles, Guidance, Toolkits: Aggregate Results

Return of Aggregate Results Guidance Document

(Version 3.1, November 2017)

http://mrctcenter.org/wp-content/uploads/2017/12/2017-12-07-MRCT-Return-of-Aggregate-Results-Guidance-Document-3.1.pdf

Return of Aggregate Results Toolkit

(Version 3.1, November 2017)

http://mrctcenter.org/wp-content/uploads/2017/12/2017-12-07-MRCT-Return-of-Aggregate-Results-Toolkit-3.1.pdf

Return of Aggregate Results to Participants Principles

(November 2017)

http://mrctcenter.org/wp-content/uploads/2017/12/2017-11-27-Return-of-Aggregate-Results-Principles.pdf

Plain Language Summaries

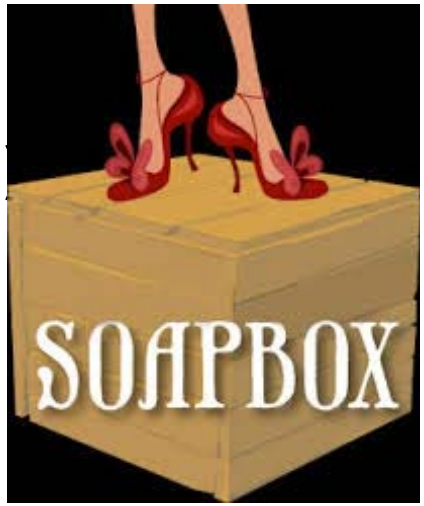
MRCT Center current project:

- **Health Literacy in Clinical Research**
  - Dynamic tools
  - Clinical research terms (“non-inferiority”)
  - Informed consent tools

➢ Collective development of:

➢ Preferred terms (e.g. MedDRA terms)

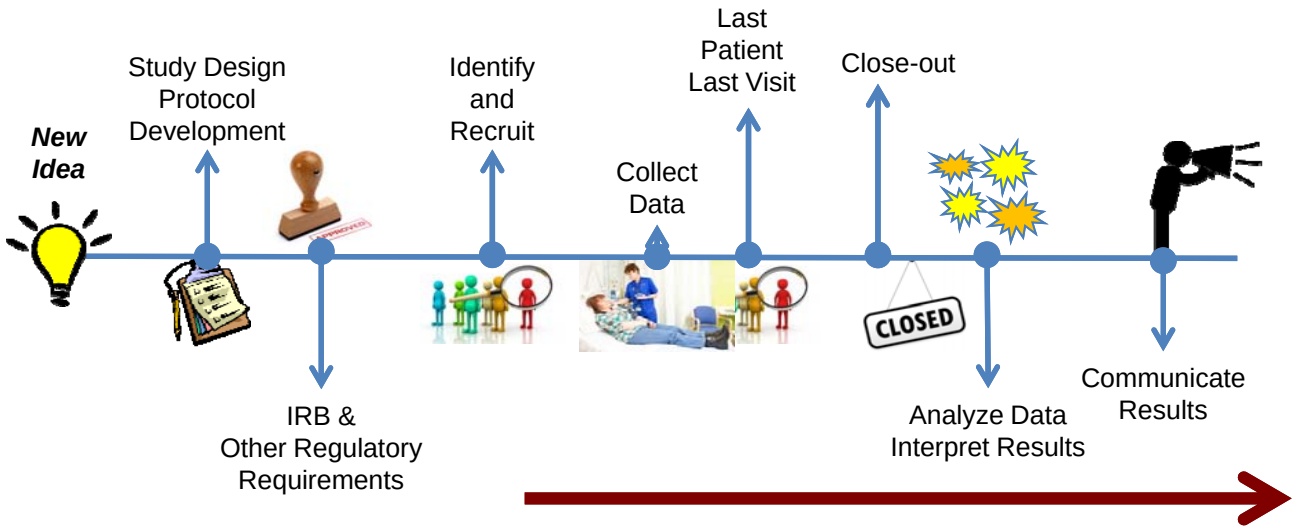
➢ Common research procedures (e.g. IV infusion)



Email: bbierer@bwh.harvard.edu
mrct@bwh.harvard.edu

Return of individual results to participants

- The plan for the return of individual results should be described in the study protocol and reviewed and approved by the IRB/REC.



- Protocol should describe each type of anticipated and unanticipated result, analysis plan (for medical significance, analytical validity and personal utility), method and form of communication and documentation, and responsibility grid.
- IRB/REC should pay particular attention to privacy, health, and well-being of participant.

The MRCT Center Tools for sharing individual results

- **Return of Individual Results Recommendations Document**

  (Version 1.2, November 2017)

  http://mrctcenter.org/wp-content/uploads/2017/12/2017-12-07-Return-of-Individual-Resullts-Recommendations-Document-V-1.2.pdf

- **Return of Individual Results to Participants Toolkit**

  (Version 1.2, November 2017)

  http://mrctcenter.org/wp-content/uploads/2017/12/2017-12-07-MRCT-Return-of-Individual-Results-Toolkit-Version-1.2.pdf

- **Return of Individual Results to Participants Principles**

  (November 2017)

  http://mrctcenter.org/wp-content/uploads/2017/12/2017-11-20-Return-of-Individual-Results-Principles-Nov-2017.pdf

Tools

Planning and Design Phase	Protocol and IC Development Phase	Active Trial Phase	Post-Trial Analysis Phase	Post-Trial Publication Phase
• Rationale Matrix for returning various types of data (Tool 1) • Points to Consider along the clinical trial timeline (Tool 2) • Selected return of results regulations and resources (Tool 3)	• Informed Consent language for return of individual results (Tool 4) • Checklist for IRB and Ethics Committees (Tool 5)	• Designation of third party (Tool 6) • End of study form (Tool 7)		• Communication of study results at the end of a trial (including study arm) (Tool 8) • MRCT Center Return of Aggregate Results Toolkit

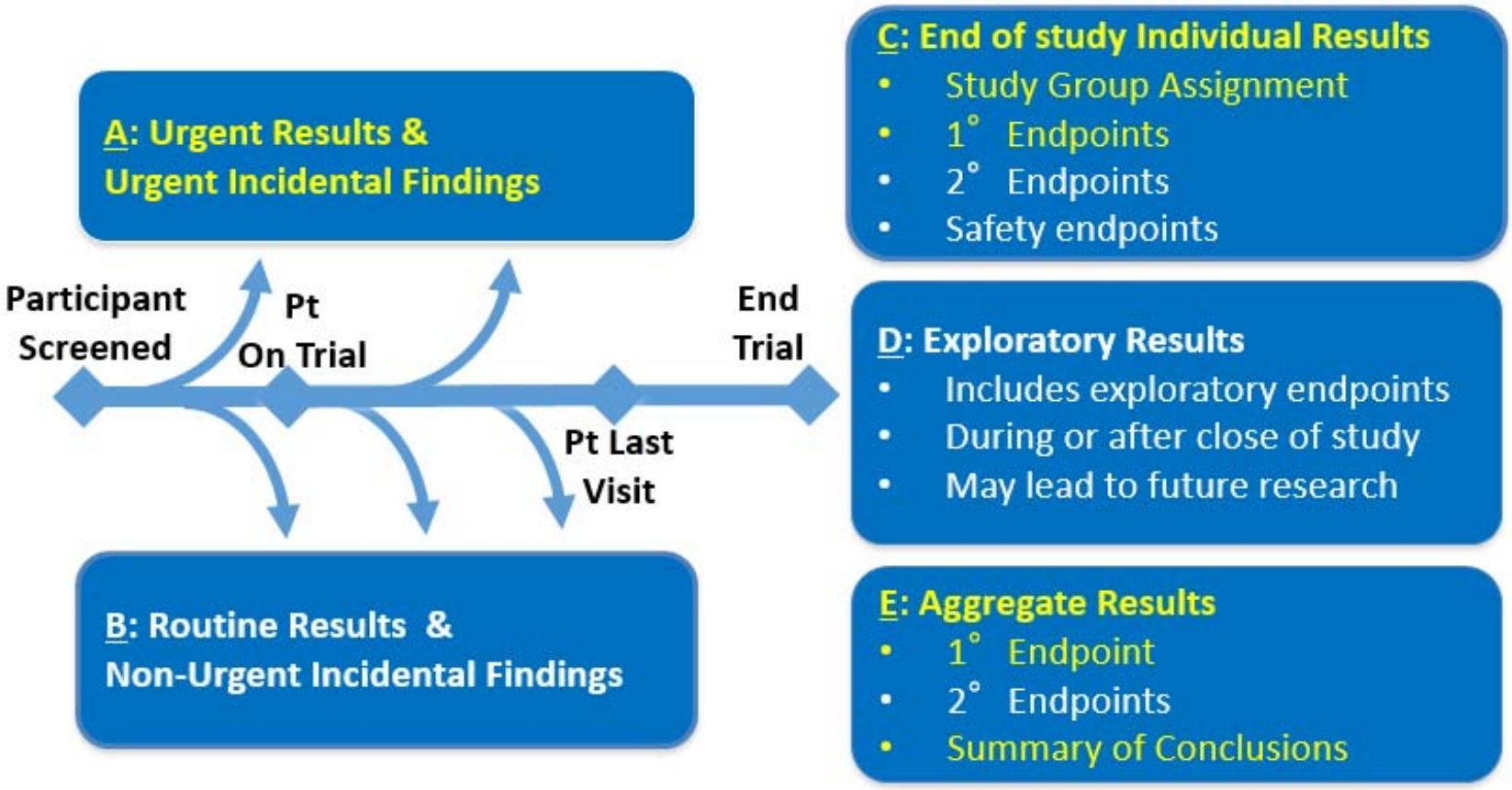
Principles for returning individual results

1. Providing individual research results **responds to the expressed interests and expectations** of many clinical trial participants that their results be communicated to them.
2. Considerations pertaining to the return of individual research results to clinical trial participants should be integrated into the clinical trial and **proactively planned**.
3. The **informed consent process** should include information about the sponsor's intention regarding the return of research results and **allow for discussion of participants' preferences** to receive these results.
4. The plan for the return of individual research results should be **reviewed by an independent ethics body** overseeing the research to ensure the rights and welfare of research participants are protected.

Principles for returning individual results

5. If results are offered, participants should be able to **choose whether or not to receive** their individual research results.
6. Sponsors and investigators have an obligation to act responsibly when returning individual results, **taking into account medical significance, analytical validity and personal utility**.
7. Individual research results should be returned in ways and at times that **maintain the integrity of the research**, insofar as the safety and welfare of the research participants are not at risk.
8. **The purpose of research is not clinical care**, and return of individual research results cannot substitute for appropriate clinical care and advice.
9. Return of individual research results should be planned and executed **in compliance with institutional policies and local, regional, and national laws** and regulations.

Data types for return to the research participant



Data types recommended for return, at a minimum, are highlighted in yellow

What should be shared? Recommendations:

- **Urgent Results & Urgent Incidental Findings:**
  - Always return as soon as interpreted and confirmed as valid
- **Routine Results & Non-Urgent Findings:**
  - Balance potential benefits against resource requirements: Case-by-case deliberation
- **End of Study Individual Results:**
  - At a minimum, offer information about study arm assignment and primary endpoints, after study concludes (unless it would compromise the integrity of ongoing studies)
- **Exploratory Results:**
  - Handle on a case-by-case basis
- **Aggregate Results:**
  - Return summary of primary endpoints and safety data, in accordance with applicable law and guidance

What should results be shared? Considerations:

- Has the participant opted in to receive results? (P1, 5)
- Are the results analytically valid? (P6)
- Does the result have clinical validity? (P6)
- Are the results urgent, actionable? (P7)
- Does sharing the result impact the integrity of the study? (P7)
- Does returning the result comply with institutional policies, legal and national laws, and regulations? (P9)

How to share results with participants?

- Considerations
  - Privacy of participant
  - Types of data
  - Access of participants to health care professional
  - Need for interpretation
  - Pros and cons of modalities
- Modalities
  - In-person meeting
  - Telephone/video-conference
  - Online patient communities or portal
  - Confidential letter

Tool: Sample Template for communication of study arm and individual study results at end of trial

Template for Communication of Individual Study Results including Study Arm Unblinding

Which group you were assigned to

[Participants] in the study were put into *[#]* groups by chance. *[If not randomized, list how many patients/people were in each group, and how this was determined.]*

____**Group A** received *[**simple explanation** of study regimen for first arm., i.e., 100 mg of drug once per day]*

____**Group B** received *[**simple explanation** of study regimen for second arm., i.e., 50 mg of drug once per day]*

_____**Group C** received a placebo treatment (a sugar pill) once per day.

You were assigned to the Group checked above.

Tool: Sample Template for communication of study arm and individual study results at end of trial (cont.)

Summary of individual results

Individual Results

The following table describes your results compared to all the participants in the study. [*the specific population that was studied, including age and gender breakdown. Include eligibility criteria, including specific genetic mutations (when appropriate).*

[Research Institution]

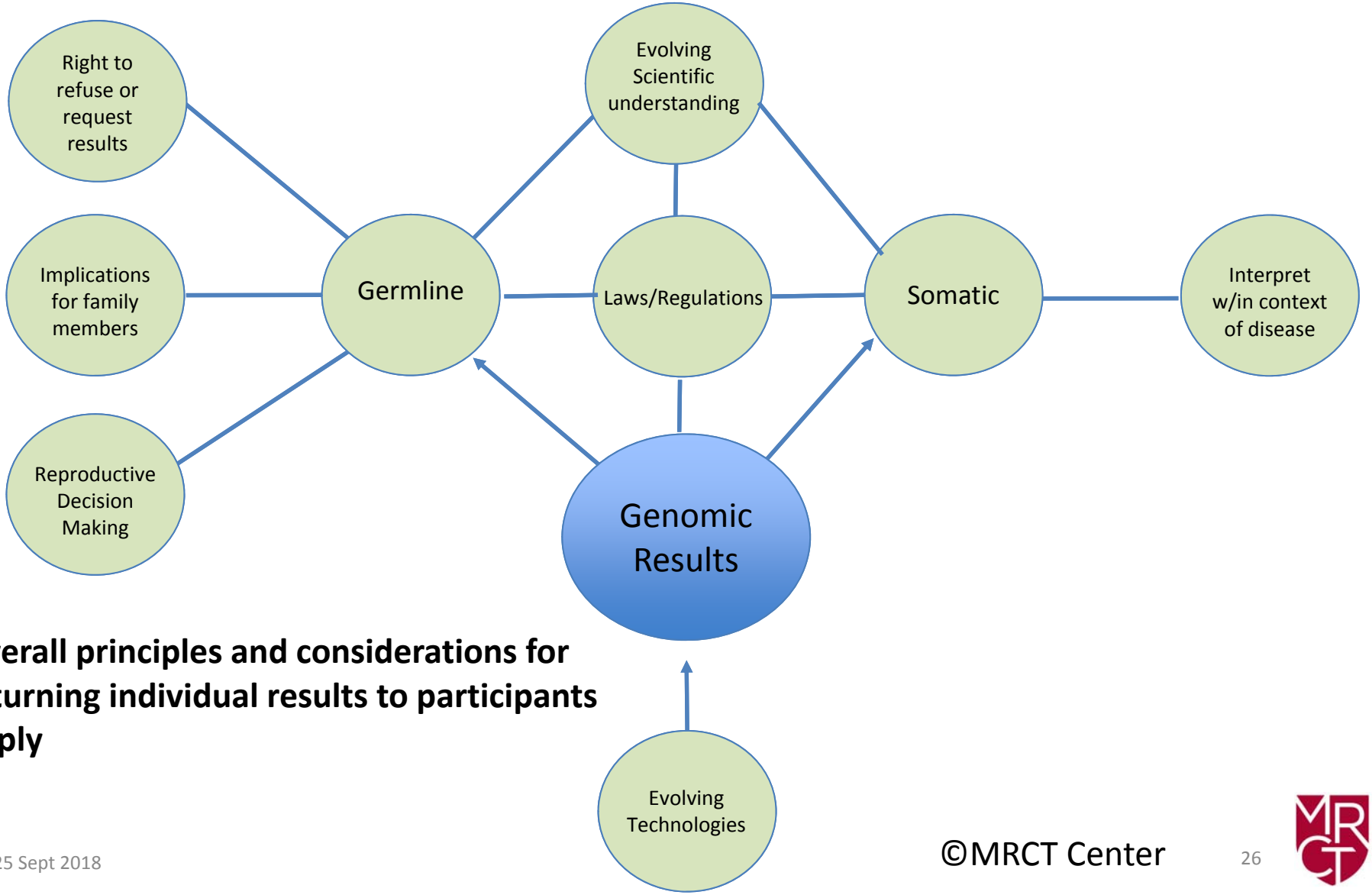
[Study Name]

Sample Study Participant Summary Report

Summary report for all participants in the same group you were assigned

		[Study Name] Participants For Ages [X – XX] Years [Total =xx patients]	
	YOUR INDIVIDUAL RESULTS	**RANGE [the lowest and highest "normal" value]**	**MEAN [the average value for all participants in the group]**
Primary Endpoint 1			
(Secondary Endpoint)*			

Special Considerations: Returning Genomic Results



Overall principles and considerations for returning individual results to participants apply

Returning Genomic Results

Orientation to technology essential to communicating complexities effectively

- Incidental vs. secondary findings
  - Analytical validity, clinical validity and medical actionability
- Duty to “hunt”?
- Right to refuse results

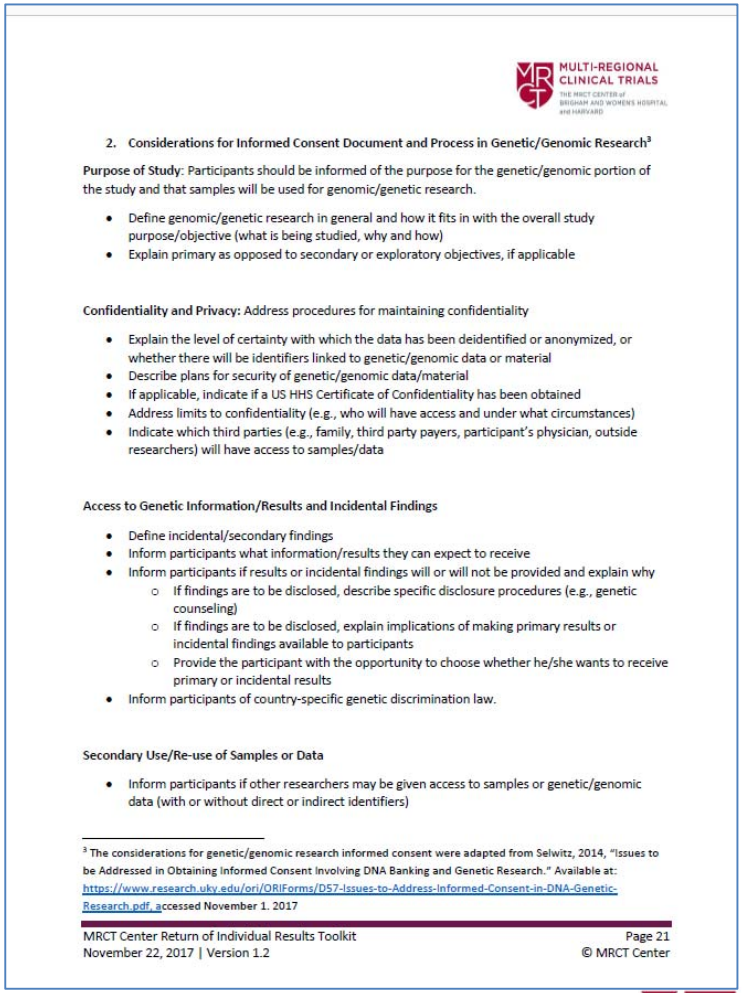
Additional considerations for returning genomic results

- To whom one can release genetic information
- International regulations and policies
- Specific guidance on considerations for informed consent

Case Study: Return of Genetic/Genomic Findings in research

Informed consent and other considerations:

- Confidentiality and Privacy
- Access to Genetic Information/ Results of Incidental Findings
- Secondary Use/ Re-use of Samples or Data
- Potential Risks to Consider
- Benefits
- Alternatives
- Costs to Participant
- Duration
- Control of the Specimens/ Materials
- Significant new findings
- Withdrawal from research study



MULTI-REGIONAL CLINICAL TRIALS
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2. Considerations for Informed Consent Document and Process in Genetic/Genomic Research[3]

Purpose of Study: Participants should be informed of the purpose for the genetic/genomic portion of the study and that samples will be used for genomic/genetic research.

- Define genomic/genetic research in general and how it fits in with the overall study purpose/objective (what is being studied, why and how)
- Explain primary as opposed to secondary or exploratory objectives, if applicable

Confidentiality and Privacy: Address procedures for maintaining confidentiality

- Explain the level of certainty with which the data has been deidentified or anonymized, or whether there will be identifiers linked to genetic/genomic data or material
- Describe plans for security of genetic/genomic data/material
- If applicable, indicate if a US HHS Certificate of Confidentiality has been obtained
- Address limits to confidentiality (e.g., who will have access and under what circumstances)
- Indicate which third parties (e.g., family, third party payers, participant's physician, outside researchers) will have access to samples/data

Access to Genetic Information/Results and Incidental Findings

- Define incidental/secondary findings
- Inform participants what information/results they can expect to receive
- Inform participants if results or incidental findings will or will not be provided and explain why
  - If findings are to be disclosed, describe specific disclosure procedures (e.g., genetic counseling)
  - If findings are to be disclosed, explain implications of making primary results or incidental findings available to participants
  - Provide the participant with the opportunity to choose whether he/she wants to receive primary or incidental results
- Inform participants of country-specific genetic discrimination law.

Secondary Use/Re-use of Samples or Data

- Inform participants if other researchers may be given access to samples or genetic/genomic data (with or without direct or indirect identifiers)

[3] The considerations for genetic/genomic research informed consent were adapted from Selwitz, 2014, "Issues to be Addressed in Obtaining Informed Consent Involving DNA Banking and Genetic Research." Available at: https://www.research.uky.edu/ori/ORIForms/D57-Issues-to-Address-Informed-Consent-in-DNA-Genetic-Research.pdf, accessed November 1. 2017

Returning Data

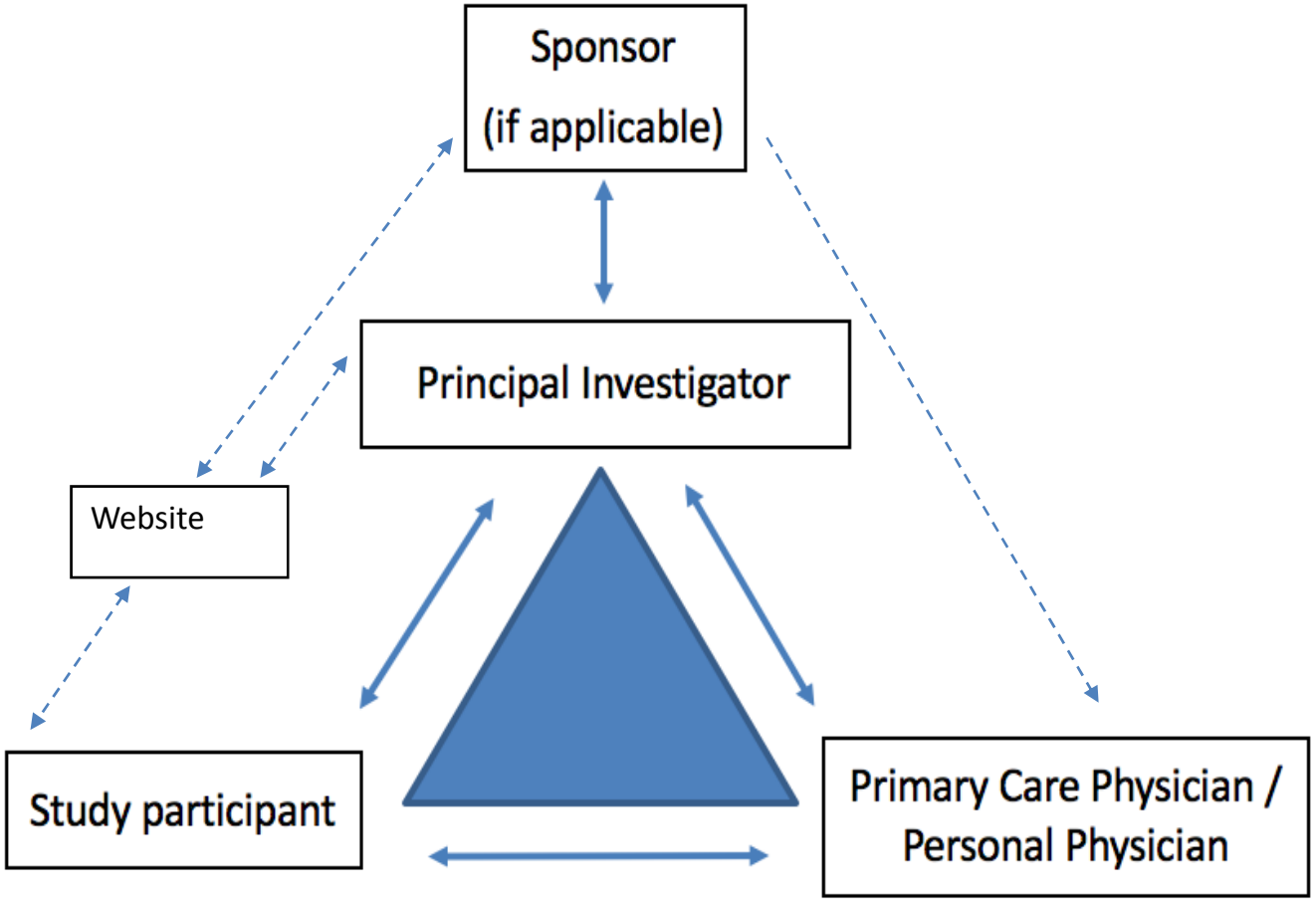
- How to return?
  - Put in context: generally probabilistic rather than deterministic
  - If an individual possesses a genetic variant, inform what is known and what is uncertain, and the significance of “variant”
- Who will return?
  - Decided in advance or just in time; may require a team approach
  - Genetic expertise may be needed to interpret complex findings

National Laws, Regulations, Ethics Guidance

- United States:
  - CLIA and HIPAA
  - FDA Regulatory Considerations
- Outside the U.S.: Variations in legal treatment of genetic/genomic results
- Research Ethics Committee requirements and advice

Who should receive results? Who should share results?

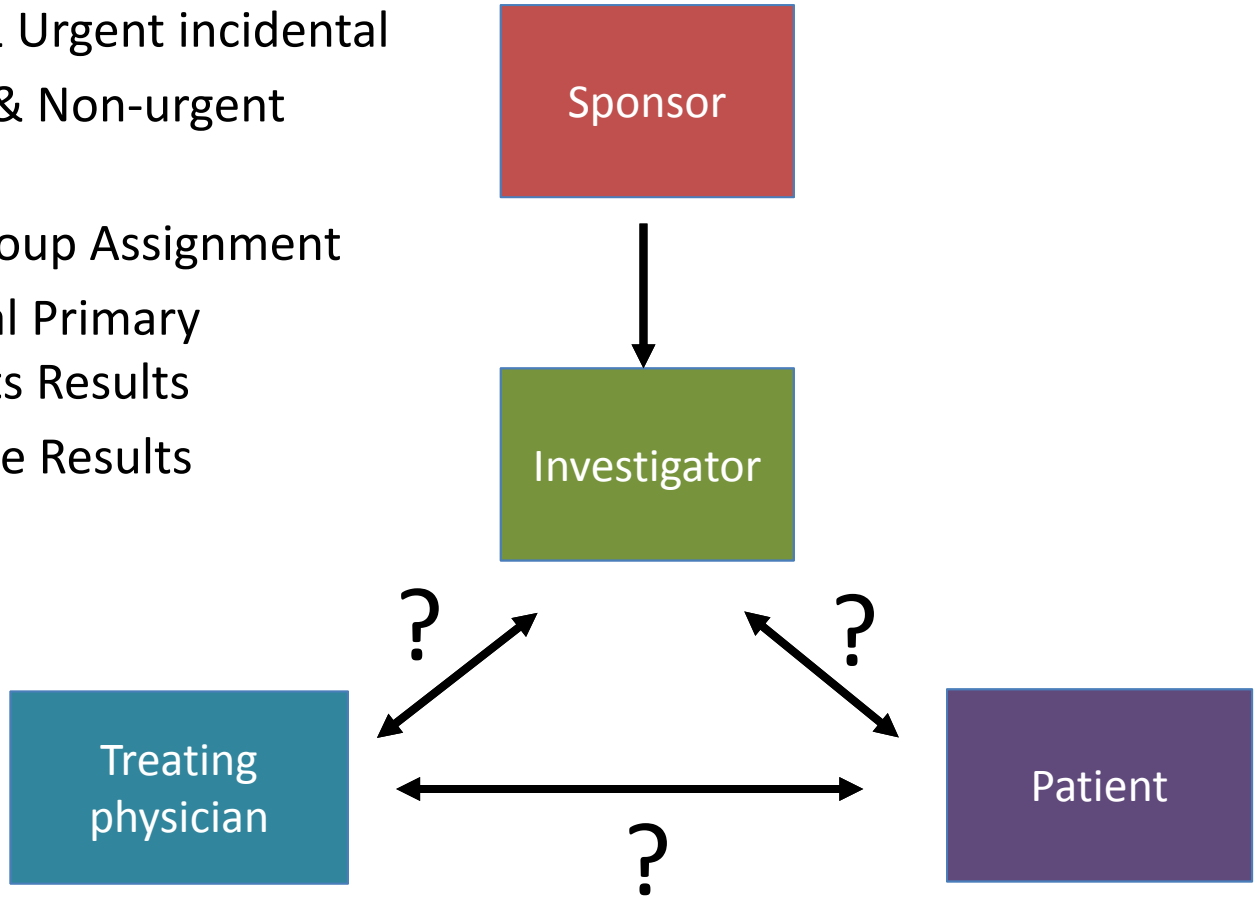
Axes of Communication for return of individual results



From: MRCT Center Return of Individual Results to Participants Recommendations Document, Version 1.2, November 2017
http://mrctcenter.org/wp-content/uploads/2017/12/2017-12-07-Return-of-Individual-Resullts-Recommendations-Document-V-1.2.pdf

Return of Results –Current and Future state of Communications

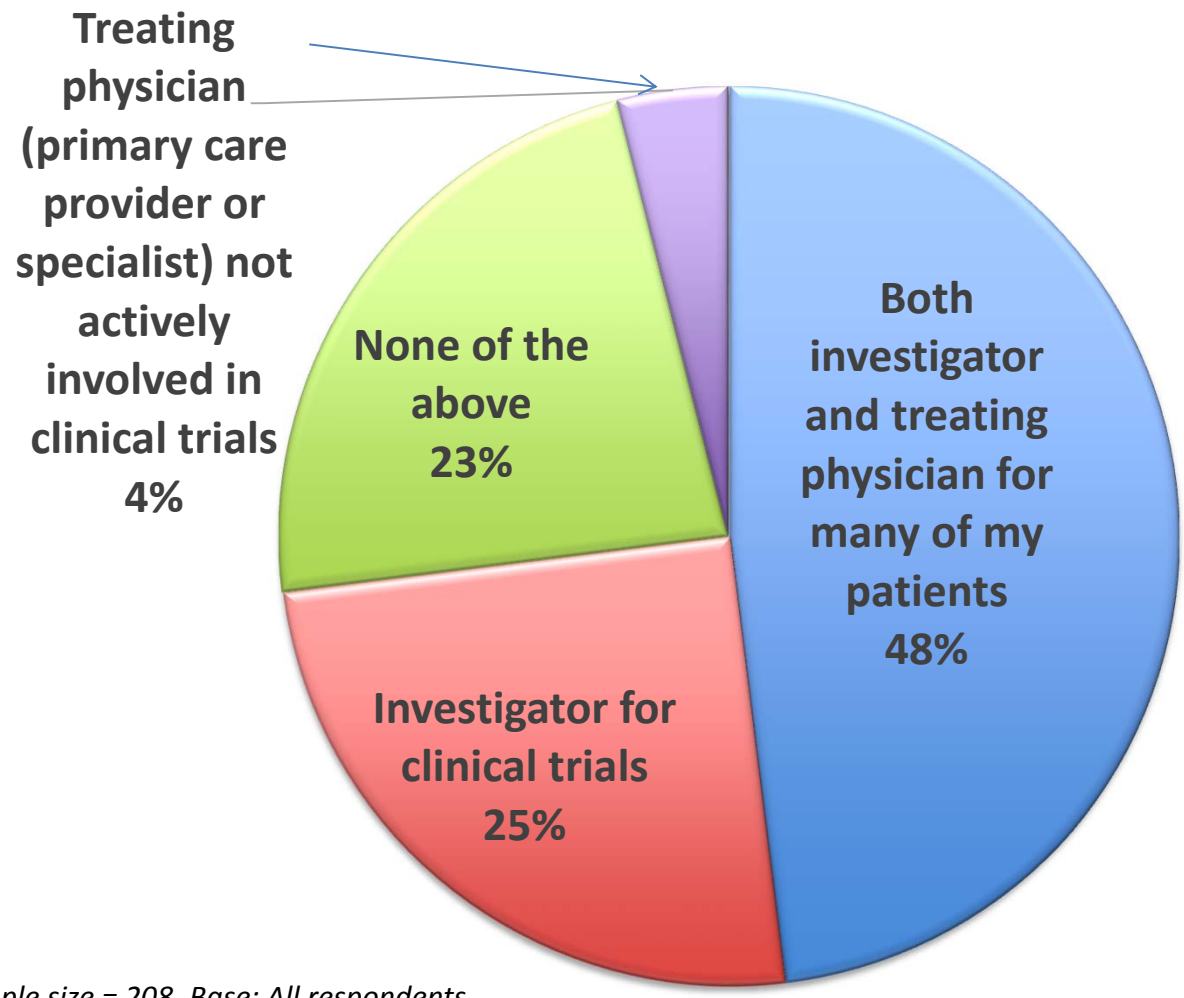
1. Urgent & Urgent incidental
2. Routine & Non-urgent findings
3. Study Group Assignment
4. Individual Primary Endpoints Results
5. Aggregate Results



We designed and conducted a study

Study objectives:	• Identify current practices for sharing results among investigators and treating physicians • Understand which results investigators and treating physicians believe should be dissemination and to whom (ideally) • Identify existing barriers to sharing results and potential solutions
Questionnaire development:	Questionnaire developed by MRCT Center workgroup and CenterWatch using data from pilot of telephone interviews of investigators and referring physicians
Dissemination method:	Online survey
Data collection period:	June - September 2017
Response size (out of 20,000 surveys sent)	n=160; survey disseminated to CenterWatch's global investigative site and physician list of 20,000

Respondent Profile



Sample size = 208, Base: All respondents

Respondent Profile

Region (n=160)	%
North America	31%
Europe	43%
Other	26%

Site Type (n=160)	%
Academic	70%
Hospital-based (non-academic)	19%
Practice-based	7%
Free-standing (no clinical care)	3%

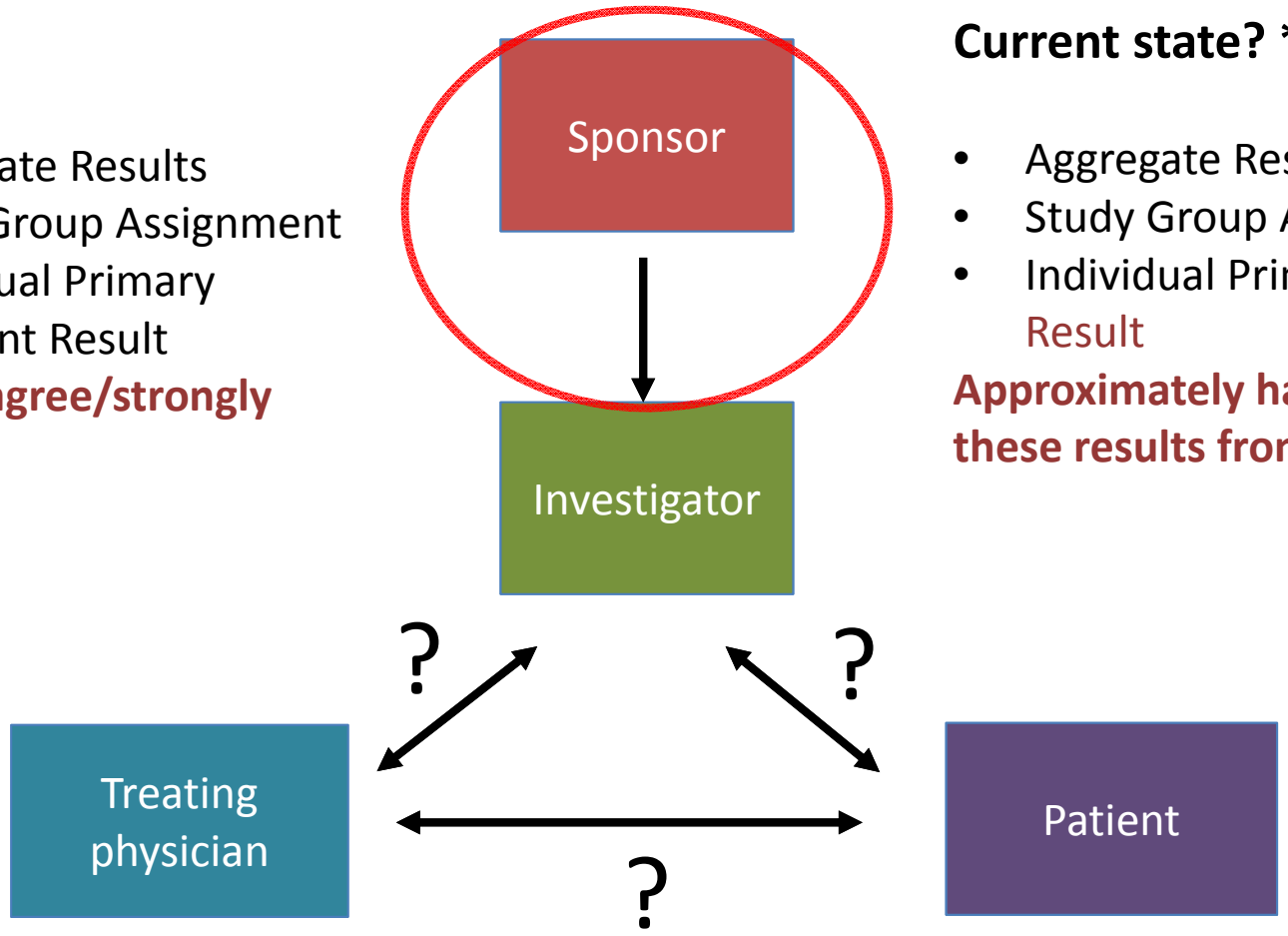
Years involved in Clinical Research (n=150)	%
4 years or less	8%
5 to 10 years	21%
11 to 20 years	36%
21 years or more	35%

Do investigators and treating physicians believe that investigators should receive results (ideally) - whether or not they are shared with patients or treating physicians?

Ideally? *

- Aggregate Results
- Study Group Assignment
- Individual Primary Endpoint Result

88%-95% agree/strongly agree



Current state? **

- Aggregate Results
- Study Group Assignment
- Individual Primary Endpoint Result

Approximately half *never* receive these results from Sponsors

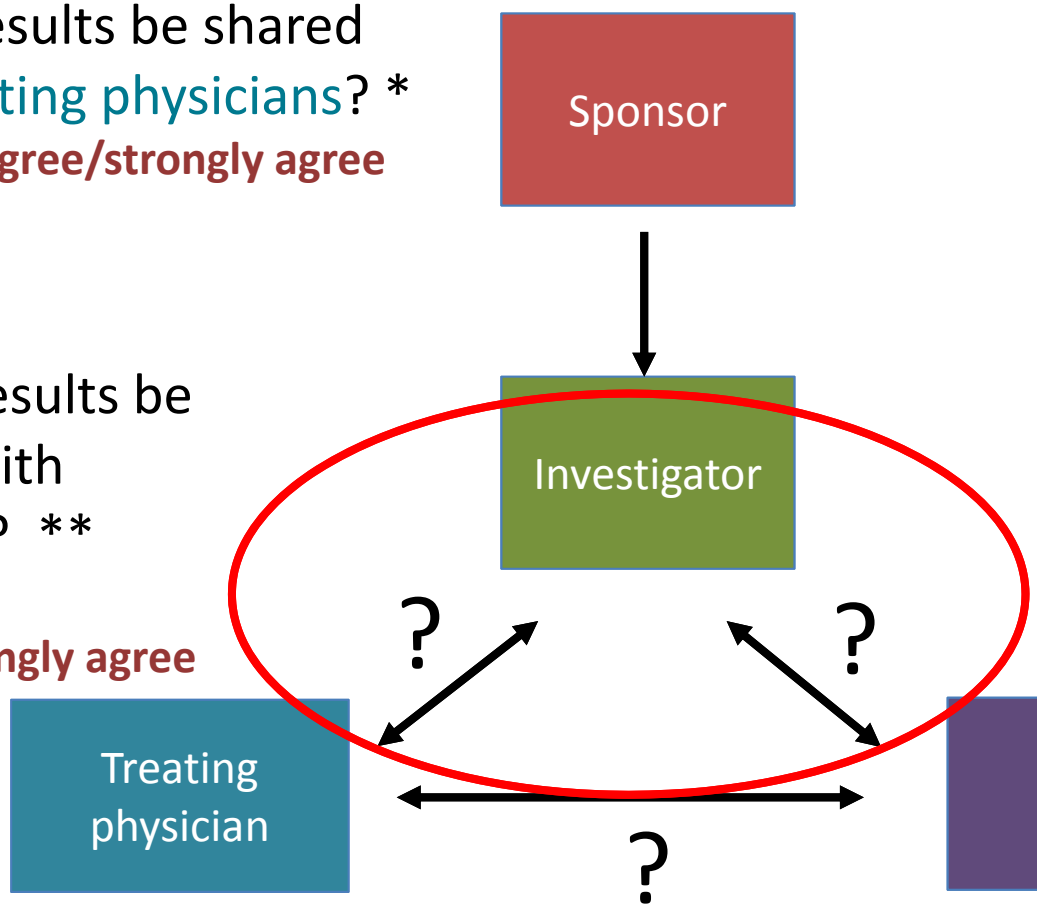
Do investigators and treating physicians believe the results should be further shared (ideally)?

Should results be shared with treating physicians? *

69%-91% agree/strongly agree

Should results be shared with **patients**? **

63%-91% agree/strongly agree



Current State?

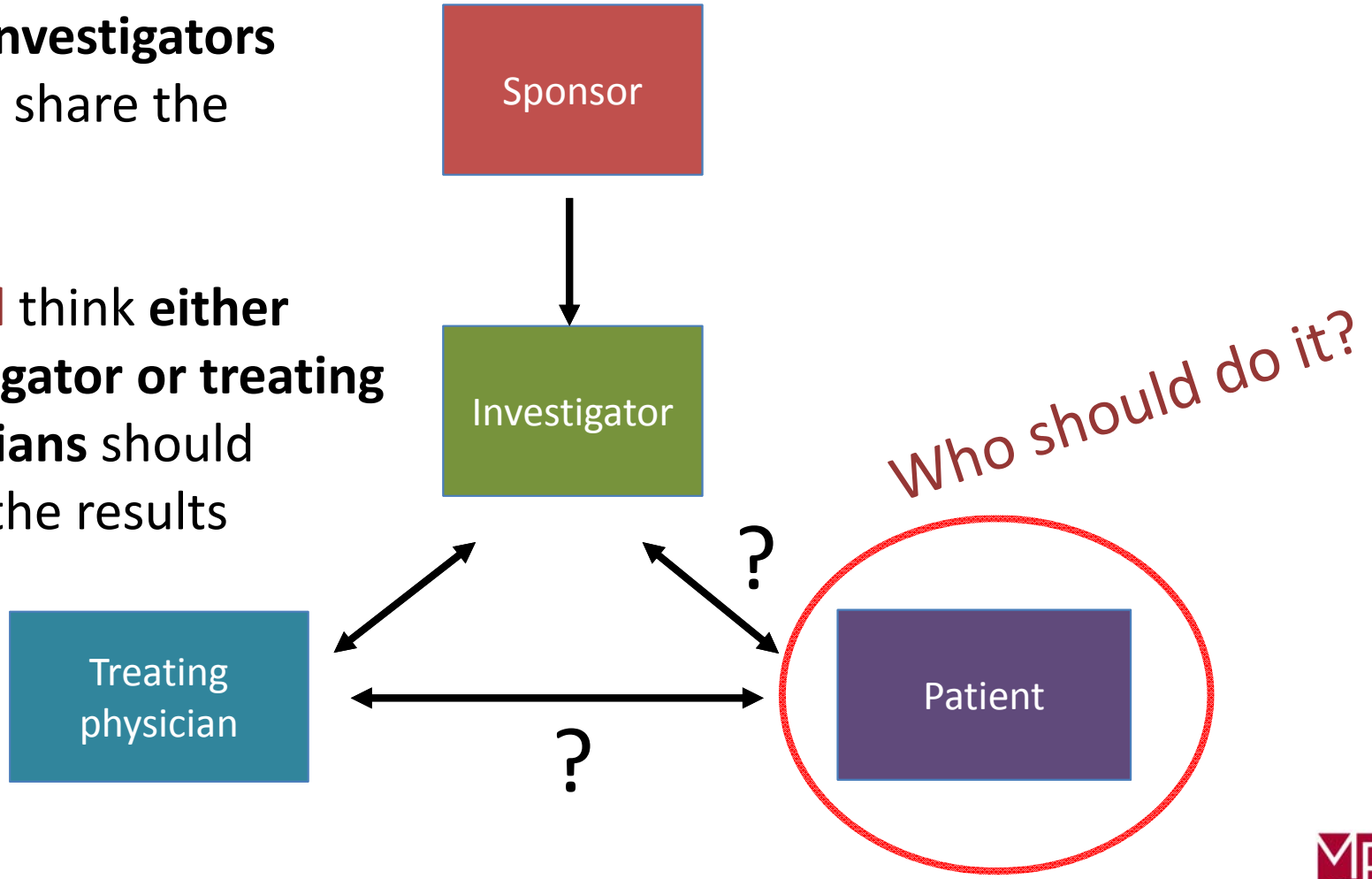
40%-83% have *never* shared Results (across each of the result categories)

Current State?

40%-71% have *never* shared Results (across each of the result categories)

Who do investigators and treating physicians believe should share results with study participants?

- Approximately **half** think **Investigators** should share the results
- A **third** think **either investigator or treating physicians** should share the results



Return of Results –overcoming barriers

- Sponsors should consistently provide results
- Investigator and treating physician **exchange contact information at beginning of trial**
- **Knowing the patient's preference** regarding desire to receive results
- Participant **consent for investigator to contact treating physician**
- **Provision of a guidance sheet** for how and when to communicate results
- **Provision of a summary document** that gives an overview and context
- **A line of communication** between investigator and treating physician
- Guidance on mitigation of **legal and privacy risks**

Key survey findings

- A majority of investigators and treating physicians surveyed believe that **investigators should be receiving results** across each of the categories and yet this is not consistently done.
- A majority of investigators and treating physicians surveyed believe these results **should be further shared** with both treating physicians and **study participants**.
- **Treating physicians could help** share results with patients.
- **Barriers to sharing were identified** and potential **pragmatic solutions could be implemented** with relative ease.

National Academies of Medicine (NAM)
Returning of Individual Research Results to Participants

- Released July 10, 2018
- Refers to MRCT Center recommendations more than a dozen times

NAM Guidance concurs with all substantive MRCT Center recommendations:

- Respect for Persons/Autonomy
- Promote and safeguard the well-being of research participants
- Return clinically actionable results
- Maintain the integrity of the research
- Decisions vary on study-by-study basis
- Parallel decision-making framework with feasibility and value dimensions
- Planning for return of individual results
- Setting participant expectations in the informed consent process
- Identify appropriate communication modality

NAM Guidance differs from MRCT Center recommendations:

- No reference to or recommendations by types of data
- Need for quality management system
- Need to harmonize federal regulations by reshaping legal and regulatory landscape (CMS and HIPAA regulations)

Summary

- Most study participants do not receive results, but wish to
- Decision as to what results to share, how and when to share
- Participant autonomy and privacy paramount
- Study-by-study, result-by-result analysis
  - Medical significance
  - Analytical validity
  - Personal utility
  - Study integrity
  - Local, regional, and national laws and regulations
- Utilize available resources

MULTI-REGIONAL CLINICAL TRIALS

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

Thank you

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