

Ethics and Collateral Findings in Pragmatic Clinical Trials: Implications of a Multi-Method Exploration

Juli Bollinger, MS

Stephanie Morain, PhD, MPH

Jeremy Sugarman, MD, MPH, MA

Kevin Weinfurt, PhD

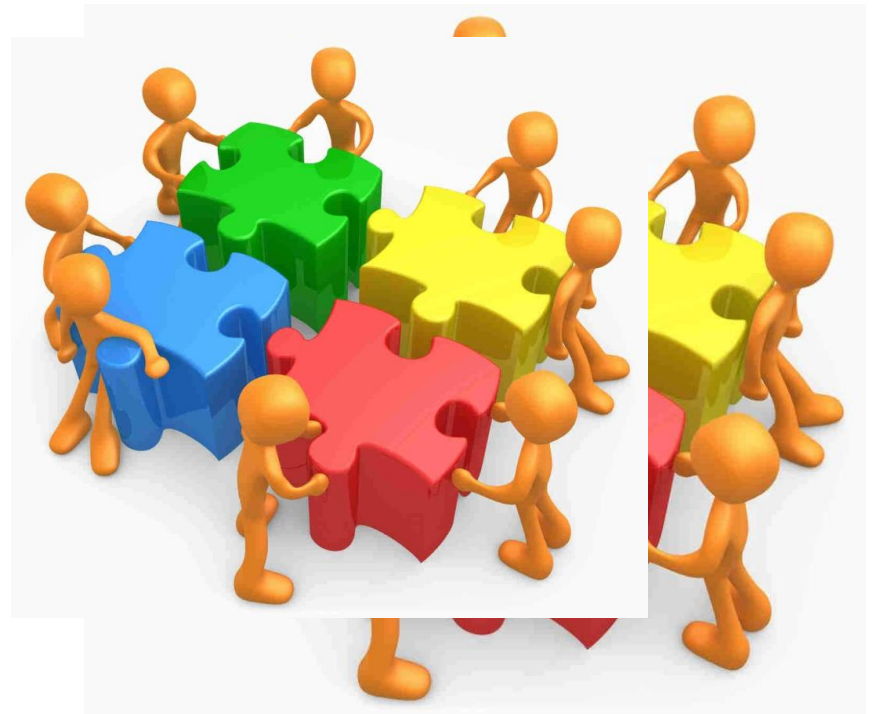
Introduction

- Pragmatic Clinical Trials (PCTs)- embedding research into routine clinical care
- Cost effective
- Less burdensome
- Information for patients, clinicians, payers, and health systems

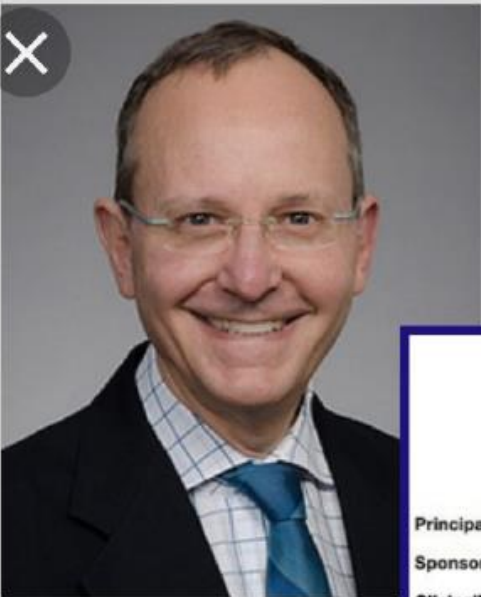


Ethical Complexities of PCTs

- Consent
- Gatekeepers/
Relationship to patients
- Privacy
- Scale



Additional complexities....



Learn more about LIRE at
www.rethinkingclinicaltrials.org

Lumbar Imaging with Reporting of Epidemiology (LIRE)

Study Snapshot

Principal Investigator: Jeffrey Jarvik, MD, MPH

Sponsoring Institution: University of Washington

ClinicalTrials.gov: [NCT02015455](https://clinicaltrials.gov/ct2/show/study/NCT02015455)

Collaborating Healthcare Systems: Kaiser Permanente, Northern California; Kaiser Permanente Washington Health Research Institute; Mayo Clinic Health System; Henry Ford Health System; Oregon Health and Science University

NIH Institute Oversight: National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS); National Center for Complementary and Integrative Health (NCCIH)

Definitions

- Incidental finding (IF)- finding that has potential importance for health, reproductive decision-making or personal utility that is “discovered in the course of conducting research but is beyond the aims of the study” (Wolf, 2013).
- Secondary finding (SF)- finding that is “actively sought by a practitioner that is not the primary target” (Presidential Commission, 2013).

PCT-Collateral Findings (PCT-CF)

- Findings arising in PCTs (discovered intentionally or unintentionally) that may have implications for health, but which were not generated to address the PCT's primary research questions

MOTIFS: Management of Trial Incidental Findings

- Project Team

- Juli Bollinger
- Gail Geller
- Jeffrey (Jerry) Jarvik
- Debra Mathews
- Elizabeth May
- Stephanie Morain
- Jeremy Sugarman
- Kevin Weinfurt

- NIH funding



National Institutes
of Health

Support

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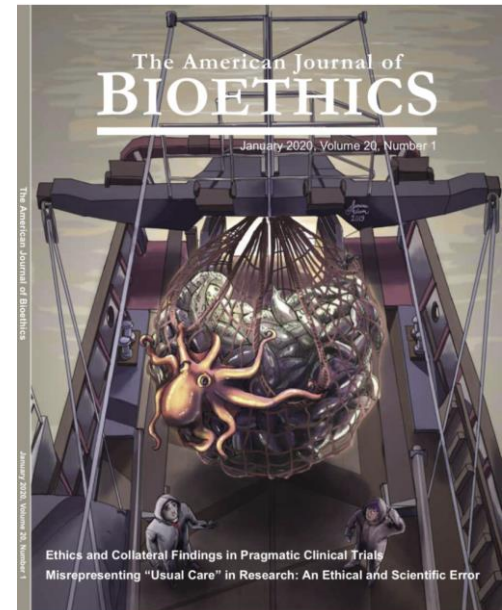
Specific Aims

1. Assess gaps in current guidance for managing incidental findings that are relevant to PCTs.
2. Gather data from stakeholders regarding their knowledge, attitudes, beliefs and expectations regarding incidental findings in PCTs.
3. Develop empirically informed guidance regarding the ethical and practical management of incidental findings in PCTs.

Aim 1: Assess Gaps

Manuscript: Ethics & Collateral Findings in Pragmatic Clinical Trials

Authors: Morain, Weinfurt, Bollinger, Geller, Mathews, Sugarman



Am J Bioeth 2020; 20: 6-18.

PCT Context & Implications for CFs

Three features challenge assessment/ethical management of PCT-CFs:

- a. (Potential) lack of explicit consent/disclosure
- b. Nature of researcher-subject relationship
- c. Large scale of PCTs

Insights from (& Limits of) Existing Scholarship

Semi-analogous areas:

1. Clinical care
2. Quality improvement
3. Clinical research
4. Population genomics
5. Environmental health research
6. Public health surveillance

Am J Bioeth 2020; 20: 6-18.

Relevant Attributes for PCT-CF Management

1. What is the nature of the finding?
2. When was it identified?
3. Where did it occur?
4. Why and how did it arise?
5. Who knows the information?

Takeaways

1. Liminal nature of PCTs challenges traditional research-care paradigm
2. Existing scholarship offers some guidance, but many open questions
3. Importance of future conceptual & empirical work

The Plan

1. Interviews and focus groups
2. Quantitative survey
3. Policy Implications
4. Q&A

STAKEHOLDER INTERVIEWS

Study Population

- Recruitment
 - Collaboratory-funded projects
 - Completed PCORI-funded projects
 - ClinicalTrials.gov
 - Delivery system leaders
- Roles
 - Investigators
 - IRB leadership
 - Delivery system leadership
 - Legal counsel
 - Clinicians

Study Population

- 39 Interviews
 - 22 Collaboratory
 - 8 Non-Collaboratory
 - 9 Delivery system leaders
- 26M/13F
- 22 PIs, 5 IRB, 1 Quality leader, 9 Delivery system leaders, 1 Clinician, 1 Legal counsel

Interview Domains

- Experience with PCTs
- Experience with CFs
- Management of CFs (actual/hypothetical)
- Factors relevant to CF management

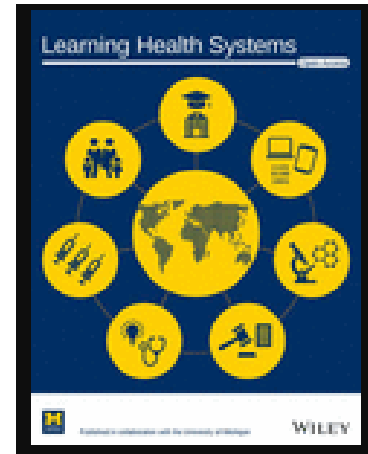
Takeaways

- PCT-CFs generally not on peoples' radar, but shared belief anticipation/planning is critical
- Lack of shared language/definitions complicates response
- CF management is highly CF-dependent
- CF management is highly context-dependent (e.g., nature of health care system)
- No clear “ownership” of issue

Publication

Manuscript: Stakeholder perspectives regarding pragmatic clinical trial collateral findings.

Authors Morain, Mathews, Weinfurt, May, Bollinger, Geller, Sugarman.



Learn Health Syst 2020; 28:5(4).

FOCUS GROUPS

Study Population

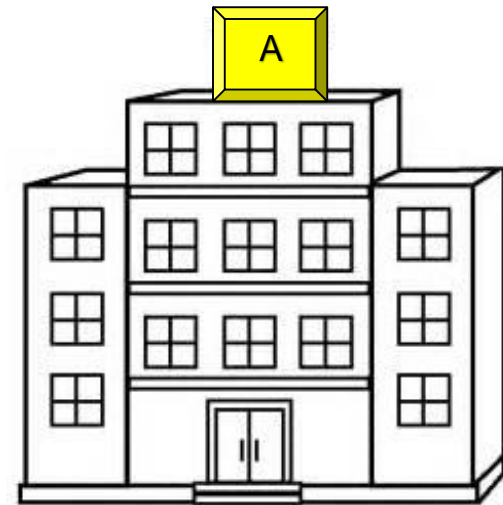
- Focus groups (n=11, including 2 pilots)
 - Baltimore, MD
 - Houston, TX
 - Seattle, WA
- Recruitment
 - Craigslist ads posted in each location
 - Eligible participants had to have seen a doctor or have been hospitalized in the past year.
- Single moderator (JB)
- \$75 incentive

Focus group characteristics

Gender		Age	
Male	25	<20	0
Female	41	20-29	9
	66	30-39	11
Race/ethnicity		40-49	15
Black or African American	24	50-56	17
White	26	60-69	8
Hispanic or Latino	6	70-79	6
Asian	5		66
Other	5	Education level	
	66	<High school	1
Health insurance		High School/GED	11
Private	29	High School + Some College	12
Medicaid/Medicare	23	Trade	2
Integrated/VA	5	AA	3
No insurance	9	BA/BS	31
	66	MA/MS	6
			66

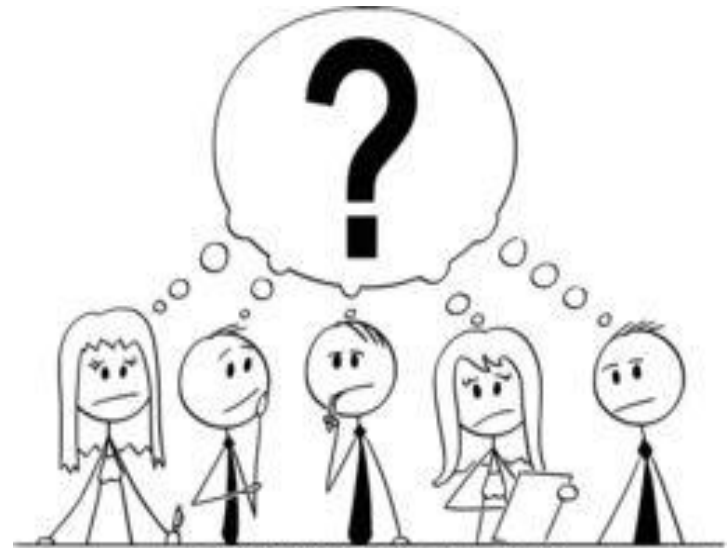
Hospital A

- Let's imagine you receive your care at Hospital A.
- Hospital A, like other hospitals, looks for ways to improve the care they offer to their patients.
- Hospital A can use the vast amounts of information, already collected in their patient EHRs, to answer questions about health care.



For example:

The team at Hospital A wants to compare two medications commonly prescribed to treat high blood pressure

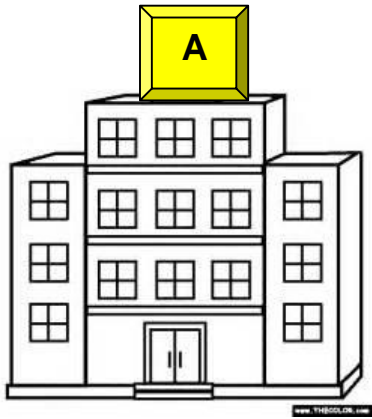


Hospital A staff

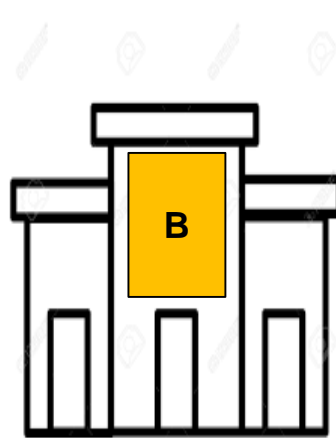
Which medication works better - **DILAX** or **Relaxil**?

Explanation of CRT

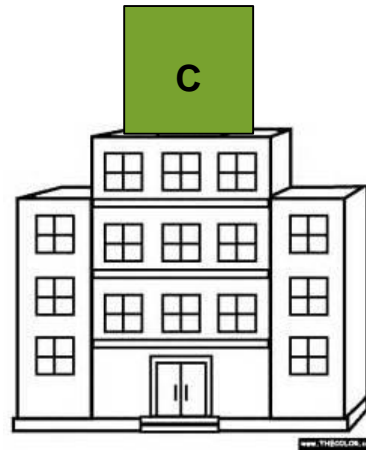
Your hospital, Hospital A, works with three other hospitals to figure out which medication works best.



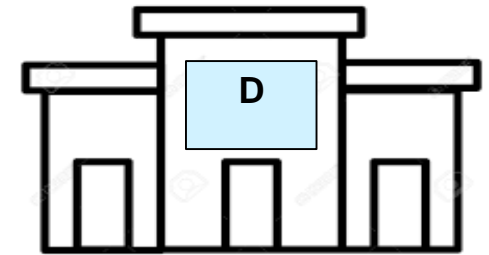
Hospital A



Hospital B



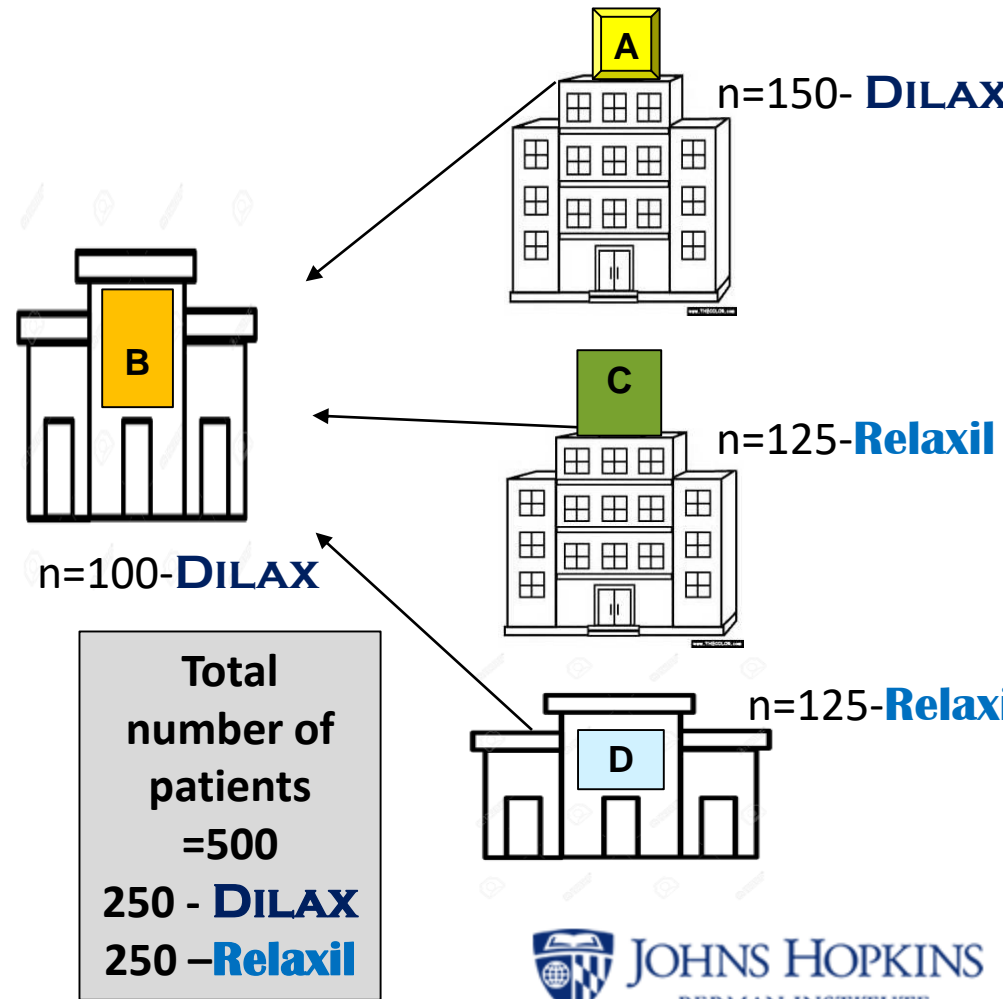
Hospital C



Hospital D

Explanation of CRT- Continued

- Each hospital shares their data with the team at Hospital B who will combine all the data and analyze it together.
- **A few important things to note:**
- Before sharing their patient information with Hospital B, each hospital removes the names of their patients (along with any other identifying information) and replaces it with a code.
- For example, John Smith becomes HABPP2 (Hospital A, blood pressure patient 2)
- Hospital B does not have access to any identifying information about the patients from the other hospitals.



Unexpected finding

While doing their analysis, the team at Hospital B notices that some patients are taking two medications that can cause an abnormal heartbeat when taken together.



The team has decided to provide this information to patients.

Takeaways

- Participants had mixed reactions
 - Anger, gratitude
- All participants wanted the PCT-CF
- Preferences for “*who*” and “*how*” varied
- Multi-modal approach favored
- Minimal detail preferred
 - Include: what was found, what to do, who to contact for more information, etc.
- Timeline delivery was important

Takeaways

- Reactions to the lack of consent
 - In most groups, the lack of consent did not register
 - Issue had to be raised by the moderator
 - Mixed reactions
 - Disrespectful
 - Efficient
 - Explanation led to resigned acceptance
 - “We probably signed something”
 - Did not diminish desire for the PCT-CF

Takeaways

Communications about PCT-CFs should:

- Be delivered in a timely fashion
- Come from recognizable/trusted source
- Attract attention, but minimize alarm/anxiety
- Limit distracting details

“If a man asks you for the time, you don’t tell him how to build a watch.”

Publication

Manuscript: Patients' Views About the Disclosure of Collateral Findings in Pragmatic Clinical Trials: a Focus Group Study.

Authors: Bollinger, Geller, Weinfurt, May, Morain, Mathews, Sugarman.



J Gen Intern Med 2020; 35: 3436-3442.



Estimating the Impact of Different Communications to Patients about PCT-CFs

A National, Online, Randomized Experiment



**NIH PRAGMATIC TRIALS
COLLABORATORY**

Rethinking Clinical Trials®

Patients' Reactions to Letters Communicating Collateral Findings of Pragmatic Clinical Trials: a National Web-Based Survey

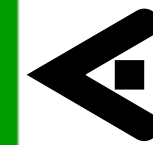
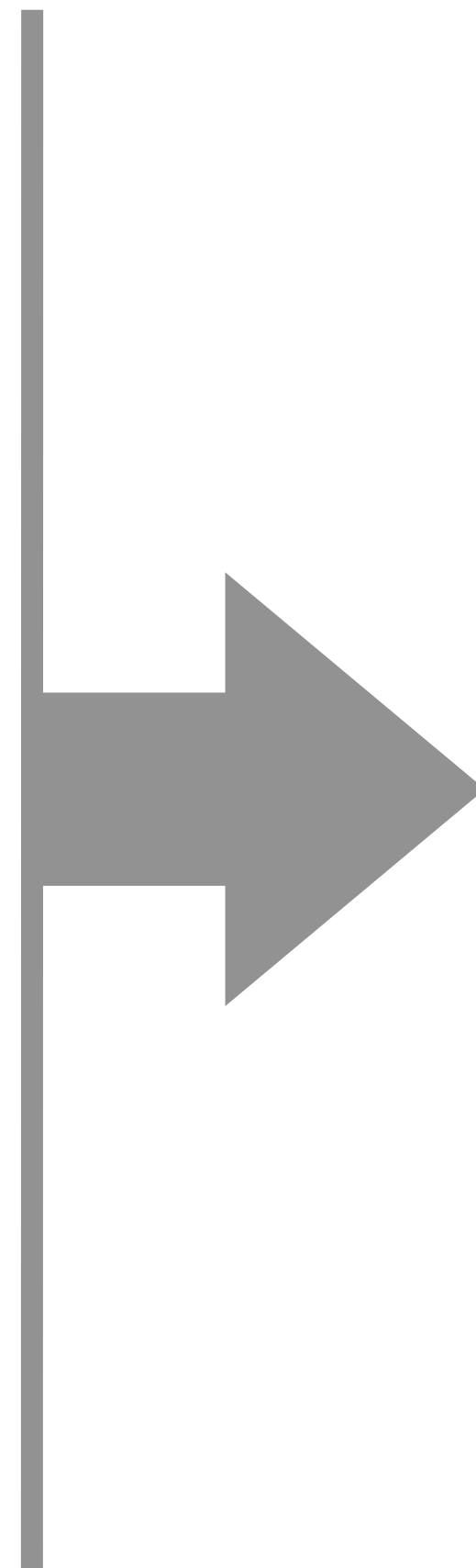
*Kevin P. Weinfurt, PhD¹, Juli M. Bollinger, MS², Elizabeth May, MA²,
Gail Geller, ScD, MHS^{2,3}, Debra J. H. Mathews, PhD, MA^{2,4},
Stephanie R. Morain, PhD, MPH⁵, Lorrie Schmid, PhD⁶, Diane L. Bloom, PhD⁷, and
Jeremy Sugarman, MD, MPH, MA^{2,3}*

What is the impact of different types of letters?

Who is letter from?

Include that finding arose from a research study?

Type of finding?



Do next?

Emotional reaction

Questions?

Subjective understanding

Other perceptions re: communication

A/B Drug Trial (BP) - Contraindicated Medications

- Multisite trial aimed at identifying the incidence of osteoporosis among patients with a spinal fracture
- Upon review of EHR data, the researchers noticed that some patients had been prescribed 2 medications which should not be taken together

A/B Drug Trial (BP) - Hematuria

- Cluster randomized trial with 12 sites aimed at comparing two medications for BP control
- Upon review of EHR data, the researchers could not determine whether any follow-up was done for trace hematuria

Multi-Site Imaging Study- Contraindicated Medications

- Multisite trial aimed at identifying the incidence of osteoporosis among patients with a spinal fracture
- Upon review of EHR data, the researchers noticed that some patients had been prescribed 2 medications which should not be taken together

Under-performing Colon Cancer Test Kit

- Cluster randomized trial with 12 sites comparing screening rates among those patients who received test kits at routine clinic visits to those who received them by mail
- All clinics used their usual test kits
- Researchers determined that one of the test kits used may not have been working well

Sample

Representative sample of U.S.
English-speaking adults

7,635 sampled and contacted

4,218 completed

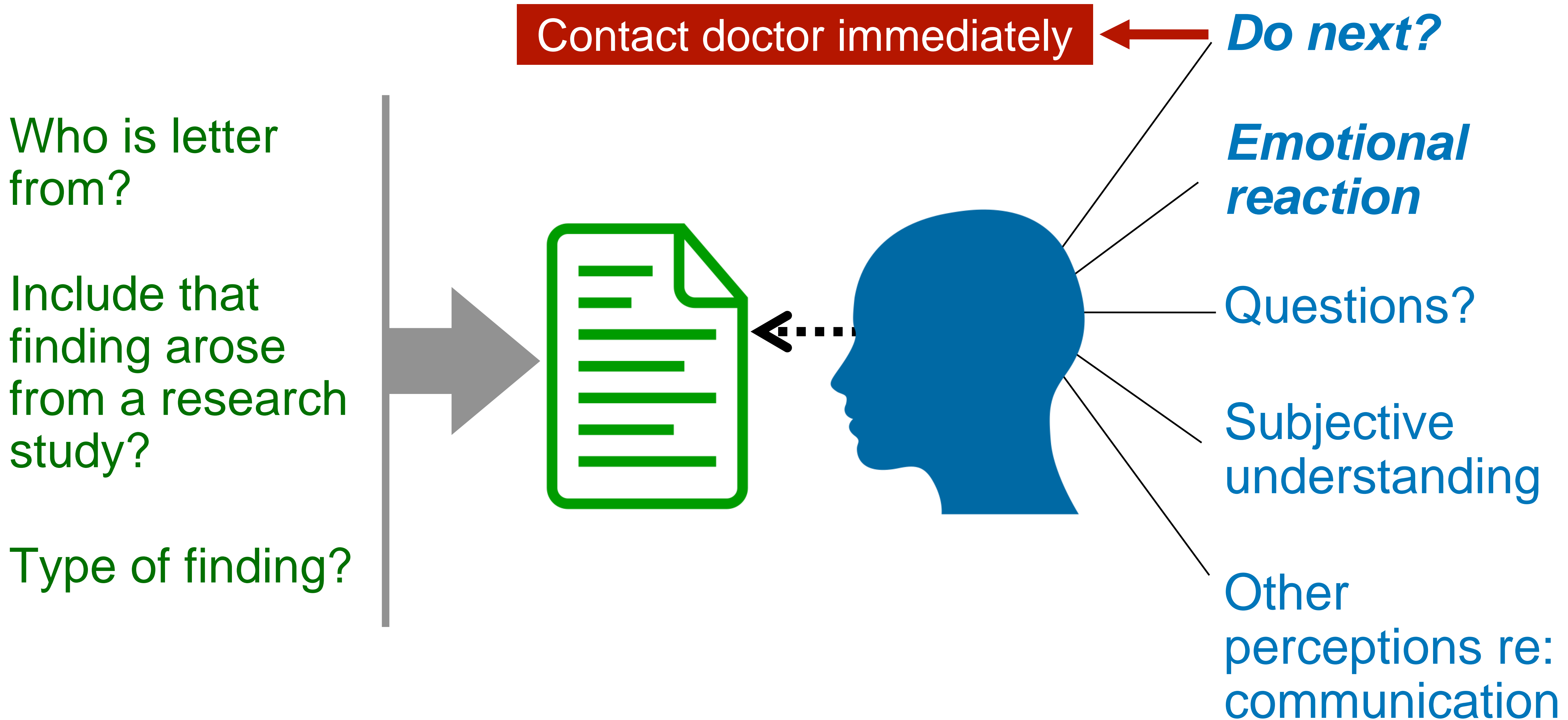
4,080 analyzable responses



Measures and Analysis

- Survey questions were pretested in 20 cognitive interviews
- Pre-specified 15% difference between groups as policy-relevant, e.g.,
 - 50% vs 60%: *No*
 - 50% vs 67%: *Yes*

What is the impact of different types of letters?



What would you do next? (Check all that apply)

- A. Talk to someone immediately
- B. Talk to someone eventually
- C. Use the internet to learn more
- D. Do something else? Specify: _____
- E. Unsure what to do
- F. Do nothing

What would you do next? (Check all that apply)

A. Talk to someone immediately 

B. Talk to someone eventually

C. Use the internet to learn more

D. Do something else? Specify: _____

E. Unsure what to do

F. Do nothing

Doctor

Other health care professional

Family member

Friend

Other (Please Specify):

	%
Talk to doctor immediately	56
Talk to other health care professional immediately	12
Talk to family member immediately	8
Talk to friend immediately	3
Talk to other immediately	2
Talk to doctor eventually	11
Talk to other health professional eventually	3
Talk to family member eventually	3
Talk to friend eventually	1
Talk to other eventually	0
Use the internet to learn more	30
Do something else	14
Unsure what to do	5
Do nothing	6

Ranged from
49% to 65%
across
experimental
conditions



VS



NO Effect

Signed by
personal MD

Signed by Chief
Quality Officer/Sr
Med Dir of Research



VS



Found Effect

Described
PCT whence
finding arose

No mention of
the PCT

*But it differs by
type of finding*

Predicted Probabilities of Intending to Contact a Doctor Immediately by Type of Finding and Level of Detail

Type of finding	Trial description	
	No	Yes
A/B drug trial (BP)—contraindicated medications		
A/B drug trial (BP)—hematuria		
Underperforming colon cancer test kit		
Multisite imaging study—contraindicated medications		

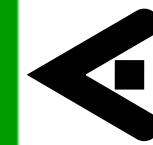
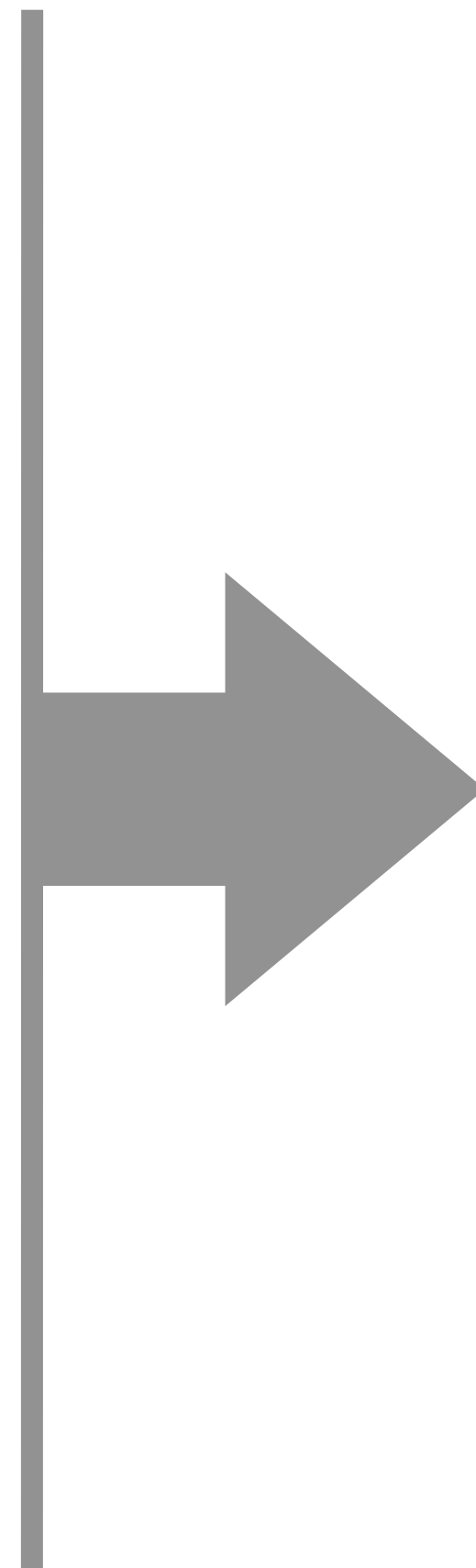
No difference \geq pre-specified cutoff for a policy-relevant difference of 15.

What is the impact of different types of letters?

Who is letter from?

Include that finding arose from a research study?

Type of finding?



Do next?

Emotional reaction

Questions?

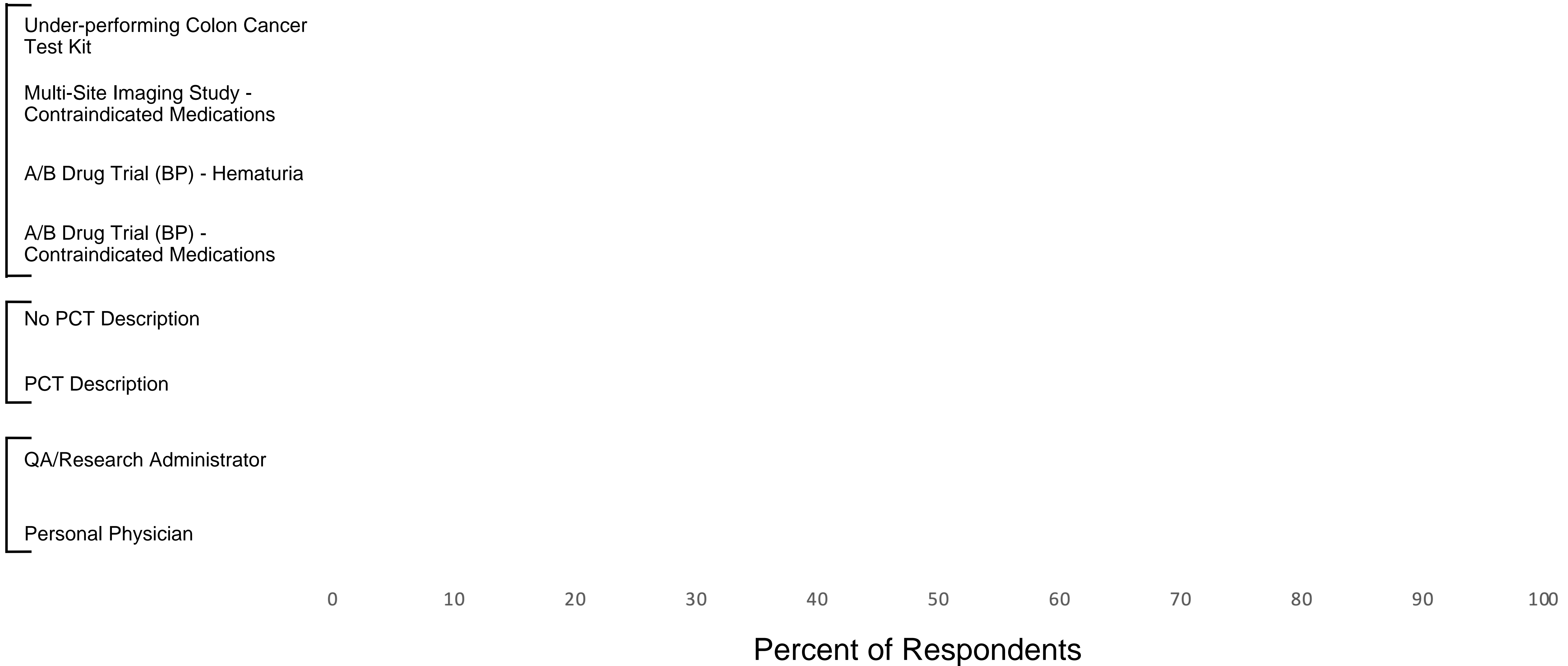
Subjective understanding

Other perceptions re: communication

Emotion	%
Concerned	60
Worried	38
Hopeful	4
Confused	24
Grateful	13
Surprised	25
In Control	4
Fearful	19
Irritated / Annoyed	28
Angry	17
Relieved	3
Overwhelmed	9
Other feeling	3
No feeling	10

Combination of Emotional Reactions to Letters

■ Negative ■ No Feel ■ Mixed ■ Positive

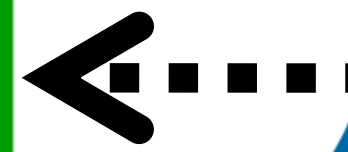
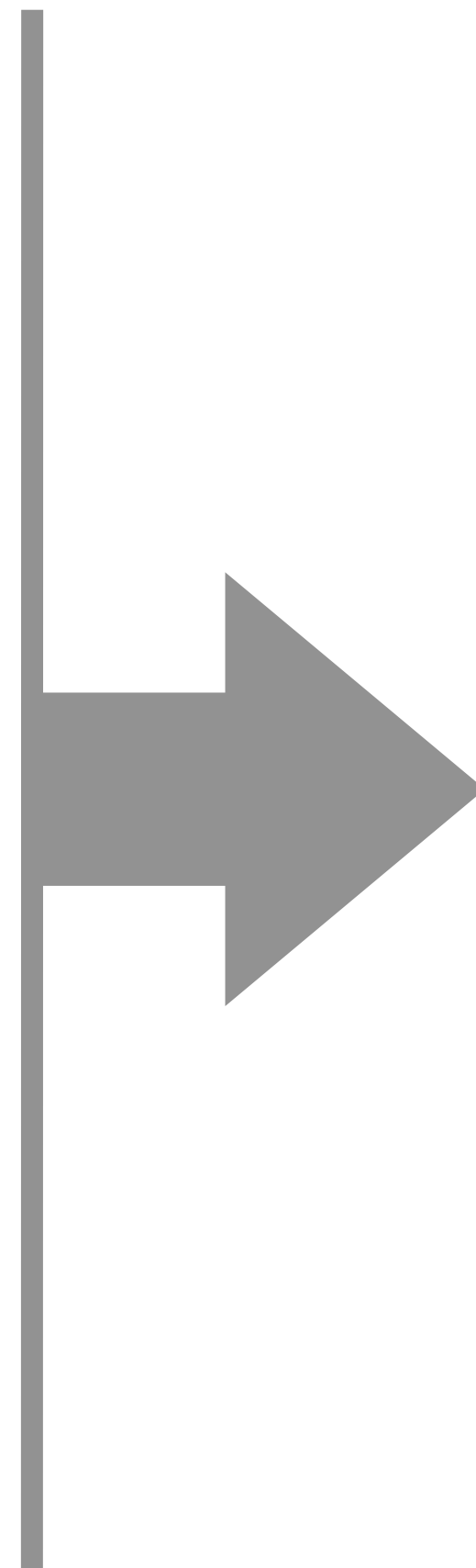


What is the impact of different types of letters?

Who is letter from?

Include that finding arose from a research study?

Type of finding?



No policy-relevant differences

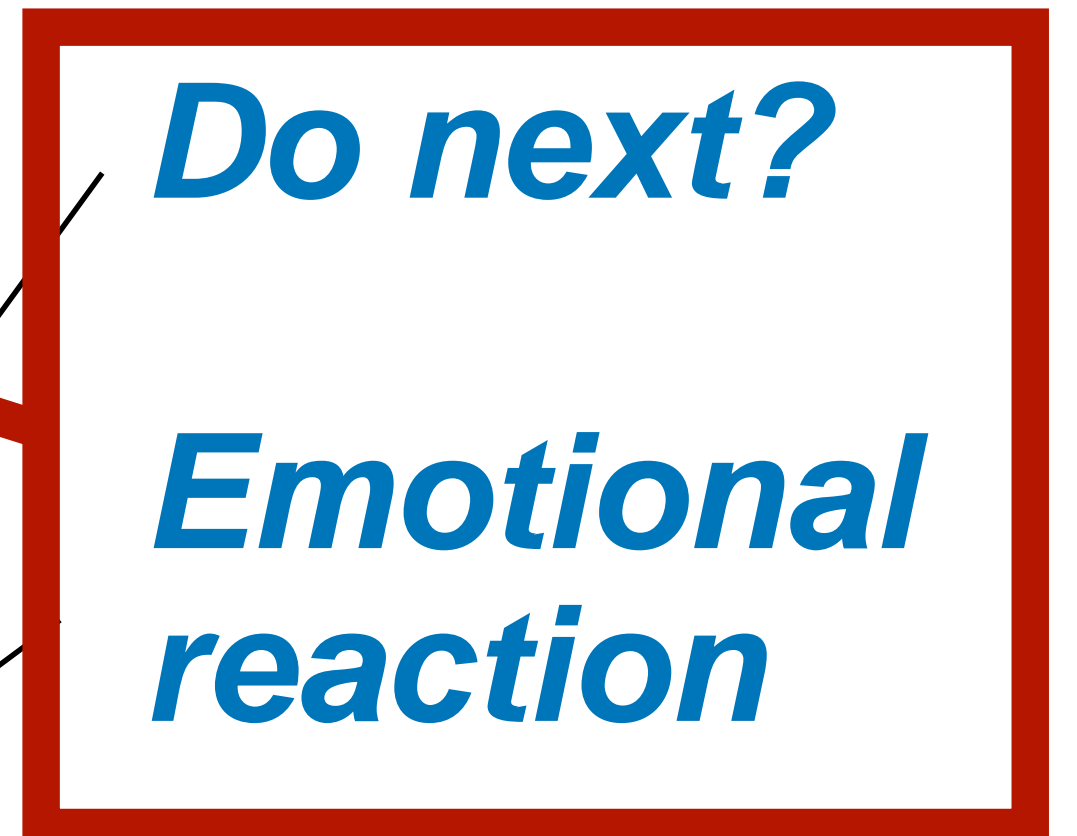
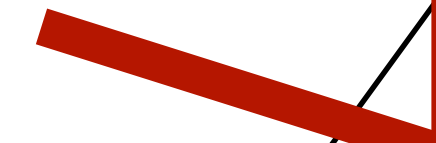
Do next?

Emotional reaction

Questions?

Subjective understanding

Other perceptions re: communication



KEY THEMES & POLICY IMPLICATIONS



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of BIOETHICS

Key Themes from Empirical Data

1. Liminal nature of PCTs complicates ethical & practical considerations regarding management of PCT-CFs
2. Management of PCT-CFs is context-specific
3. Institutions must play central role
4. Patient expectations & preferences may not align with those of other stakeholders

1: Liminal Nature of PCTs

- PCTs are akin to—but ethically distinct from—clinical care or explanatory research
- Uncertainty & lack of shared agreement as to who “owns” the issue of PCT-CFs

2: Management is Context-Specific

- No “one-size-fits-all” approach

ETHICALLY RELEVANT CONSIDERATION	DESCRIPTION
Clinical relevance	Severity, actionability of PCT-CF
Timeliness of identification	Time between data collection and PCT-CF identification
Uniqueness of knowledge	Is information uniquely known to research team or instead readily ascertainable by others?
System-level impact	Costs/burdens associated with evaluation, notification, downstream management; opportunity costs
Whether prospective research consent was obtained	Disclosure of PCT-CF might be disclosure of unconsented underlying research activity

3: Institutions are Key Stakeholders

- Evaluation/assessment
- Whether/not to disclose, & to whom
- Preparing for system-level impacts, & weighing corresponding opportunity costs

4: Patient Expectations

- Most want info—but might not be happy about it
- Patients value information for reasons BEYOND clinical actionability

Emotion	%
Concerned	60
Worried	38
Hopeful	4
Confused	24
Grateful	13
Surprised	25
In Control	4
Fearful	19
Irritated / Annoyed	28
Angry	17
Relieved	3
Overwhelmed	9
Other feeling	3
No feeling	10

Policy Recommendations

- Prospectively anticipate & plan for PCT-CFs before study implementation
- Prepare clinicians for discussing PCT-CFs with patients & for subsequent management
- Use multiple modes to communicate to patients

Planning for PCT-CFs

Roles for:

- Investigators
- Health systems
- IRBs
- Funding sponsors

Prepare Clinicians

- Discussions with patients about:
 - Rationale for PCTs (& waivers of consent)
 - Clinical relevance of finding
- Awareness of relevant resources for subsequent clinical follow-up

Communicating to Patients

- Patients have heterogeneous preferences for AND access to communication channels
- Design approaches to provide key information, while minimizing risk of undue anxiety

Publication

Manuscript: Identification and management of pragmatic clinical trial collateral findings: A current understanding and directions for future research

Authors: Morain, Mathews, Geller, Weinfurt, Bollinger, May, & Sugarman



Call for Peer Commentaries


Target Article

Think Pragmatically: Investigators' Obligations to Patient-Subjects When Research is Embedded in Care

Stephanie Morain   & Emily Largent 

Published online: 18 Apr 2022

 Download citation

 <https://doi.org/10.1080/15265161.2022.2063435>

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