Management of Incidental Findings in Pragmatic Clinical Trials

Juli Bollinger, Debra Mathews, Stephanie Morain, and Jeremy Sugarman

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Disclosure: Jeremy Sugarmn

I have relevant personal/professional/financial relationship(s) with respect to this educational activity with the following organizations:

- Merck KGaA, Bioethics Advisory Panel and Stem Cell Research Oversight Committee
- IQVIA, Ethics Advisory Panel
- Portola Pharmaceuticals, Inc., Consultant

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….

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
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  - Elizabeth May
  - Stephanie Morain
  - Jeremy Sugarman
  - Kevin Weinfurt
- NIH funding

NIH
National Institutes of Health

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.

Support

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Learning Objectives

1. To summarize the ethical challenges for management of collateral findings (CFs) in the context of PCTs
2. To describe original qualitative data from interviews with key stakeholders on the ethical management of CFs in PCTs
3. To describe original focus group data regarding patients' views on the ethical management of PCT-CFs

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Conceptual Model

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2019 Advancing Ethical Research Conference November 17-20 • Boston, MA

Disclosure: Stephanie Morain

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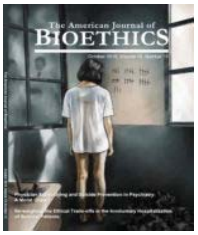
Aim 1: Assess Gaps

Manuscript: Ethics & Collateral Findings in Pragmatic Clinical Trials *(forthcoming)*

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



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

Relevant (Dis)Similarities to PCTs: Clinical Care

Similarities	Dissimilarities
• Need to consider both potential benefits & harms from disclosure	• Physician-patient relationship distinct from that of researcher-subject • Individual informed consent may not have occurred • Timeliness in identification

Relevant (Dis)Similarities to PCTs: QI

Similarities	Dissimilarities
• May involve similar methods, similar (low) risk • May assume individual duty to participate	• Routine QI typically conducted within single institution; PCTs generally multi-institutional • Some PCTs may confer additional risks, suggesting greater obligations of reciprocity

Relevant (Dis)Similarities to PCTs: Clinical Research

Similarities	Dissimilarities

• Findings identified by researchers
• In biobanking, research with stored samples…
  • researcher-subject has similarly distal relationship;
  • related challenge of the "cold call"
	• PCTs embedded into clinical care
	• Individual informed consent may not have occurred
	• Timeliness in identification

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?

Relevant Attributes for PCT-CF Management

1. *What* is the nature of the finding?
   - Severity
   - Certainty
   - Actionability

Relevant Attributes for PCT-CF Management

2. *When* was it identified?
   - When data obtained
   - When data analyzed
   - When CF recognized

Relevant Attributes for PCT-CF Management

3. *Where* did it occur?
   - Fee-for-service versus integrated delivery system

Relevant Attributes for PCT-CF Management

4. *Why* and *how* did it arise?
   - If greater deviation from clinical care, perhaps greater duties of reciprocity
   - Yet, if more closely approximates research, perhaps relationship (& corresponding duties) more akin to physician-patient

Relevant Attributes for PCT-CF Management

5. *Who* knows the information?
   - *Uniquely* known

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

Next Steps

1. Open Peer Commentaries

Stakeholder Interviews

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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

Preliminary Themes

- 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

Not on Radar, yet Anticipation/Planning Critical

- "I think the bottom line for me is that, you know, this is an example of why we've done a terrible job as a research community, …in thinking about the role of research in sort of more of a social, medico-social context, and we should have been long-prepared for these kinds of things. And, frankly, I find it great that these issues are being brought up now, because these things should be handled prospectively and they're not. They're always handled post hoc and on the fly." (Respondent 2)
- "So, you know, honestly, I hadn't thought about it before, but I'm not even slightly surprised, and I'm sure this is the tip of the iceberg in terms of other potential incidental findings that may be of clinical relevance that were never considered in the original design." (Respondent 4)
- "I think there needs to be a process before the trial's even implemented. You know, in the development of the protocol itself, I think some decisions need to be made about what they might do with incidental findings. … But there still should be a process I think in the development of the protocol itself." (Respondent 15)

Lack of Shared Language/Definitions Complicates Response

- "I really think that this is closer to a quality improvement exercise, quality assurance, quality improvement rather than part of the research that's being done. And so, you know, it's an opportunity for health care systems to take information that's being gathered as part of a research project and then to turn it into quality assurance information. And the whole line between what constitutes a pragmatic clinical trial and what constitutes quality assurance initiatives I think is already blurry and I think this issue helps to blur it even more." (Respondent 1)
- "…most of the times and the few times that we have had incidental findings be part of an IRB approval discussion, you know, it's the usual things. It's the CT scan or MRI of the brain are-- usually it's an MRI of the brain for some other purpose that detects an unexpected structural abnormality or a lot of discussion around genomic research. But in this case, you know, it's people's medical record and so it shouldn't be incidental; somebody's ordered it." (Respondent 34)

CF Management is Highly CF-dependent

- "…what was the relative significance of the finding, what was the probability that a provider wouldn't know of the finding, is there any historic precedence on how to deal with these incidental findings, and what did people think about-- would there be or not be benefit in contacting people." (Respondent 7)
- "…one of the other things to bear in mind is that, I mean, we don't do any of these things in real time as far as the outcomes or adjudication. There is some intrinsic delay in terms of how that information gets to the team. So, for example, let's say that everyone is getting now admitted with syncopy or something, we would not know that immediately…" (Respondent 9)
- "…when I talk about a care gap, I'm talking about there's a piece of information for which there's a clearly recommended action, that, "If this is observed, then one must do this." That's a clear expectation. That's what I mean by a care gap. And if it's like, "Well, here's an interesting thing that's sort of on the cutting edge and we're not sure what to do about it," then we'd say, "Well then be quiet."" (Respondent 12)

CF Management is Highly Context-dependent

- "Well, and you know a big consideration--is the infrastructure present within a particular health care system to deal with whatever needs to be done following the return of information? So, if primary care providers, for example, have to have a conversation with their patients about this, do they have the time? Is there a way of easily bringing the patients in or contacting them, setting up that conversation? Who's going to pay for the extra time that it takes in order to do this? ... So I think that the flexibility and the ability of the existing infrastructure to deal with this extra workload as well as the costs associated with it are real considerations that everyone needs to think about." (Respondent 1)
- "…because our trial was really embedded into their clinical care, we didn't create a lot of new processes or give them a new test to use. And they were processing them at their lab with their people. And, of course, they have internal policies that they need to follow that govern how they process their […] tests. And, so, we knew that we couldn't just go in and change their policies. We would have to make them aware of what we were finding and then talk to them about whether or not there were policies that could be changed to avoid some of the outcomes that we were seeing." (Respondent 5)
- "I don't know how to articulate it if you ask me the difference, but it's actually quite different because one is in my hospital, right, those are my hospital patients, and, you know what I'm saying, so I feel like I'm much more comfortable that here's what I would do, I'm the one talking to the family. This other one, these hospitals are 120 miles away, right, I don't know this family, I never talked to this family, you know, and somebody else is allowing me to oversee care." (Respondent 25)

No Clear "Ownership" of Issue

- "Probably somebody in [the quality office] along with again the academic--usually there's a chief academic officer for the system that I would imagine that research and clinical trials roll under, and then […] the chief clinical officer for the system, who's the lead physician for the system, so ultimately those types of senior leaders for a system would be involved with a decision there unless a precedent's been set." (Respondent 10)
- "If I was going to be crazy about it, if it's one letter, because emails are easy, you can send it to the PI and the chair and the IRB. I don't know if our IRB has the facility to take in that kind of information, and all we're trying to do now is not-- it's not a quality issue about the interpreting physician, although if you have lots of those that were serious it clearly would be-- but it's to make sure that the information gets to the individual who can help take care of that incidental finding, assuming it is clinically significant." (Respondent 11)
- "So typically something like this would come up, if you found a signal, you would have-- well, first of all the way that this would happen is you have your IRB and your research regulatory folks. So I mean, to me that's sort of the first conversation you would have. Then in research in our organization, research reports up to our Chief Medical Officer. And our Chief Medical Officer reports to the President, and then ultimately sort of at the top of that is the CEO. But I think where this-- where the interface of the decision-making would occur would be with the research compliance ethics and then the Chief Medical Officer. And then once that group, those are sort of the senior executive leaders of that discussion, and then you would come up with a plan in terms of working with our medical group, our physician practices in terms of how you actually deal with this." (Respondent 28)

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
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Next Steps

- Analyze data for differences across
  - Professional role
  - Home institution type
  - Gender

Focus Groups

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Aim 2: Gather Data

- 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

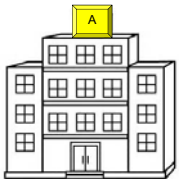
Gender		Age	
Male	25	<20	0
Female	41	20-29	9
	66	30-39	11
Race/ethnicity		40-49	15
Black or African American	24	50-56	17
White	26	60-69	8
Hispanic or Latino	6	70-79	6
Asian	5		66
Other	5	**Education level**	
	66	<High school	1
Health insurance		High School/GED	11
Private	29	High Schoool + Some College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

Focus group discussion guide

1. Introduction
   - Examples of ways people can learn about new, unexpected information important to their health
   - Explanation of EHRs
2. Scenario
   - Multi-center, cluster-randomized, pragmatic clinical trial (no expressed consent) using EHRs
   - PCT-CF: patients taking contraindicated medications
3. Discussion
   - Communicating the PCT-CF: Do you want it? How? Who? What? When?
   - Drafting the communication

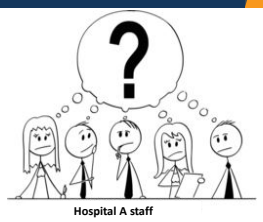
Hospital A

- 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:

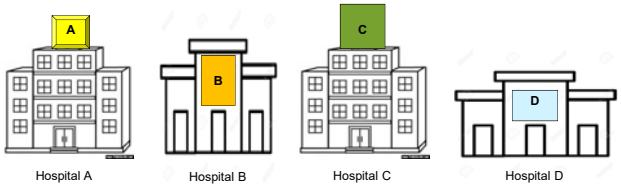
The team at Hospital A wants to compare two medications commonly prescribed to treat high blood pressure



Which medication works better - DILAX or Relaxil?

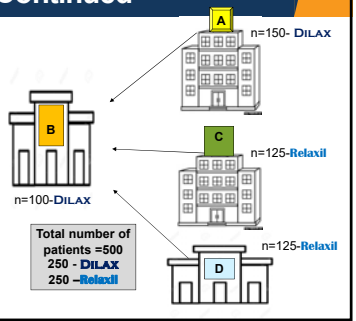
Explanation of CRT

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



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.

Results (preliminary)

- Reactions
- Desire for the PCT-CF
- Communicating the PCT-CF
  - How should the PCT-CF be returned?
  - Who should return the PCT-CF
  - What information should be returned?
  - When should the information be returned?
- Lack of consent

Reactions

- Mixed
  - Concern/anger
    - How did my doctor miss this?
    - Why was this not caught before?
  - Gratitude
    - It might not have been found but for the researchers
    - Potentially life-saving

Desire for PCT-CF

- All participants wanted the PCT-CF
- Reasons
  - The finding was viewed as serious, potentially life-threatening
  - The finding was actionable
- Age of the information did not diminish interest

Communicating the PCT-CF: How?

- Mode
  - Diverse preferences
  - Multi-modal approach favored
    - Accommodates preferences
    - Ensures receipt
- Delivery features
  - Attracts attention
  - Conveys legitimacy

Communicating the PCT-CF: Who?

- A recognizable person or entity
- An individual or entity with the expertise to interpret the finding for the patient

Communicating the PCT-CF: What?

- Substantive facts
  - What was found, what to do next, who to contact for more information, etc.
- Level of detail
  - "Less is more" - avoid distracting information

"If a man asks you for the time, you don't tell him how to build a watch."

Communicating the PCT-CF: When?

- In all groups ***timely*** delivery of the PCT-CF was important
  - Influenced preferences for "who" and "how"
  - Underscored views about the importance of information

"I would like it immediately, so if e-mail is the fastest to let know, then I want an e-mail…"

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

Reactions to the lack of consent

- Explanation led to resigned acceptance
  - This type of research is common and permissible
  - "We probably signed something" about this on a form
- Did not diminish desire for the PCT-CF

Takeaways

- 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.

Takeaways

The communication should:

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

Next Steps

- Utilize data collected from focus groups to design a survey, which will address aim 3 of the project:
  - Develop empirically informed guidance regarding the ethical and practical management of collateral findings in PCTs

Questions?

Thank You

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