Reducing the Mystery Between Study Participants, Study Design and Study Results

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Clinical Trials Coordination Center (CTCC)
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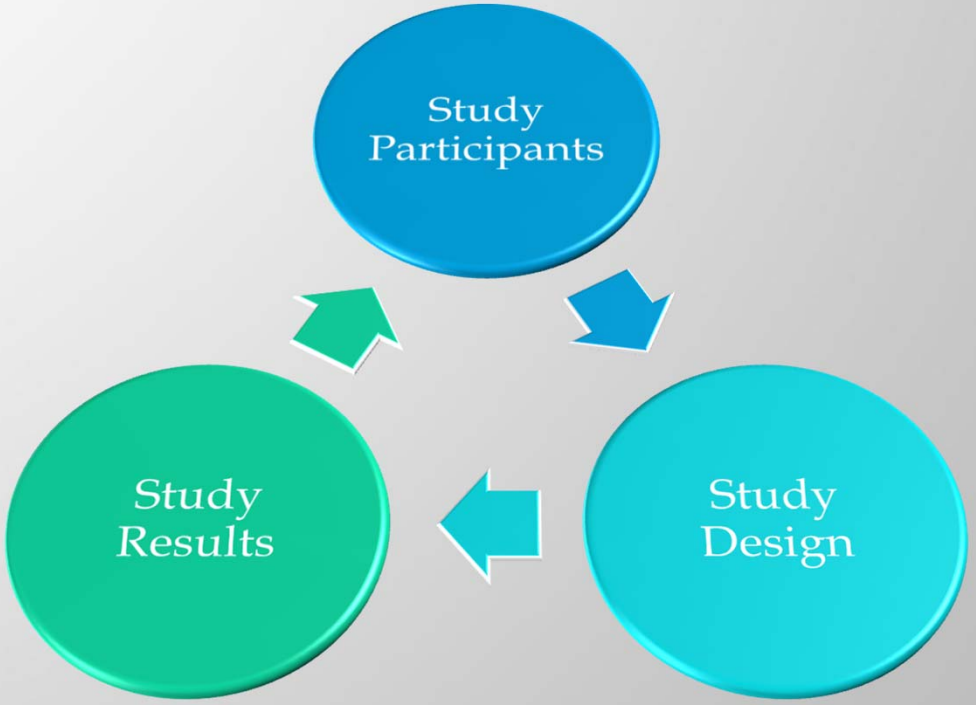
Objectives

- Communication plan
  - What is it?
  - Why is it important?
  - When should it be created?
- Making a study participant part of the team
  - Pre-Enrollment - Study design (focus groups)
  - Implementation (newsletters, teleconferences)
  - Post study completion (dissemination of study results)
- What does it mean to the study participant?

Empowering study participants = Successful clinical trials



What is a Communication Plan?

- Comprehensive document that outlines:
  - Recruitment and retention strategies
  - Strategies for dissemination of study results
  - The process for review and interpretation of top line data after database lock
- Document that contains customized strategies to meet study needs

What is a Communication Plan?

- Why is it important?
  - Aligns multiple recruitment strategies for the community under investigation to increase awareness and information sharing
  - Leverages existing and future communication vehicles for retention
  - Describes methods of study result dissemination
- When is it created?
  - NOW!

Communications Work Plan

Timing: Date

△

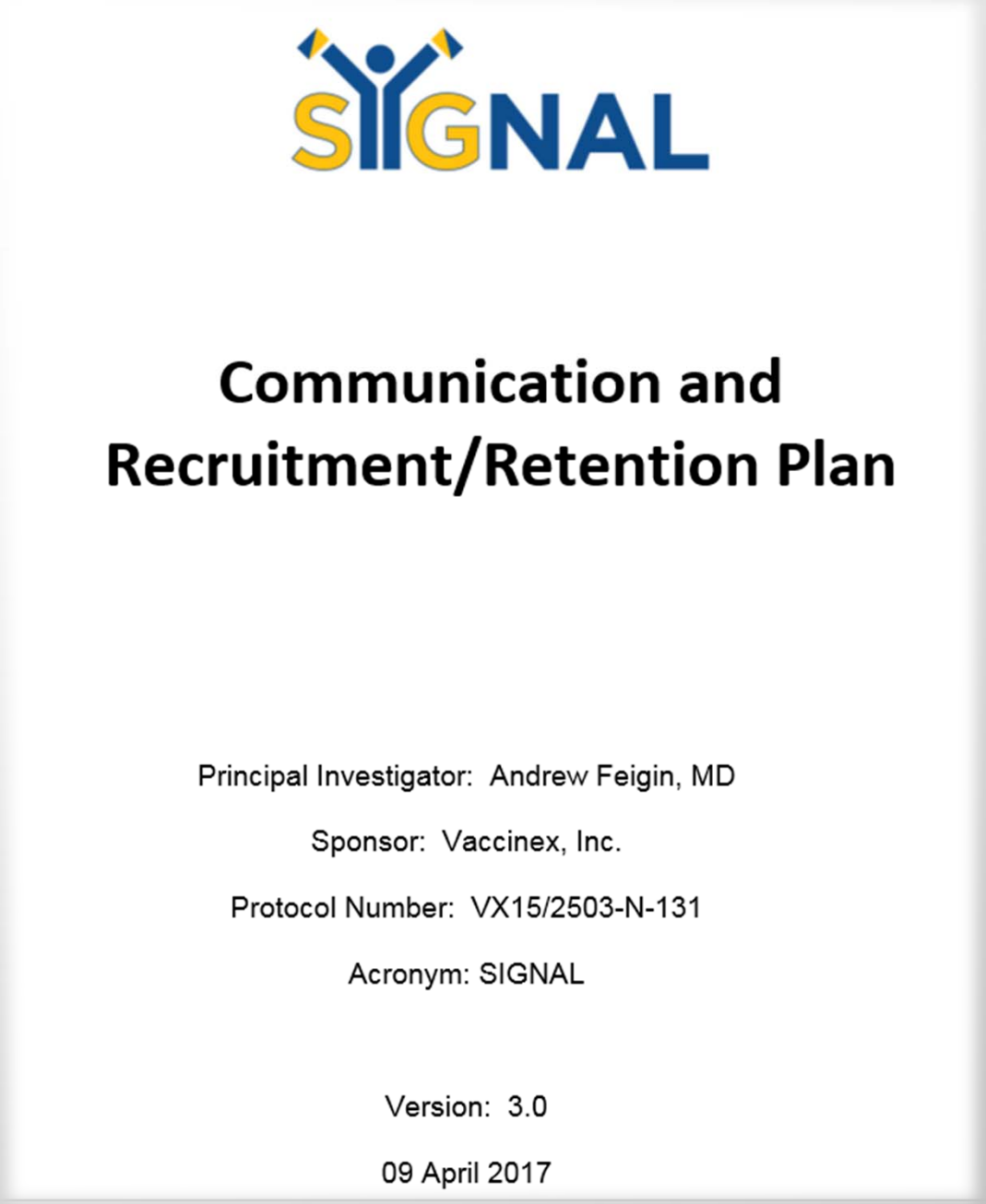
Activities:
- Coordinating Center creates plan based on protocol design
- Solicit feedback from investigators, coordinators and study participants
- Coordinating Center submits plan to IRB

**Communication Plan may require an amendment during the study

End products:
- Final plan including templates (e.g., press release, teleconference announcement, treatment assignment)
- IRB approval

Communication plan sample

- Develop plan with Sponsor and/or relevant parties



Communication plan table of contents

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Partnership with study participants… Pre-enrollment

- Give participants a leadership voice
- Understand and meet information needs of participants in research
  - Seeker → In trial → Completer
- Bring clinical trial awareness to the community
  - Road trip to HD support groups across 3 Midwest states
- Seek participant insight in study design
  - Focus Group

Highlights from focus group participants

- “For the first time in ages, I knew you were listening to what I had to say, making notes...to be considered… before you approached the FDA.”
- “The opportunity to impact protocol development from patient perspective.”
- “It was fascinating to learn about the approval process and all the hoops that must successfully be hurdled for proceeding with getting a medication to market.”

Industry Collaborations in Clinical Trial Development: Leveraging In-person Patient and Caregiver Input in HD

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[1]Huntington Study Group, [2]Raptor Pharmaceuticals Inc., [3]University of California, San Diego,
[4]University of British Columbia, Vancouver, Canada, [5]Johns Hopkins University School of Medicine, Baltimore, MD

Background

- Huntington's disease (HD) is a progressive, fatal, neurodegenerative disorder that casus deterioration in motor function, emotional and behavioral problems, and loss of cognitive ability
- HD also has a significant impact on caregivers and other family members
- Tetrabenazine remains the only approved agent for the treatment of chorea associated with HD. Thus, patient participation in clinical trials evaluating novel therapeutic options for the management of symptoms or that may delay disease progression is of vital importance
- Understanding the attitudes, challenges, and real-life experiences of patients with HD, as well as their caregivers, in relation to clinical trial participation may facilitate more effective design and planning of patient-friendly randomized clinical trials
- For these reasons, Raptor Pharmaceuticals, in collaboration with Health Interactions, a medical communications company, partnered with the Huntington's Study Group (HSG), a not-for-profit global network of researchers, clinicians, advocacy groups, and families with expertise in HD, and the Huntington's Disease Society of America (HDSA), to pilot a unique clinician-moderated, patient-centric advisory board

Objectives

- Objectives of the advisory board included the following:
  - A desire to understand the attitudes and perceptions of patients with HD and their caregivers towards clinical research in HD
  - Collection of input on specific aspects of Raptor Pharmaceuticals' phase 3 clinical trial plans such as protocol design, study schedules, and more general factors that could impact the ability and willingness of patients with HD to participate in clinical trials

Materials and Methods

- Twelve participants (7 patients with HD, 5 caregivers) were identified and recruited by the HSG and HDSA (*Table 1, Figure 1*)
  - Patient participants represented a diverse group of individuals with adult-onset HD, including non-symptomatic patients
  - Patients and caregivers had varying degrees of previous experience with, and understanding of, clinical trials and their

Materials and Methods

- All participants completed an online pre-meeting survey, providing feedback about factors affecting enrollment in clinical trials
  - The survey assessed a variety of concerns, including general thoughts about clinical trials, travel and time constraints, trust and confidentiality, side effects of trial medications, and concerns related to cessation of current therapeutic regimens
  - Responses were scored using a 4-point scale (1-not important, 2-somewhat important, 3-important, 4-very important)
- Additional input was solicited through facilitated discussion with advisors at the advisory board meeting

Table 1. Baseline demographics and advisory board participant characteristics FPO

	Patients with HD (n=7)	Patient caregivers (n=5)
Mean (range) age, years		
Female, n (%)		
Mean (range) disease duration, years		N/A
Relationship to patient	N/A	
Prior experience with clinical trials		

Results

- Patient and caregiver responses to the pre-meeting survey revealed key insights about clinical trials
  - 100% of participants reported that participation in clinical trials for HD was "highly important"
    - 100% of patients reported a desired to help bring new treatments for HD to market as an underlying rationale. A majority of patients reported an interest in trying out new treatments for themselves as an additional, supporting rationale
  - How participants prefer to learn about clinical research (*Figure 1*)
    - Patients and caregivers stated that they would like to be contacted about clinical research by a healthcare professional, HD organization, HD support group, or directly from the HD study site

Figure 1. Preferred communication channels for information regarding clinica FPO

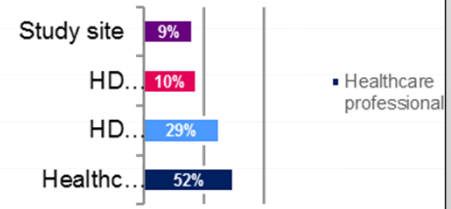
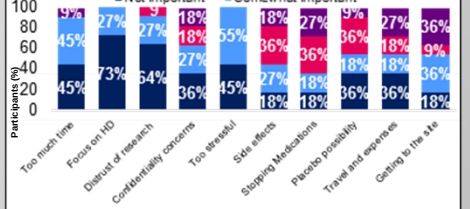


Figure 2. Factors deterring patients and caregivers from participation in clinical trials



  - Among those who have not participated in clinical trials, location, transportation, and costs were regarded as greater barriers to participation than time involvement or potential risks (*Figure 2*)
  - Assuming costs are not an issue, many advisors expressed willingness to travel up to 5+ hours to participate in clinical trials
- Additional insights were gained from the facilitated discussion among HD patients and caregivers
  - Impact of the double-blind period in placebo-controlled trials
    - Due to the relatively slow rate of disease progression in early-stage HD, patients and caregivers understood the need for prolonged periods of study (between 18- and 30-months) to evaluate the effects of therapeutics with the potential for disease modification
    - Advisors found the necessary double-blind period acceptable, but commented that an open-label extension would "be very important for recruitment and retention"
    - Patients and caregivers were not concerned about the need for a washout period at the end of the double-blind study / before initiation of the open-label extension

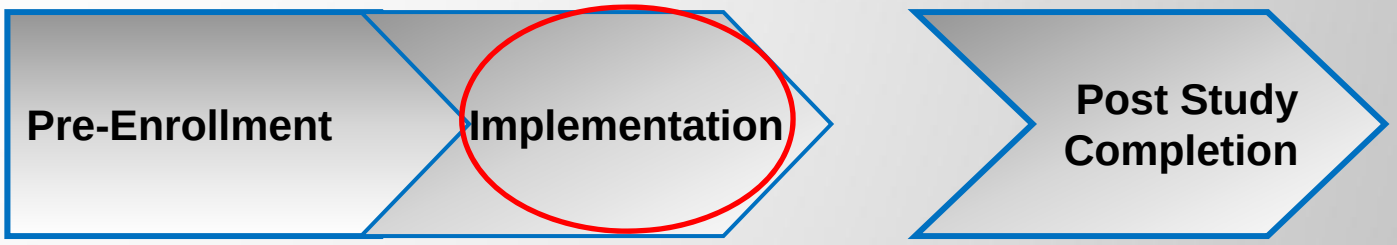
Results

- Pill burden and other dosing parameters
  - Advisors indicated that doses of up to eight capsules, twice-daily would be acceptable
  - Options such as larger capsules or easy-to-open pouches containing the appropriate number of capsules per day or per dose were suggested to assist with dosing
  - Noting that it is easier to swallow relative to liquids, patient advisors commented that capsules that could be opened and sprinkled over foods like apple sauce would be advantageous
- Use of concomitant medications in the clinical trial
  - Some patients stated that it would be important to permit use of medications like tetrabenazine if it were deemed necessary by their treating physician
  - Patients and caregivers reported an understanding of the requirement to be on stable medications for 2 months prior to enrollment, but appreciated the ability to adjust medications, if needed, during the study
- Additional outcomes measures recommended by advisors
  - Patients and caregivers both expressed interest in patient- or caregiver reported outcomes, as well as quality of life assessments
  - Advisors expressed substantial interest in inclusion of non-motor outcomes, commenting that treatment of the "wider" symptoms of HD represented a "good reason to enroll in a long-term trial

Conclusions

- Collaborations among the pharmaceutical industry, research networks, patient advocacy groups, patients, and caregivers that facilitate discussion of the design and implementation of clinical trials may represent a new best practice in the space
- Such approaches consider the preferences of patients and caregivers affected by the disease, allowing for optimization of protocols while ensuring the integrity of the data to be collected in the study
- Interactions among trial stakeholders provide opportunity to clarify study rationale and gain important information about the investigational agent with members of the community in a compliant manner
- Restricting engagements with patients and caregivers of the intended population for the study, and replicating these meetings in a variety of geographic regions may validate or improve trial-specific feedback, in addition to highlighting important region-specific differences

Communications Work Plan



Timing:

Date

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Activities:

- Sites submit template letters and recruitment materials to local/central IRB

End products:

- Local/central IRB approves template letters for disseminating new findings in real time
- Local/central IRB approves recruitment materials
- Implement Recruitment strategies

Participant engagement – Implementation

- Moderated calls
  - Key stakeholders (sponsor, study PI, sites, family advocacy groups)
  - Purpose
    - Provide general overall importance of clinical trials
    - Provide general study updates
    - Thank the participants
- Tools
  - Newsletters distributed and posted on study website
  - Social media postings
  - Presentations at community events

Communications Work Plan

Timing:

Date

△

Activities:

- Distribute Notice of Results letter to key stakeholders
- Sites contact study participants
- Post and distribute press release
- Set up teleconferences with participants and other key stakeholders

End products:

- Sites informed of results and next steps
- Study participants informed of results and next steps
- Advocacy community informed of results

**Local/central IRBs may require re-submission of materials

Avoiding the pitfalls of communicating research results

- *"…Falls through the cracks between IRBs and investigators who are collectively responsible for protecting and promoting the welfare of participants until a study is concluded…" (Dorsey, 2008)*
- Consent
  - Federal regulations and IRBs require disclosure only of information that may affect ongoing participation but not disclosure of research results

Dorsey, et al. Communicating clinical trial results to research participants. *Arch Neurology*. Vol 65 (no.12), Dec 2008.

Communicating Clinical Trial Results to Research Participants

E. Ray Dorsey, MD, MBA; Christopher A. Beck, PhD; Mary Adams, MTS; Gary Chadwick, PharmD, MPH; Elisabeth A. de Blieck, MPA, CCRC; Colleen McCallum, MSW; Leslie Briner; Lisa Deuel, BA; Anthony Clarke, PhD; Rick Stewart, BS; Ira Shoulson, MD; and the Huntington Study Group TREND-HD Investigators

Background: Communicating clinical trial results to research participants is seldom accomplished in a timely or an effective manner.

Objective: To evaluate the effectiveness of a plan to communicate results in an industry-sponsored randomized controlled trial for Huntington disease.

Design, Setting, and Participants: Postal survey to research participants at 28 of 41 research sites (including 217 of 316 participants) in Canada and the United States.

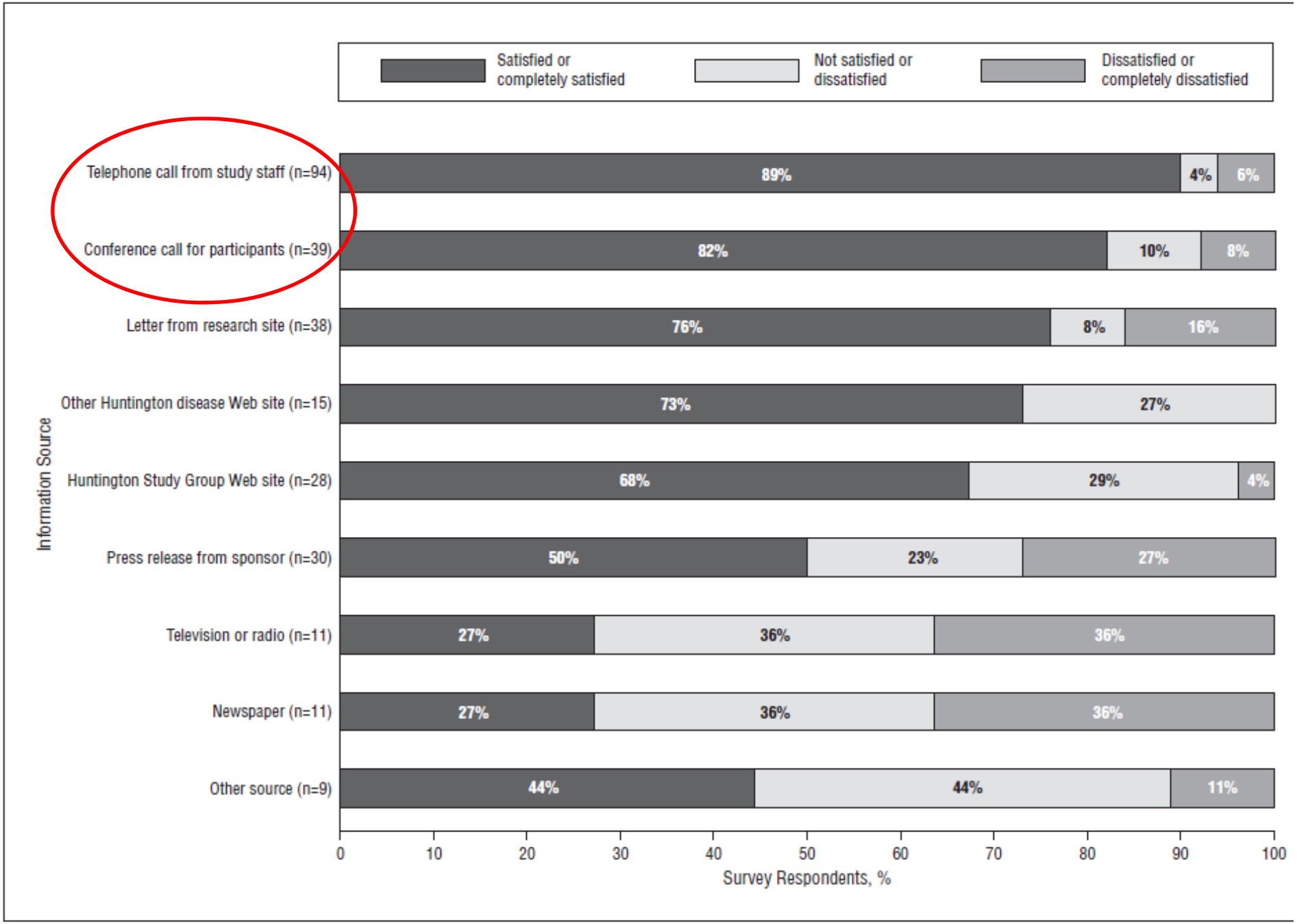
Intervention: We communicated trial results by means of (1) a media release from the investigators within a day after a sponsor-issued press release; (2) a subsequent telephone call from the site staff to the participants; and (3) a conference call for research participants 2 weeks after the results were released.

Main Outcome Measures: Source and timing for learning study results and satisfaction with their communication.

Results: Of the 217 study participants surveyed, 114 (52.5%) responded. Most (73.1%) first learned the study results from their site's telephone call, and 46.3% learned the results within 1 day of the sponsor's press release. Participants reported high or complete satisfaction with the site telephone call (89.3%) and conference call (82.1%) but relatively low satisfaction with the sponsor's press release (50.0%). Most respondents reported good understanding of the risks and benefits of the experimental treatment and the next steps for their participation.

Conclusion: Surveyed research participants learned of the clinical trial results soon after public release and highly valued the personalized and accurate communication efforts by the study investigators.

Arch Neurol. 2008;65(12):1590-1595


Satisfied or completely satisfied
Not satisfied or dissatisfied
Dissatisfied or completely dissatisfied
Telephone call from study staff (n=94)
Conference call for participants (n=39)
Letter from research site (n=38)
Other Huntington disease Web site (n=15)
Huntington Study Group Web site (n=28)
Press release from sponsor (n=30)
Television or radio (n=11)
Newspaper (n=11)
Other source (n=9)
89%
4%
6%
82%
10%
8%
76%
8%
16%
73%
27%
68%
29%
4%
50%
23%
27%
27%
36%
36%
27%
36%
36%
44%
44%
11%
Information Source
0
10
20
30
40
50
60
70
80
90
100
Survey Respondents, %

Sharing research results…

- Create a standard practice for communicating trial results
- Organize interactive/moderated teleconference/webinar with participants, families, researchers and sponsors
  - Develop script of results
  - Sites to contact participants about date and time of webinar/teleconference call
  - Request a recorded transcript of the call
- Press release of research results
  - Sponsor and individual sites
  - Post on public websites and link with advocacy groups and other organizations
- Finalize and submit main manuscript for publication
  - Distribute treatment allocation

Communication cascade

Audience	Medium	Point Person
FDA	Letter	Sponsor
Public/Private Investors	Teleconference	Sponsor
Steering Committee	Teleconference	Coordinating Center
Investigator/Coordinator	Teleconference	Coordinating Center
Study Participants	Teleconference/letter	Coordinating Center, participating sites
Public/Advocacy Audiences	Press release Teleconference Social media	Coordinating Center, participating sites

Notice of Results template (IRB Pre-approved)

Appendix B. SAMPLE Notice of Results Teleconferences

CONFIDENTIAL

Dear SIGNAL Investigators and Coordinators, Site Monitors, Steering Committee Members and Safety Monitoring Committee:

The SIGNAL leadership group has reviewed the results of the primary analyses of SIGNAL and is prepared to announce the preliminary findings.

The HSG is invested in communicating results of the SIGNAL study in a timely manner to the site investigators, coordinators and study participants. The purpose of this email is to invite the SIGNAL Site Investigators, Coordinators, Site Monitors, Members of the Steering Committee, and the Safety Monitoring Committee and the study participants and their caregivers to attend a conference call to summarize the preliminary results of the SIGNAL study.

Vaccinex will make a public announcement about the SIGNAL results on **<insert date>.**

Teleconference for: SIGNAL Site Investigators, Coordinators, Steering Committee, Safety Monitoring Committee, Site Monitors and SIGNAL **Operations Team:**

- The HSG will conduct a teleconference on **<insert date>** from **<insert time> ET** to review the SIGNAL study with the Investigators, Coordinators, Site Monitors, Steering Committee members and Safety Monitoring Committee members.
  <insert time> ET ,<insert time> CT, <insert time> PT

North American Conference Call #: <insert number>
Participant Pin: <insert code>

Teleconference for: Study Participants and Caregivers:

- On **<insert date>** at **<insert time> ET**, we plan to have a conference call with all study participants and their caregivers for approximately XX minutes. Study participants and caregivers will need to call in at this time and will have the opportunity to ask questions. We are organizing this call so participants and caregivers learn of the study results in a timely manner and directly from the research team. We are relying on you to get this information to the study participants.

  Because time is of the essence, we ask that you contact study participants ASAP. Please direct them to the appropriate date, time of call and call in numbers listed below:

  <insert time> ET , <insert time> CT, <insert time> PT
  North American Conference Call #: <insert number>
  Participant Pin: <insert code>

Dissemination of study results: highlights of participant comments

- "Since Cohort A subjects can't be involved in Cohort B, then what – what are our options, is there anything else we can sign up for, maybe the next line of studies?"
- "…are we going to be able to have an option to stay on the study for an extended time period to help collect data and help the statistics?"
- "So…is there a possibility if you did open-label studies we would be able to participate even though we have been in this study?"

Business Wire
A Berkshire Hathaway Company

Teva Announces FDA Approval of AUSTEDO™ (deutetrabenazine) Tablets for the Treatment of Chorea Associated with Huntington's Disease

Approval represents the first new treatment option for chorea associated with Huntington's disease in nearly a decade

April 03, 2017 05:04 PM Eastern Daylight Time

JERUSALEM--(BUSINESS WIRE)--Teva Pharmaceutical Industries Ltd. (NYSE and TASE: TEVA) today announced that the U.S. Food and Drug Administration (FDA) has approved AUSTEDO™ (deutetrabenazine) tablets for the treatment of chorea associated with Huntington's disease (HD). Previously referred to by the developmental name SD-809, AUSTEDO™ is the first deuterated product approved by the FDA and only the second product approved in HD. The product was previously granted Orphan Drug Designation by the FDA.

Treatment Allocation and Assignment templates

Appendix C. SAMPLE - Model Letter to Sites regarding IRB Approval of Treatment Allocation Distribution to Participants

TO: SIGNAL Investigators and Coordinators

FROM: [*insert study PIs, sponsor, Steering Committee, as applicable*]

DATE: [*insert date*]

SUBJECT: Treatment Assignment(s) for SIGNAL Participants

Dear Investigators and Coordinators,

We are nearly complete with all SIGNAL study activities. To that end, attached are the following:

- Model treatment assignment letter to inform SIGNAL study participants of their treatment assignments

Insert the following if standard template is used. If the template letter is revised, the University of Rochester RSRB representative should be consulted:

The University of Rochester IRB has determined that since the link to the study results included in the letter provides factual information that will be publically available, their review and approval of the letter is not required. However, please comply with your IRB requirements regarding review and approval of the letter before distributing to your SIGNAL study participants.

In the coming months after unblinding of the SIGNAL database and site IRB approval (if applicable), we will send to the attention of each SIGNAL Site Investigator a list of treatment assignments for each SIGNAL participant enrolled at your site. Your site's customized letter to each SIGNAL participant should include the individual participant's treatment assignment and the link to the SIGNAL study results.

Please contact the CTCC Project Managers if you have any questions or concerns.

Thank you for your support on this study.

Appendix D. SAMPLE - Model Treatment Assignment Letter To Subjects from Each Site

[*Insert Date*]

[*Insert Subject ID, if preferred*]

Dear SIGNAL Study Participant:

On behalf of the SIGNAL study team, we appreciate your dedication and participation in the study entitled, "A phase 2, multi-center, randomized, double-blind, placebo controlled study in subjects with late prodromal and early manifest Huntington disease (HD) to assess the safety, tolerability, pharmacokinetics, and efficacy of VX15/2503" (SIGNAL).

The SIGNAL study followed [*insert number of subjects*] participants for up to 18 months. Research participants were randomly assigned to take VX15/2503 or placebo.

Your treatment assignment was [*insert treatment assignment*].

In the coming months, a summary of the SIGNAL Study results will be available at www.clinicaltrials.gov [*and insert any applicable websites*].

Thank you again for your participation in the SIGNAL study. *For more information about the HSG, please visit the following website: www.huntingtonstudygroup.org.* If you have questions regarding this study, please contact your study team.

Sincerely,

[*Insert Site Investigator Name*]
Site Investigator

What does it mean to the participants?

- You participated in the Raptor AdBoard what did you learn as a result?
- What did you get out of the SIGNAL study result teleconference?

Multi-Method Dissemination

Thank you