Direct-to-Participant Trials

Steven R. Cummings, MD
Director, S.F. Coordinating Center
Senior Scientist Sutter Health System
Professor of Medicine, Epidemiology, and Biostatistics
UC San Francisco
Acknowledgements

No relevant financial interests
Direct-to-Participant (D2P) trials

No physical clinical sites. No geographic limit on recruitment.

Not “Virtual:” Patients are real and relationships are essential
Not “Internet-based:” D2P trials use other means
Outline

Stories of 3 trials
• KALM
• REMOTE
• HOME

Lessons:
• Simplicity
• Participant perspective
KALM

History

• 1998: Dr. Susan Love asked: “How can I use my online ‘Army of Women’ for research?”

• Started “1747” in 2000
  o $900k from eLilly Ventures
  o To conduct a proof-of-concept D2P trial
KALM (2000)

- Proof of concept & build key elements
- RCT of Kava-kava and Valerian root vs. placebo
- For anxiety and insomnia
- Enrolled people with anxiety or insomnia by questionnaire
- Few exclusions
- Endpoints: less anxiety, better sleep, and AEs at 4 weeks

KALM elements

One Center
• Participant-facing EDC and website
  o No paper
• Identity confirmed by ‘Idiology’ using public databases
• Participants established e-signatures
• eConsent with quiz. Approved by WIRB
• Managed study ‘drugs’: FedEx delivery with proof of I.D.
• Recruit: ads on websites; emails to friends and groups
• Simple: 15 screens and <10 steps to enroll and follow-up

KALM Results

In 8 weeks

- 1,551 screened, 391 randomized from 45 states
- >80% adherence
- All groups improved
  - No significant differences

KALM Results

• Results analyzed within 1 hour of ‘last data in’
• Sent individual results to participants within 1 day

• Cost: $3,224 / participant (Adjusted for inflation)

Lilly adopted the technology

• A trial of Cialis (for erectile dysfunction)
• Run by Operations, Regulatory, Legal & Data
• Became complex and used sites at baseline
  o They were concerned about confirming I.D. and consent
• “The most expensive study per patient we have done”
• Abandoned the model

REMOTE
Conception and Birth of “REMOTE”

• About 2009
• We proposed a simple trial for Overactive Bladder (OAB)
• Use a urodynamics validated “3IQ” to enroll patients
• Tested Detrol, an established treatment
• Andy Lee (Pfizer, Operations)
  o Tried to enroll in KALM
  o Helped design, promote, and secure Pfizer funding.
  o Then moved to Genzyme.
REMOTE by Pfizer

• Pfizer’s goal: Mimic a clinic site-based trial for OAB
• Run by project management, Ops, Legal, Regulatory, Security took control
• Got FDA approval; allowed study drug shipment to home
• Early support from Bob Temple (2008)
  o “I don’t see any insurmountable barrier.”
  o “We are interested in more efficient methods…this fits.”
  o “The attitude here is going to be favorable.”
• He assembled the FDA team to approve “REMOTE”
REMOTE Process

All the elements of D2P trial
• Run from a single center by mytrus.
• Web-based recruitment
• Establish identity (public data bases)
• e-signature
• Interactive eConsent with quiz
• Shipped study drug to homes
• Approved by WIRB
To replicate site-based trials
A complex protocol

- Women with OAB are older and many not internet savvy
- The protocol had many steps
  - >100 screens and >90 interactions to enroll
Examples of the complexity

• Prescribing laws limited recruitment to 9 states, some required exams by (impersonal) contract MDs
• “To prevent hacking:” getting an eSignature required Captcha recognition and 2-factor authentication
• Many lab tests and stringent exclusions (‘bacteruria’)
• Run-in: carry a plastic ’hat’ all day to measure urine
  o Mobile e-diary to enter volumes. Entry error meant exclusion
• After eConsent, staff had to read the full consent by phone
Web-based recruitment from many sources

20,901 viewed the introduction

- 17,950 Viewed study introduction online video
- 13,373 Viewed account registration page
- 7,230 Completed account registration page
- 5,157 Reconfirmed e-mail address
- 1,519 Eligible on incontinence and demographics

1,519 eligible
We lost 44-84% of interested and eligible women at each step

Only 1.6% of eligible and interested women made it through all of the hoops
A recruitment problem?
Complexity strains recruitment

If 25% (instead of 2%) of interested and eligible women had avoided hurdles, the trial would have achieved its goal of 283
Worry about an FDA audit

- Pfizer assigned 1 to 3 site monitors to stay in the coordinating center most days during recruitment and enrollment.
- Despite an EDC with no paper source documents, the monitors required that web entries and (redacted) email correspondence be printed and reviewed and archived.
- Over 20 binders of paper.
A trial in children and families with autism
Autism: A trial with the

Dr. Bent (REMOTE P.I.) ran a ‘pilot’ placebo-controlled trial of omega-3 fatty acid for hyperactivity.

Reached the goal in 6 weeks:
• 864 e-mails to the network, 127 (15%) families responded
• 96 completed informed consent
• 57 kids (and teachers) from 28 states were randomized
• 100% completion
• “Thanks!” from rural families for a chance to join research

Home

Applying lessons learned to design a trial with an FDA-approved drug
Funded by NIA
Preventing Fractures in Parkinson’s Disease

• ≥ 65 y.o, PD patients have a 10-15% annual risk of fractures
• Due to multiple falls, poor protective reflexes
• Test zoledronate vs. placebo
  o Increases bone density
  o Reduced fractures in other groups
  o One I.V. infusion lasts ≥ 2 years
  o FDA-approved; generic
Parkinson’s Fracture Prevention Trial

- 3,500 participants > age 65
- Will need nationwide recruitment not limited by sites
- Partnered with Parkinson’s Foundation: the patient’s view
- No clinic visits. Conducted from patients’ homes.
  - Patient surveys: 90% liked the home-based design
  - Easier for disabled or cognitively impaired who may benefit most
The HOME Team
SFCC (data system; endpoints), K. Lyles (Duke: MD lead); Parkinson’s Foundation, P.S.G., PCORnet, UCSF (tele-neurology & eConsent) PCM Trials (nurses & drug management)
Simple criteria
PD, ≥ 65 y.o.
Few exclusions

Recruitment sources
Foundation community
Health systems
PD Trialists (P.S.G.)

No ‘web-based’ recruitment
By MDs or groups they know

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Foundation Call Center
• eConsent
• Eligibility

Home

1
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Few exclusions
Recruitment sources
Foundation community
Health systems
PD Trialists (P.S.G.)

Foundation Call Center
- eConsent¹
- Eligibility

Tele-neurology
- Confirms PD

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Home
Nurse visit
- eGFR
- IV ZA or Pbo
Simple criteria
- PD, ≥ 65 y.o.
- Few exclusions

Recruitment sources
- Foundation community
- Health systems
- PD Trialists (P.S.G.)

Foundation Call Center
- eConsent
- Eligibility

Teleneurology
- Confirms P.D.

Endpoints
- Survey EHRs
- Contact patients

AEs: 24/7 M.D.

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Recruitment sources
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Foundation Call Center
• eConsent
• Eligibility

Teleneurology
• Confirms PD

Endpoints
Survey EHRs
Contact patients
AEs: 24/7 M.D.

Nurse visit
• eGFR
• IV ZA or Pbo

Budget: $9,150 / patient
• A successful example
• A trial comparing 2 doses of aspirin by DCRI
• Simple protocol
• Recruiting from PCORnet health systems
• Has enrolled >15,000 of its 20,000 goal
Summary

• Methods for D2P trials are established
• Simplicity for the participant is essential
• Recruiting from communities and providers participants know may be more successful than from the web
• Change state laws to allow shipping ‘study drugs’
Thanks to Pioneers

- Susan Love, MD (Susan Love Foundation)
- Bradly Jacobs, MD (UCSF, 1747, Mytrus,)
- Steve Bent, MD (UCSF, 1747, Mytrus)
- Andy Lee, MD (Pfizer → Genzyme → Merck COO)
- Anthony Costello (Mytrus, Medidata)
- Bob Temple, FDA
Thank you
Summary and Lessons
Direct-to-Participant Trials

• The concept and technologies work well
• FDA is supportive
• eConsent has taken off, online and in sites
• REMOTE: an example of how to kill innovation
  o Force innovation to adapt to your system
  o Be risk averse
• Simplify protocols
• Involve participants in planning
Site-based trials
History

- 1998 Susan Love: “How to use my online ‘Army of Women’

- Started 1747 in 2000
  - $900k from eLilly Ventures
  - Alph Bingham & Will Dere
Site-based trials

- Slow recruitment
- Limited access
- Sites are expensive
Direct-to-Participant (D2P) Trials

1 site

Faster recruitment?
Less expensive?
Clinical Coordinating Center performs all functions

- Recruits participants
- Informed consent
- Dispense study drug
- Collect data
- Manage adverse events
- Analyze results
- Return results to participants
Participant’s view
- 15 screens
- <12 interactions
- Few calls to the 24/7 MD help desk

Establish an e-signature
KALM

One Center
• Participant-facing EDC and website
  o No paper
• Identity confirmed by Idiology
• Established an e-signature
• Interactive eConsent with quiz; approved by W.I.R.B.
• Managed study ‘drugs’: FedEx delivery with proof of I.D.
• Recruit: ads on websites; emails to friends and groups
• Approved by Western IRB

Register

Confirm identity

REGISTRATION

Please fill out the following information so that we can register you in our database and move you on to the next step of the trial. Unfortunately this study is only open to residents of the United States. We are working to offer participation in future studies to residents of Canada and other countries. If you want to provide us with your personal physician’s information you can do so here. It is not required.

Information about me

First Name *
Last Name *
Address *
Address 2
We cannot accept a PO box as your address.
City *
State *
Zip Code *
Email *
Confirm Email *
Phone *

Information about my doctor

Do you have a regular/primary MD?

Yes
No
If so, please fill forms below.
My Doctor’s First Name
My Doctor’s Last Name
Answer 3 questions unique to you

by Idiology

"On the Internet, nobody knows you're a dog."
### Inclusion and exclusion

#### PRE-QUALIFY

In order to determine whether or not you are appropriate for this study we need to gather a bit of information from you. Make sure that you will have access to your email account and the web during the 4 week study period.

When complete, please click the 'submit' button.

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is your age?</td>
<td>- select -</td>
</tr>
<tr>
<td>In what country do you live?</td>
<td>1 1 0</td>
</tr>
<tr>
<td>What is your birthday? (mm/dd)</td>
<td>1915</td>
</tr>
<tr>
<td>What is your gender?</td>
<td>Male Female</td>
</tr>
<tr>
<td>If Female: Are you pregnant?</td>
<td>Yes No</td>
</tr>
<tr>
<td>If Female: Are you breast-feeding?</td>
<td>Yes No</td>
</tr>
<tr>
<td>Has a doctor ever told you that you had a history of hepatitis or liver disease?</td>
<td>Yes No</td>
</tr>
<tr>
<td>DURING THE PAST 2 WEEKS, have you taken any medicines prescribed by a physician to help you sleep OR TREAT ANXIETY, such as Restoril, Klonopin, Xanax, Valium, Alivian, Dainene, Seconal, or Nembutal?</td>
<td>Yes No</td>
</tr>
<tr>
<td>ON AVERAGE, DURING THE PAST 2 WEEKS, about how many alcoholic drinks per day have you had? (NOTE: 1 DRINK = 8 OZ WINE, 12 OZ BEER, 1 OZ 80 PROOF LIQUOR)</td>
<td>- select -</td>
</tr>
<tr>
<td>Do you feel that you have had a problem getting to sleep or staying asleep over the</td>
<td>Yes No</td>
</tr>
</tbody>
</table>
TRIAL CONSENT

This is a form required of all people who participate in research. Read all the lines. If you have questions or don't understand, you can send questions by email before you press the consent form submit button.

CONSENT TO BE A PARTICIPANT IN A RESEARCH STUDY

A RANDOMIZED TRIAL OF HERBAL TREATMENTS, KAVA AND VALERIAN, FOR STRESS, ANXIETY AND INSOMNIA

PURPOSE AND BACKGROUND

Dr. Brad Jacobs and his associates are conducting a study to learn about the effects of two herbal products, Kava and Valerian Root, on stress, anxiety and sleep.

We are inviting you to participate in this study because you have indicated that you have at least some symptoms that might be associated with stress, namely anxiety or trouble sleeping.

PROCEDURES

If you agree to participate in this study, the following will happen:

You will answer some questions about your level of stress, anxiety, sleep and daytime sleepiness and some questions about other things, such as how much coffee you drink.

If your answers to the questions indicate that you are eligible for the study, you will be randomly assigned to one of three groups and study medicine will be sent to the mailing address that you provide. A member of the study staff will contact you by telephone to ensure that you received the package of study medicine and to answer any questions.

You will have one chance of receiving Kava (Group K), one chance of receiving Valerian (Group V), and one chance of receiving Placebo (Group P).
ASSESSMENT OF UNDERSTANDING OF THE INFORMED CONSENT

If you wish to participate, please take a moment to answer the following questions to let us know that you have understood some key points about this study. To answer these, you may refer back to the previous information in this form.

1. Kava and Valerian root are (Mark only one):
   - [ ] Drugs you normally get by doctor’s prescription
   - [ ] Herbs that do not require a doctor’s prescription

2. Which of the following side effects have been noted in people who have taken Kava during other studies? (You may select more than one answer; Mark answers that are correct)
   - [ ] Skin rash
   - [ ] Nausea
   - [ ] A stuffy or runny nose
   - [ ] Pain in joints

3. Which of the following side effects have been noted in people who have taken Valerian during other studies? (You may select more than one answer; Mark answers that are correct)
   - [ ] Nightmares
   - [ ] Headache
   - [ ] Diarrhea
   - [ ] Drowsiness

4. Which of the following things should you avoid while you are participating in this study? (Mark answers that are correct). You should not:
   - [ ] Take sedatives or medicines for sleep
   - [ ] Engage in strenuous exercise
   - [ ] Take prescription medicines for high blood pressure

5. If you agree to participate you will receive either Kava, or

Quiz about consent (must get 100%)
<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>IF FEMALE: Are you breast-feeding?</td>
<td>Yes ☐ No ☐</td>
</tr>
<tr>
<td>IF FEMALE: Are you pregnant?</td>
<td>Yes ☐ No ☐</td>
</tr>
<tr>
<td>DURING THE PAST 2 WEEKS, have you taken any medicines prescribed by a physician to help you sleep or treat anxiety, such as Restoril, Klonopin, Xanax, Valium, Ativan, Dalmane, Seconal, or Nembutal?</td>
<td>Yes ☐ No ☐</td>
</tr>
<tr>
<td>ON AVERAGE, DURING THE PAST 2 WEEKS, about how many cups of caffeinated coffee have you had per day?</td>
<td>- select -</td>
</tr>
<tr>
<td>ON AVERAGE, DURING THE PAST 2 WEEKS, about how many cups of caffeine-containing tea have you had per day?</td>
<td>- select -</td>
</tr>
<tr>
<td>ON AVERAGE, DURING THE PAST 2 WEEKS, about how many cans of caffeine-containing sodas have you had per day?</td>
<td>- select -</td>
</tr>
<tr>
<td>DURING THE PAST 2 WEEKS, have you often been bothered by feeling down, depressed, or hopeless?</td>
<td>Yes ☐ No ☐</td>
</tr>
</tbody>
</table>
Ship study ‘drug’ by overnight mail
Confirm receipt
### 4 Week Data

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>On average, during the past 2 weeks, about how many cups of caffeinated coffee have you had per day?</td>
<td>- select</td>
</tr>
<tr>
<td>On average, during the past 2 weeks, about how many cups of caffeine-containing tea have you had per day?</td>
<td>- select</td>
</tr>
<tr>
<td>On average, during the past 2 weeks, about how many cans of caffeine-containing sodas have you had per day?</td>
<td>- select</td>
</tr>
<tr>
<td>During the past 2 weeks, have you often been bothered by feeling down, depressed, or hopeless?</td>
<td>Yes □ No □</td>
</tr>
<tr>
<td>During the past 2 weeks, have you often been bothered by lack of interest or pleasure in doing things?</td>
<td>Yes □ No □</td>
</tr>
</tbody>
</table>

A number of statements which people have used to describe themselves are given below. Read each statement and then select the button below the statement that indicates how you feel right now, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best. When you are satisfied with your responses, please select the submit button.
Results

• Preplanned analysis was done within 1 hour of last participant’s data entry
• Participant results sent by email within 24 hours
• No differences
To mention

• Adaptable – health system recruitment; e-consent
• Migraine: 2 trials
  o Personal connection more successful
  o No visits a major plus
To mention

• HOME
  o Patient-centered; designed with input from patients: advocate and Parkinson’s Foundation
  o Designed to be conducted from home
  o Phone, text, email…
  o 3 sources of competitive recruitment
  o Teleneurology scoring
  o Include patients with dementia
  o Home exam & testing and IV drug vs. pbo
  o EMR reporting but plan direct queries and x-ray confirmation
Pfizer-centric Trial
The participant’s own results were reported within 1 day.
Some of the complexity

• States require local exams to prescribe “study drug” by mail; limited to 8 states
• Collected urine all day and enter volumes
  o Mobile device did not allow correction of errors
• “Security:” CAPTCHA plus 2-step I.D. with time limit “to prevent hacking”
• In case of FDA visit, full-time monitor(s), eg reviewed redacted emails. Volumes of paper.
• Required reading consent to participants
  o Even after successful eConsent.
Intensive recruitment online ads and targeted emails
What?

Dr. Stephen Bent
Associate Professor at UCSF

Dr. Stephen Bent and Mytrus Inc. are looking for women experiencing accidents for a clinical research study sponsored by Pfizer.

The trial will test the effectiveness and safety of Detrol (tolterodine ER), an approved medication, for reducing wetting accidents among women who have an overactive bladder (urge urinary incontinence).

Who?

Women who...

- Live in the United States
- Have regular internet access
- At least 21 years old
- Have overactive bladder symptoms (urge urinary incontinence). Take our survey now to find out.
- Are NOT planning to become pregnant.
- Are NOT taking a medication to treat their symptoms.

How?

Convenience

- You will participate from your home or work using the internet!

Safety

- Your identity will be verified over the internet.
- Blood and urine tests will be done at the beginning and end of the research study.
- Dr. Bent and his study team will contact you before you start the study and are always available.

Compensation

- You will be paid for your time and effort.

If you feel you're eligible and interested in learning more, please click the button to proceed.
Consent: Video, text, and audio

Viewing Informed Consent

Here are some ways you can choose to view the informed consent for this study. The video below provides an explanation of the process from Dr. Jacobs.

After you have reviewed the informed consent material, we'll provide you with a short quiz to confirm your understanding.

Have a question?

✉️ Email Us
or CALL anytime
1-800-999-7777

Click here to print a copy of the consent. This will allow you to read it. (It is 6 pages long)

Click here to listen to the consent. (It is 9 minutes long)

Start the Quiz
FDA

• Bob Temple arranged internal FDA meetings
• Final meeting with Pfizer & Mytrus team approved with key variance; delivery of drug across state lines; not dispensed by investigator
Quiz to confirm understanding

Stop being in the study

Can you stop being in the study?

- Yes, at the end of 14 weeks.
- No, I must complete the study in full if I agreed to be part of the study.
- I can only leave (drop out of) the study if the study doctor says it is ok.
- Yes, I can leave (drop out of) the study at any time without it causing problems with my normal healthcare.

• Get 100%
• Electronic signature
states). After the study investigator reviewed the test results, women who remained eligible were enrolled in the placebo run-in phase. At this point, participants were sent single-blind study medication by courier to their home. Participants were asked to confirm receipt of trial medication via the study website and were instructed to take one capsule once daily. Participants also received a mobile feature phone (Nokia 6301) with a custom application installed for entering bladder e-diary data, together with detailed instructions on completing the e-diary; the use of the e-diary was validated before beginning patient recruitment. Women were instructed to collect and measure the volume of 24 hours of urine on days 5 and 12, report all micturitions and UUI episodes and the time of occurrence on days 5 through 7 and 12 through 14, and enter this information into the e-diary. At the end of the placebo run-in phase, women who had polyuria (>3000 mL per 24 hours), a voided volume >500 mL for any single micturition, a mean of <8 micturitions per 24 hours in a 3-day e-diary, or a mean of <1 UUI episode per 24 hours in a 3-day e-diary were automatically excluded. Women who were unable to enter e-diary data also were automatically excluded. The study investigator also reviewed all screening data against protocol eligibility criteria and excluded any ineligible subjects. The investigator could not
Detrol worked!

- Placebo (n = 6)
  Baseline = 9.9
  LS Mean (SE) Change/24 h = -0.8

- TOL ER (n = 11)
  Baseline = 11.5
  LS Mean (SE) Change/24 h = -2.4

LS mean (95% CI) difference = -1.6 (-3.9, 0.6)
An Internet-Based Randomized Controlled Trial of Omega-3 Fatty Acids for Hyperactivity in Children with autism

Linking the autism community and researchers

Sponsored by Autism Speaks, the Simons Foundation, and National Institute of Mental Health
Study Team and Funding

• Kennedy Krieger / Johns Hopkins
  o Paul A. Law, MD, MPH (Principal Investigator)
  o Tara Zandi, MA
  o Kiely Law, MD, MPH
  o Jay Nestle, BS
  o Amy Daniels, PhD

• University of California, San Francisco
  o Stephen Bent, MD (Principal Investigator)
  o Robert Hendren, DO
  o Felicia Widjaja, BS
  o Jae Eun Choi, MS

• Funded by
  – NIH CTSA Supplement Grant (Advancing Study Designs for Comparative Effectiveness Research)
  – Simons Foundation SFARI Pilot Award
Objectives

- DETERMINE IF OM3 reduces hyperactivity in children with autism
- Assess change in social functioning
- Evaluate performance of an Internet Based-Randomized Controlled Trial
Methods

- Sample Selection: 5-8 y.o. with autism and hyperactivity
- Recruitment: Children in IAN with an established diagnosis
- Screening: Hyperactivity questionnaire
- Consent: online
- Baseline measures: Aberrant Behavior Checklist (ABC)
- Randomization: Automated, overnight mail of meds
- Data Collection: All online using IAN (JAWS) platform
- FDA: IND approved.
Results

• In 6 weeks (Sept-Oct 2012)
  o 864 e-mails sent to children of target age
  o 127 families expressed interest (15%)
  o 96 families completed informed consent
  o 57 children (and their teachers!) from 28 states were eligible and randomized

• In 3.5 months (end of Dec 2012)
  o All 57 children and all 57 teachers completed final outcomes (100% completion rate)
## Results – Change in Primary Outcome Measure

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Placebo (n=28)</th>
<th>Omega-3 (n=29)</th>
<th>Difference in change*</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC-Hyperactivity</td>
<td>-3.4</td>
<td>-5.3</td>
<td>1.9</td>
<td>-2.2 to 5.2</td>
<td>0.38</td>
</tr>
<tr>
<td>ABC-Irritability</td>
<td>-2.1</td>
<td>-2.0</td>
<td>-0.1</td>
<td>-3.3 to 2.8</td>
<td>0.50</td>
</tr>
<tr>
<td>ABC-Stereotypy</td>
<td>-0.5</td>
<td>-2.0</td>
<td>1.6</td>
<td>0.0 to 3.2</td>
<td>0.05</td>
</tr>
<tr>
<td>ABC-Lethargy</td>
<td>0.1</td>
<td>-2.1</td>
<td>2.2</td>
<td>0.5 to 4.1</td>
<td>0.01</td>
</tr>
<tr>
<td>ABC-Innapp. Speech</td>
<td>-0.9</td>
<td>-0.6</td>
<td>-0.3</td>
<td>-1.4 to 1.0</td>
<td>0.73</td>
</tr>
</tbody>
</table>