Decentralized Clinical Trials

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Disclosure

The speaker, Francis Farrell, has no personal or professional financial relationships with a commercial entity producing healthcare goods or services.

The planning committee members, Katie Rea, MSCR, BSN, RN, CCRC; Lori Elder, RN, BSN, CCRA; Kimberly Underwood, BS, CCRC; and Maria Davenport, MPH, CCRP; have no personal or professional financial relationships with a commercial entity producing healthcare goods or services.

Activity Code: 148273

Learning Objectives

Upon completion of this presentation, participants should be able to:

1) Define what is meant by a decentralized clinical trial (DCT)
2) Have a general understanding of the current regulatory landscape for DCTs
3) How a DCT methodology was used to conduct a COVID-19 public health seroprevalence study

Agenda

- Definition of a Decentralized Clinical Trial (DCT)
- Advantages and Challenges of Conducting a DCT
- Current state and regulatory guidance of DCT
- Example of a DCT methodology to conduct a public health surveillance study

Definition of a Decentralized Clinical Trial

- Decentralized clinical trials (DCT) are defined as studies "executed through telemedicine and mobile/local healthcare providers, using processes and technologies differing from the traditional clinical trial model."

Clinical Trial Transformation Initiative, *CTTI Recommendations: Decentralized Clinical Trials* 2 (2018), available at https://www.ctti-clinicaltrials.org/sites/www.ctti-clinicaltrials.org/files/dct_recommendations_final.pdf.

DCT Execution

- DCTs leverage “virtual” tools, such as telemedicine, sensory-based technologies, wearable medical devices, home visits, patient-driven virtual health care interfaces, and direct delivery of study drugs and materials to patients’ homes. **In a fully decentralized clinical trial, subject recruitment, delivery and administration of study medication, and acquisition of trial outcomes data all proceed without involving in-person contact between the study team and the patient/subject.**

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8093545/

Advantages of Decentralized Trials

- Potential for increased recruitment and retention
  - Decreased travel
  - Less interference with other commitments such as work and childcare
  - Potential for increased participant access
    - Elderly
    - Lower socioeconomic backgrounds
    - Individuals in remote locations
    - Ethnic minorities
- Potential to decrease and/or increase trial size
  - Decrease via digitalized tools for data collection
  - Increase via the virtual environment that is less dependent on staffing
- Lower cost

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8093545/

Challenges to Decentralized Clinical Trials

- Drug shipment and management to participants
  - Unauthorized access, temperature stability, dosing diaries
- Many wearable devices still lack clinical validation and regulatory approval
  - Transmission issues, battery life, internet infrastructure, privacy
- Management of the upfront participant interest generated through wide solicitation

First "Virtual" Clinical Trial Allowing Patients to Participate Regardless Of Geography
Tuesday, June 07, 2011 - 05:30am Press Release

- The Research on Electronic Monitoring of OAB Treatment Experience – REMOTE – is a U.S.-based Participatory Patient-Centered (PPC) clinical trial designed to assess the safety and efficacy of Detrol LA (tolterodine tartrate), a treatment for overactive bladder (OAB)
- Investigators in the REMOTE trial plan to enroll about 600 patients from about 10 states across the United States. Enrolled patients will participate in the study screening process through the Internet, actively manage their own trial activity and report results directly to a trial investigator who keeps close oversight of patient eligibility and safety.
- The REMOTE clinical trial pilot is consistent with the mission of the FDA's Clinical Trials Transformation Initiative (CTTI) to improve the quality and efficiency of clinical trials.

https://www.pfizer.com/news/press-release/press-release-detail/pfizer_conducts_first_virtual_clinical_trial_allowing_patients_to_participate_regardless_of_geography

Clinicaltrials.gov
Web-based Methodology Trial to Evaluate the Efficacy and Safety of Tolterodine ER in Subjects With Overactive Bladder (REMOTE)

- **Results:** With a goal of 283 randomized participants, 5157 registered on the trial website. Of 456 who passed initial screening, identification verification, and signed consent, 237 passed additional medical screening and were countersigned by the investigator. After laboratory testing, 118 entered the placebo run-in; **only 18 passed e-diary assessments and were randomized to treatment.** At week 12, the mean change from the baseline in micturitions/24 hours (primary endpoint) was -2.4 for tolterodine ER versus -0.8 for placebo [treatment difference (95% CI): -1.6 (-3.9, 0.6)].

https://doi.org/10.1016/j.cct.2014.04.009

- Out of 237 participants screened, 118 participants received single-blind placebo matched to tolterodine 4 milligram (mg) capsule once daily during run-in period for 2 weeks. Only 18 participants were randomized to receive double-blind treatment due to early termination of the study.

https://clinicaltrials.gov/ct2/show/study/NCT01302938

Pfizer: we won't abandon social media in trials because virtual study failed
But pharma company admits to disappointment with patient recruitment to REMOTE study

Pfizer has vowed to continue to use social media and the internet to boost patient recruitment rates in its clinical trials despite the failure of a 'virtual' study pilot.

The REMOTE trial of Pfizer's overactive bladder drug Detrol LA (tolterodine tartrate) began recruiting last year with the aim of attracting 600 patients from 10 states across the US.

Dubbed a 'trial in a box', it was the first randomised clinical trial that patients could participate in entirely from home - regardless of where, or how close to clinical sites, they lived – by using mobile phone and web-based technology.

The hope was this approach would save time, produce better data and increase patient compliance, but earlier this year the trial was halted after Pfizer failed to persuade sufficient numbers of patients to take part.

So, what went wrong with the REMOTE trial? One element seems to be that the company was trying to do too much, too fast.

"We were testing a number of modules at once: online recruitment, screening, and consent; at-home study drug delivery; mobile- and web-based tools for all data reporting; online identity verification; a centralised investigator site," Lipset explained.

https://www.pmlive.com/pharma_news/pfizer_wont_abandon_social_media_trials_virtual_study_failed_408636

Decentralized trials are staying put, but sites and sponsors aren't quite prepared: Survey

- The survey, conducted by Florence Health, found that on a scale of 10, trial sites' confidence level for managing DCTs was five. The confidence level among sponsors was not much higher, coming in at six. The trepidation comes as 89% of sponsors indicated they use elements of DCT in at least some of their studies.

- One contributor to the diminished confidence is navigating the numerous forms of technology that both sites and sponsors need to adopt in order to maximize flexibility. For example, only 68% of sites use telemedicine in their operations, highlighting a divide in adopted technology that limits the industry as a whole.

https://www.fiercebiotech.com/biotech/decentralized-trials-arent-going-anywhere-sites-and-sponsors-arent-quite-prepared-survey (2/24/2022)

FDA NEWS RELEASE

FDA Takes Additional Steps to Advance Decentralized Clinical Trials: May 2, 2023

Today, the agency released a new draft guidance that provides recommendations for sponsors, investigators and other stakeholders regarding the implementation of DCTs to advance medical product development and research. Examples of decentralized elements include obtaining laboratory tests at a local facility rather than a research medical center or conducting a clinical follow-up visit in the trial participant's home using telemedicine.

- design considerations for a DCT;
- conduct of remote clinical trial visits and clinical trial-related activities in a DCT;
- use of digital health technologies to remotely acquire data in a DCT;
- roles and responsibilities of the sponsor and investigators in a DCT;
- obtaining informed consent (IC) and institutional review board oversight of the IC process in a DCT;
- determination of the appropriateness of investigational products for use in a DCT;
- packaging and shipping of investigational products in a DCT; and
- safety monitoring of trial participants in a DCT.

https://www.fda.gov/news-events/press-announcements/fda-takes-additional-steps-advance-decentralized-clinical-trials

Draft Guidance Highlights

In fully decentralized clinical trials, all activities take place at locations other than traditional trial sites. These trial-related activities may take place at the homes of trial participants or in local health care facilities that are convenient for trial participants. In hybrid DCTs, some trial activities involve in-person visits by trial participants to traditional clinical trial sites, and other activities are conducted at locations other than traditional clinical trial sites, such as participants' homes.

FDA's regulatory requirements for investigations of medical products are the same for DCTs and traditional site-based clinical trials.[6] Section 3606(a) of the Food and Drug Omnibus Reform

RECOMMENDATIONS FOR IMPLEMENTING DCTS

In a DCT, some or all trial-related activities will occur at locations other than traditional clinical trial sites (e.g., the participant's home or local health care facilities). DCTs may involve a network of locations where trial personnel and local HCPs work and where trial-related services (e.g., imaging and laboratory services) are provided, all under the oversight of the investigator.

For inspectional purposes, there should be a physical location where all clinical trial-related records for participants under the investigator's care are accessible and where trial personnel can be interviewed. This location should be listed on Form FDA 1572 or for investigational device exemption (IDE) applications must be included in the IDE application.

Digital Health Technologies

DHTs may **allow transmission of data remotely from trial participants wherever they are located.**

The sponsor should consider the following information regarding the use of DHTs in a DCT:

The draft guidance for industry, investigators, and other stakeholders *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations*[16] provides recommendations to sponsors, clinical investigators, and other parties for measuring clinical events and characteristics of interest using DHTs to acquire data remotely from participants in clinical trials for drugs, biological products, and devices. The guidance discusses selection of DHTs for clinical trials; verification, validation, and usability testing; use of DHTs to collect data for clinical trial endpoints; training on the use of DHTs; and management of risks related to the use of DHTs in clinical trials. Other issues regarding the use of DHTs in clinical investigations are discussed in other FDA guidances.[17] Sponsors should ensure that DHTs used in a DCT are available and suitable for use by all trial participants. **When a trial permits participants to use their own DHTs, sponsor provided DHTs should be available as an option.**

Roles and Responsibilities

Sponsors should strive for diversity and inclusiveness in trial populations.[19] Outreach through local health care institutions (e.g., pharmacies, clinics) may facilitate recruitment of diverse participants in areas where there are limited or no traditional clinical trial sites. Bringing trial-related activities to participants' homes, including through the use of DHTs, may reduce the need for travel and improve engagement, recruitment, and retention amongst potential participants with challenges accessing traditional clinical trial sites. The use of local HCPs close to potential participants' homes may improve engagement, recruitment, and retention of diverse participants (e.g., race, ethnicity, age, sex, and geographic location). Further, the use of local HCPs may reduce cultural or linguistic barriers to participation in clinical trials.

Informed Consent and Institutional Review Board Oversight

Obtaining informed consent remotely may be considered as part of a DCT. Institutional review board (IRB) oversight is required to ensure the process is adequate and appropriate.[31]

- Investigators may obtain electronic informed consent from trial participants at their remote locations provided that all applicable regulatory requirements regarding informed consent are met.[32] The process of obtaining electronic informed consent remotely may include a remote visit if needed.

Investigational Products in a DCT

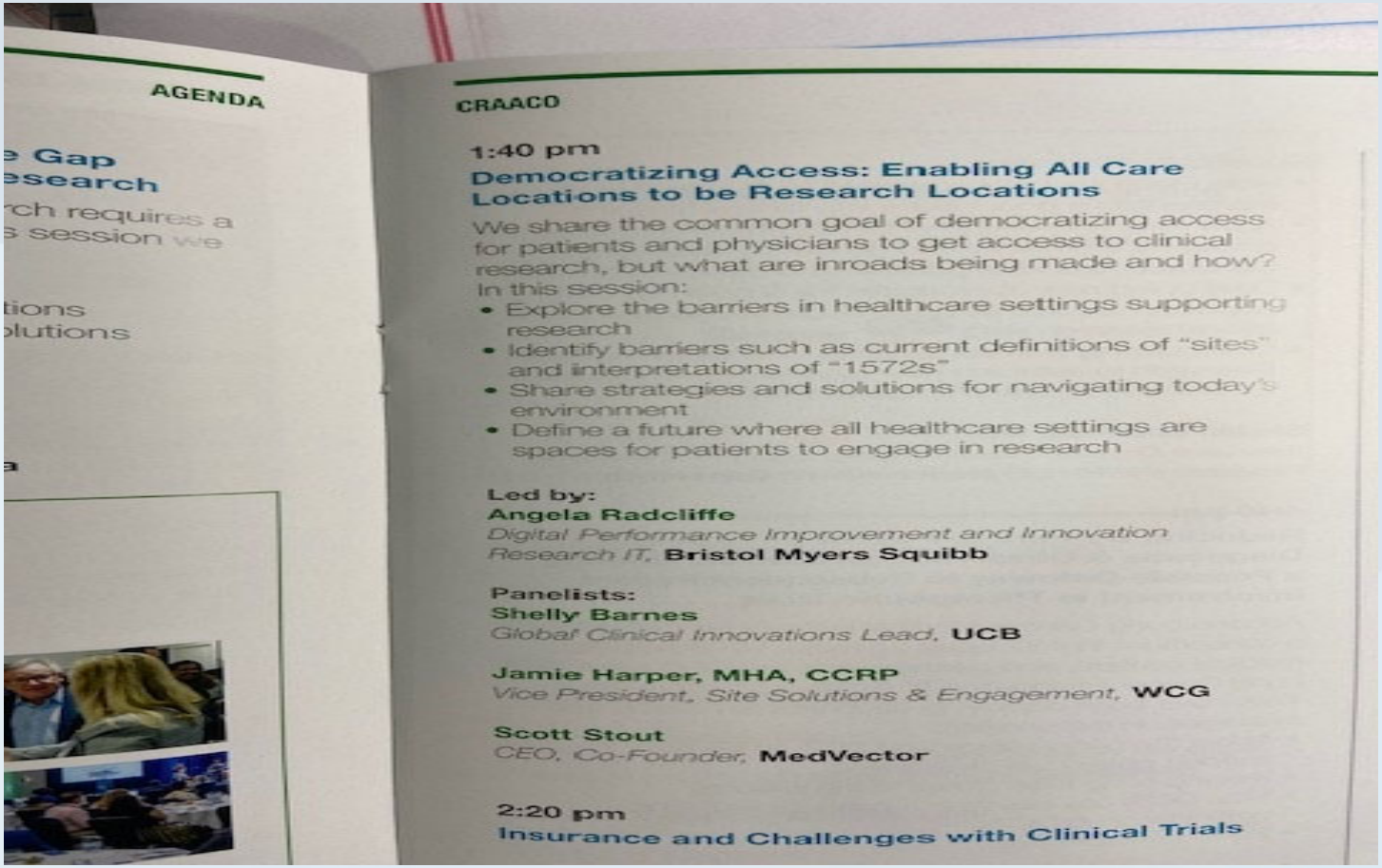
An investigator must administer an IP only to participants under the investigator's personal supervision or under the supervision of a subinvestigator responsible to the investigator.[35] The nature of the IP should be considered when determining whether administration outside of a clinical trial site in a DCT is appropriate. IPs that involve complex administration procedures; have a high-risk safety profile, especially in the immediate post-administration period; or are in early stages of development such that the safety profile is not well defined may need in-person supervision by the investigator at a trial site.

For IPs for which the safety profile is well-characterized and that do not involve specialized monitoring during the immediate period following administration, it may be appropriate for local HCPs or trial personnel working remotely to administer the IP at local health care facilities or participants' homes*. Hybrid DCTs may be designed for drugs that require supervised but infrequent (e.g., monthly) administration when administration can be done at trial sites with follow-up done remotely.

Discussed at the Clinical Research as a Care Option Meeting May 22-23, 2023 RTP, NC

Do you interpret this to mean that local HCPs that are not key personnel on the study can administer IP? Is so, this opens up many opportunities for rural research?

CRAACO Session Title



AGENDA

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CRAACO

1:40 pm

Democratizing Access: Enabling All Care Locations to be Research Locations

We share the common goal of democratizing access for patients and physicians to get access to clinical research, but what are inroads being made and how? In this session:

- Explore the barriers in healthcare settings supporting research
- Identify barriers such as current definitions of "sites" and interpretations of "1572s"
- Share strategies and solutions for navigating today's environment
- Define a future where all healthcare settings are spaces for patients to engage in research

Led by:
Angela Radcliffe
Digital Performance Improvement and Innovation Research IT, **Bristol Myers Squibb**

Panelists:
Shelly Barnes
Global Clinical Innovations Lead, **UCB**

Jamie Harper, MHA, CCRP
Vice President, Site Solutions & Engagement, **WCG**

Scott Stout
CEO, Co-Founder, **MedVector**

2:20 pm
Insurance and Challenges with Clinical Trials

Conducting a Virtual Clinical Study via REDCap
Fall, 2020

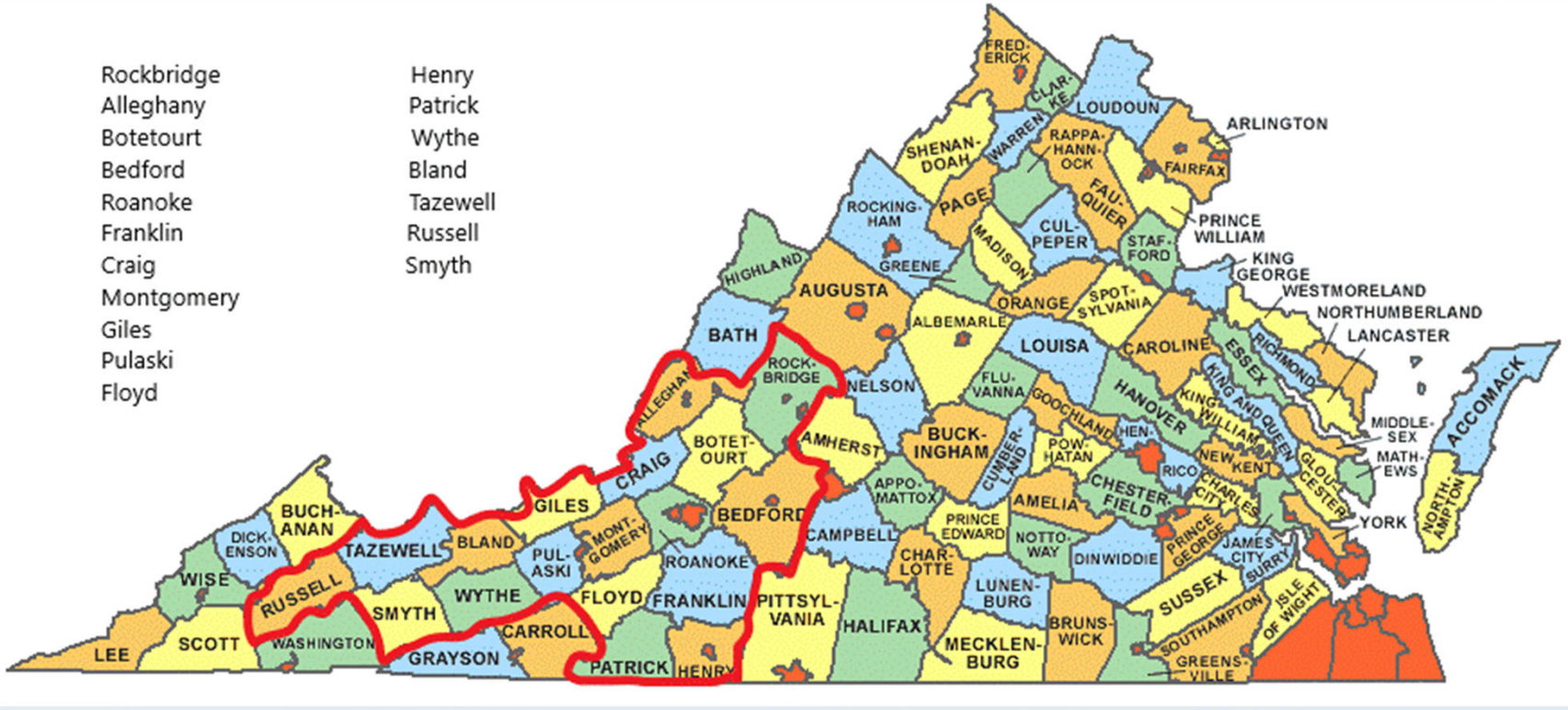
Near Southwest Virginia COVID-19 Seroprevalence Study

Study Design

- Consent 5250 participants in 22 municipalities from Smyth to Rockbridge County to have blood drawn to detect the presence of COVID-19 antibodies
  - Study start 10/2020 and must be completed by 12/31/2020
- Strive to achieve equipoise by municipality regarding race/ ethnicity using 2019 census data
- Be open to non-Carilion Clinic participants
- Contract with a third-party vendor with assurance that no one will be billed for the services
    - Carilion Clinic family and community medical practice sites were not an option given COVID-19 restrictions
- Allow Hispanic/ Spanish speaking participants to participate via a Spanish survey
- Given the complexity of the study coupled with the large geographic footprint, in person consenting by dedicated CRCs was not an option

Rockbridge
Alleghany
Botetourt
Bedford
Roanoke
Franklin
Craig
Montgomery
Giles
Pulaski
Floyd

Henry
Patrick
Wythe
Bland
Tazewell
Russell
Smyth



Step 1: Contact of potential participants

- Develop a REDCap survey with study instructions, list of questions and information on locations for blood collection
  - Merge with EPIC EMR and distribute via email address and physical address
    - Greater than 5,000 surveys were sent to potential participants

- **This strategy was extremely ineffective:**
  - At study conclusion 15 % participation rate from email and 0.3 % from direct mailing

Step 2: How can we effectively connect with potential participants

- Social Media!
  - Facebook and media pitch
    - At study conclusion 67 % participation rate
    - < $500 spent in this effort
- Response was within the thousands within 24 hours
  - Necessitated the need to place blocks/ holds within REDCap to maintain our projected demographic distribution

Step 3: Development of a bilingual survey

- Working in collaboration with study team members (Carilion Clinic Infectious Diseases physician and a clinical research assistant) who are fluent in Spanish, our Health Analytics team was able to generate a REDCap survey that could be toggled between English and Spanish
  - 18 % of our participants completed this survey; however, we don't know how many participants completed the survey in the Spanish format entirely

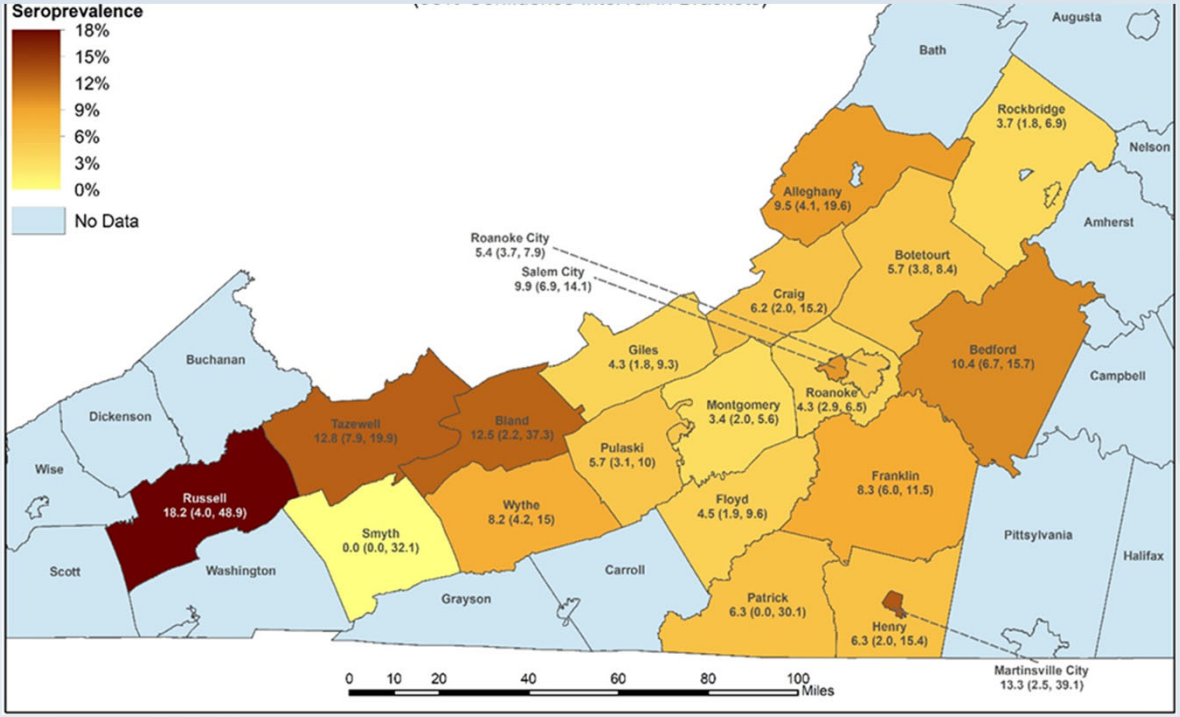
Step 4: How do you generate laboratory orders for 5,000 participants?

- All hands-on Deck!
  - Mobilized a team of CRCs, research admin, and temporary support staff to place over 5,000 laboratory orders in EPIC
    - Orders had to be placed in a timely fashion for participant uptake (within ~ 3 days of survey submission)
  - Automated emails were generated in REDCap to inform participants of location of nearest blood collection site and instructions for blood collection; generated auto reminders if one did not donate a sample within five days
  - Result sent to MyChart prior to communication to participant by email, phone, or letter
    - Mobilized non-research Carilion Clinic employees with EPIC access to assist with result dissemination

Top Level Results:

- 5646 people submitted a questionnaire
  - Analysis underway to ascertain potential correlations of seropositivity with survey data including location, age, social distancing practices, education and work status and vaccine compliance and acceptance
- Participation was achieved in all 22 municipalities
  - Significant interest in several rural counties with no prior Carilion Clinic research participation
  - 3257 participants blocked to enrollment in study due to pre- designed enrollment criteria
    - 98 % of these “blocked” participants elected to remain on a waiting list
- 718 participants with no prior connection to Carilion Clinic were recruited into the study
- 4152 participants had their blood drawn at a patient service center (PSC) yielding a conversion rate from questionnaire submission to a physical laboratory test of 73.5 %
  - Minimal difference in conversion rate as a function of race/ ethnicity

Percent Seroprevalence by County



Comparison of the aggregate study data (“Sample”) distributions (in percentage by category) to the aggregate 2019 Census data (“Population”)

GENDER

#	Female	Male
# Sample:	68.3	31.7
# Population:	50.9	49.1

RACE

#	White	Black	Asian	Other	Two+
# Sample:	91.7	3.4	3.4	0.9	0.6
# Population:	85.2	10.2	2.2	0.4	2.0

ETHNICITY

#	non-Hispanic	Hispanic
# Sample:	97.3	2.7
# Population:	96.7	3.3

AGE

#	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-85+
# Sample:	0	0.9	8.8	18.5	19.6	19.5	21.3	9.8	1.6
# Population:	10.1	12.1	13.6	11.2	11.8	13.7	13.4	9.2	4.9

Seroprevalence by County

County	Has testing results	Positive	Positive Rate	Age
ALLEGHANY, VA	67	6	8.96%	56.0 ± 13.7
BEDFORD COUNTY	187	19	10.16%	54.0±16.3
BLAND	16	2	12.50%	61.3± 13.9
BOTETOURT	422	25	5.92%	54.0± 15.0
BUENA VISTA	17	2	11.76%	48.1±19.4
BUENA VISTA CITY	30	1	3.33%	53.7±14.1
CRAIG	66	5	7.58%	55.7±13.3
FLOYD	134	6	4.48%	53.2±15.1
FRANKLIN COUNTY	417	34	8.15%	55.2±15.4
GILES	147	7	4.76%	43.4±82.1
HENRY	64	4	6.25%	55.5±13.0
MARTINSVILLE	15	2	13.33%	58.6±12.0
MONTGOMERY	446	15	3.36%	51.6±15.5
PATRICK	17	2	11.76%	54.8±18.5
PULASKI	199	11	5.53%	51.5±15.3
RADFORD	146	8	5.48%	50.5±14.1
ROANOKE COUNTY	559	25	4.47%	53.0±15.1
ROANOKE CITY	464	25	5.39%	48.8±15.2
ROCKBRIDGE	249	9	3.61%	54.5±16.5
RUSSELL	12	2	16.67%	45.8±16.3
SALEM	278	27	9.71%	52.1±16.2
SMYTH	10	0	0.00%	55.0±10.9
TAZEWELL	130	16	12.31%	49.3±13.4
WYTHE	114	9	7.89%	46.5±14.0
BEDFORD CITY	11	0	0.00%	57.1±7.0
OTHER	0	0	0.00%	0
Total	4217	262	6.21%	52.2±21.7

Seroprevalence by Age

Age Group	Pos	Positive Rate	Neg	Total
12-16	1	16.67%	5	6
17-21	4	8.00%	46	50
22-26	14	11.38%	109	123
27-31	15	5.95%	237	252
32-36	17	5.38%	299	316
37-41	27	6.80%	370	397
42-46	25	6.79%	343	368
47-51	29	6.62%	409	438
52-56	27	7.30%	343	370
57-61	38	7.41%	475	513
62-66	27	5.21%	491	518
67-71	15	3.46%	419	434
72-76	17	6.39%	249	266
77-81	4	3.57%	108	112
82-86	1	2.56%	38	39
87+	1	16.67%	5	6
Other	0	0.00%	9	9
Total	262	6.21%	3955	4217
* based on population have the testing results				

Study Summary:

- Virtual trials are possible with technological solutions and appropriate participant pool/research objectives
- Must be a compelling topic to motivate participation, i.e., presence of COVID-19 antibodies
- Not meant to replace high-touch, interventional trials, but could use these methodologies to supplement trial design and reduce burden on participants
- Offers options for large scale projects that would not be successful with traditional enrollment procedures or are limited by personnel resources, participant and staff safety concerns (pandemic), or geographical distribution of participants