Retention of Research Participants in a Longitudinal HIV Clinical Trial: Best Practices Identified by Systematic Surveys of Study Staff

(Results from the REPRIEVE Retention Champion Initiative)

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ACTG AIDS CLINICAL TRIALS GROUP

Kowa

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Outline

- Background: Retention in Clinical Trials
- Background: HIV and Cardiovascular Disease
- Context: The REPRIEVE Trial to inform practice
- Understanding barriers and facilitators for participant retention
- Survey findings and implementation
- Leveraging REPRIEVE to learn more about COVID-19

Background: Retention in Clinical Trials

- Participant retention in Clinical Trials is imperative for data integrity and analysis of study outcomes
- Drop out rates of 15-40% are observed in many clinical trials[2]
- The literature recognizes a variety of retention strategies utilized in various clinical trials—often discussing recruitment and retention in tandem [1-12]
  - ** *More focus on recruitment than retention*[3]
- Noted that trials with high retention rates tend to use multiple retention strategies[1]
- Literature notes that successful strategies should be tailored to meet individual site/ study/ population needs and that it is important to work closely with the clinical staff at the study sites[4,9]

Context: The Longitudinal HIV Clinical Trial

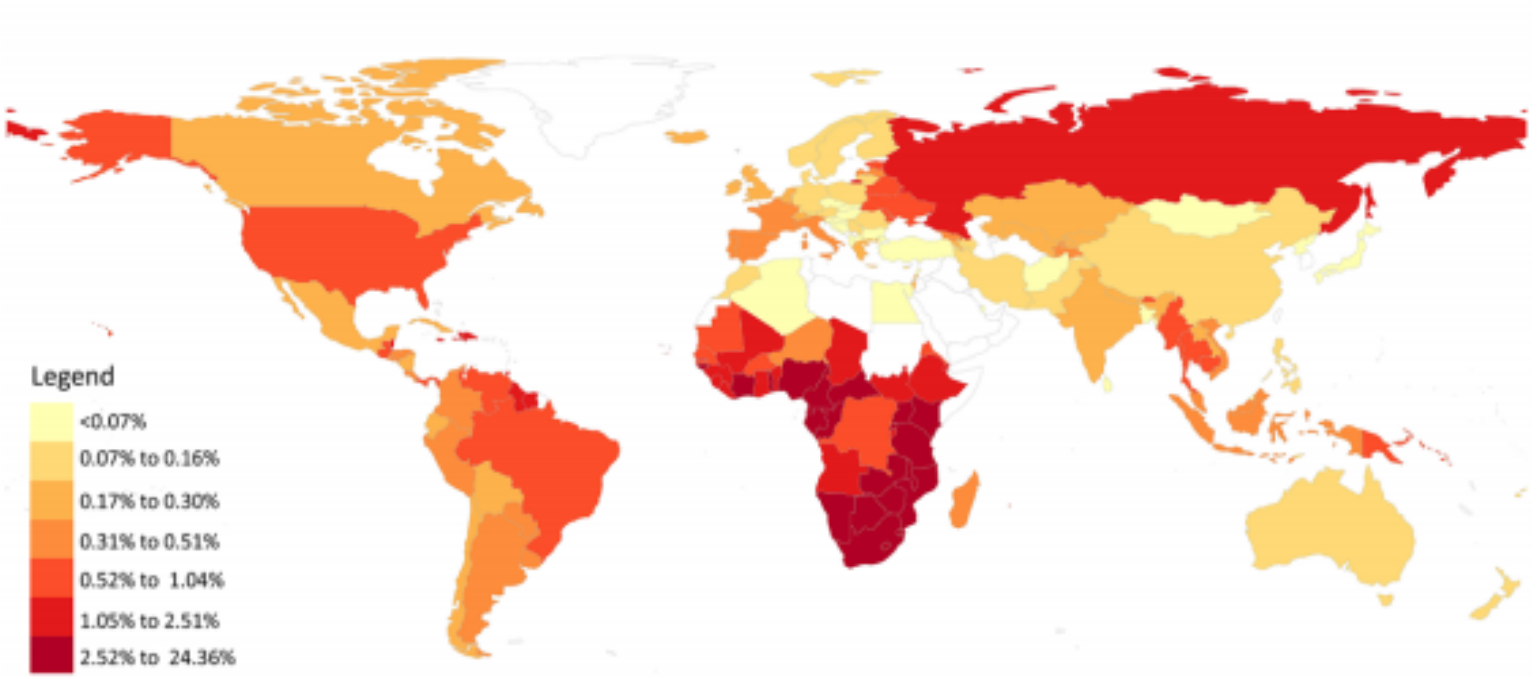
Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE)

- **Hypothesis:** Statin therapy will prevent ASCVD- related major adverse CV events in HIV-infected persons on antiretroviral therapy who are at low-moderate traditional CVD risk
- REPRIEVE:
  - is the largest CVD prevention trial in HIV and represents a new paradigm of primary prevention to study comorbidities in HIV. Primarily CVD but also evaluating kidney function and frailty.
  - completed enrollment of 7,770 participants in July, 2019 and is in it's 5th year of follow-up.
  - is funded by the NIH NHLBI with support from NIAID, Kowa Pharmaceuticals, Gilead Sciences and the AIDS Clinical Trial Group (ACTG)

Background: CVD in the Setting of HIV

Population Attributable Fraction (%) of Prevalence of CVD by Country

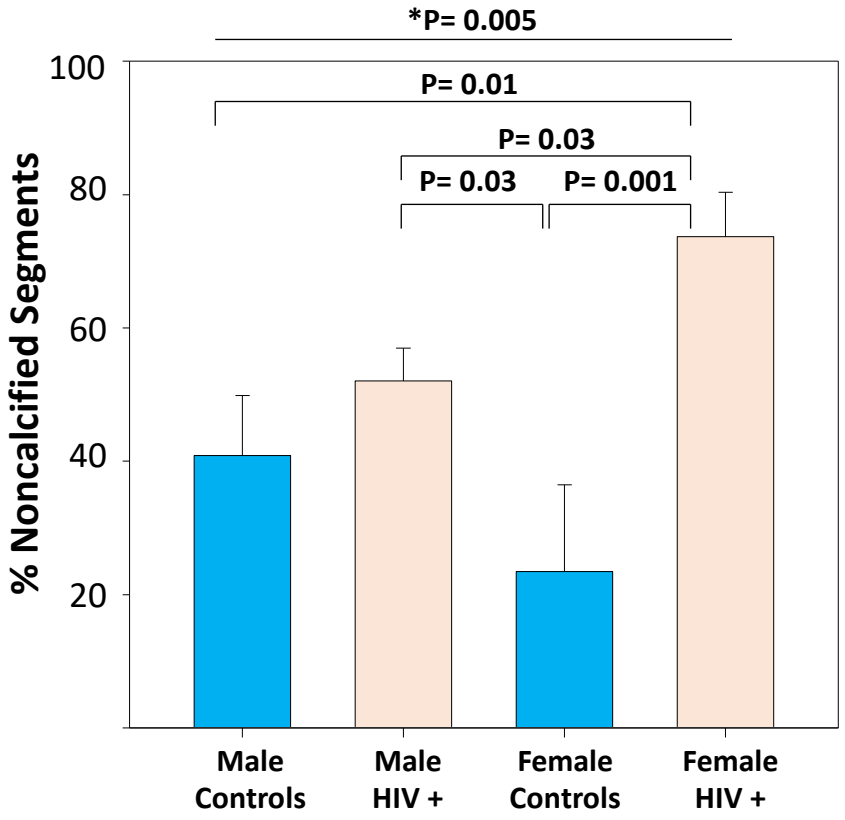
- Systematic review of longitudinal studies on CVD in HIV, 80 studies with ~800,000 individuals with HIV and a follow-up of 3.5 million person years
- Relative risk of CVD in persons living with HIV is 2.16 (95% CI, 1.68–2.77) compared to PWOH
- Authors report impact of HIV and CVD was highest among individuals in sub-Saharan Africa



Shah et al. Circulation, 2018

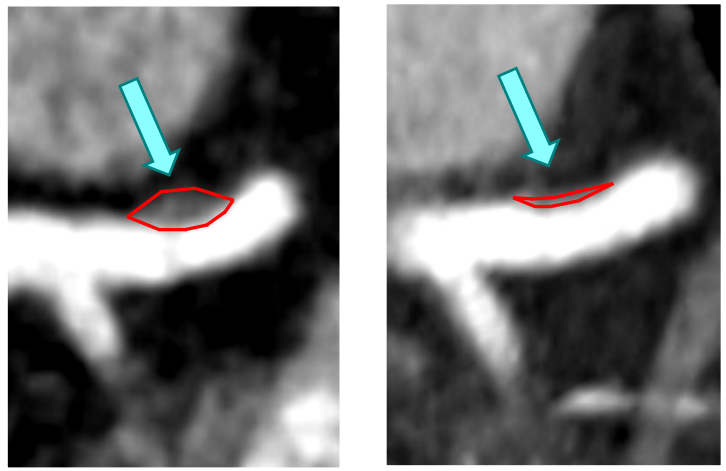
Background: HIV and CVD

*In HIV, CVD is associated with increased **non-calcified plaque** and **immune activation***



Fitch and Srinivasa, et al. J Acquir Immune Defic Syndr. 2014

Statins may have unique effects on coronary plaque and immune activation in people with HIV.



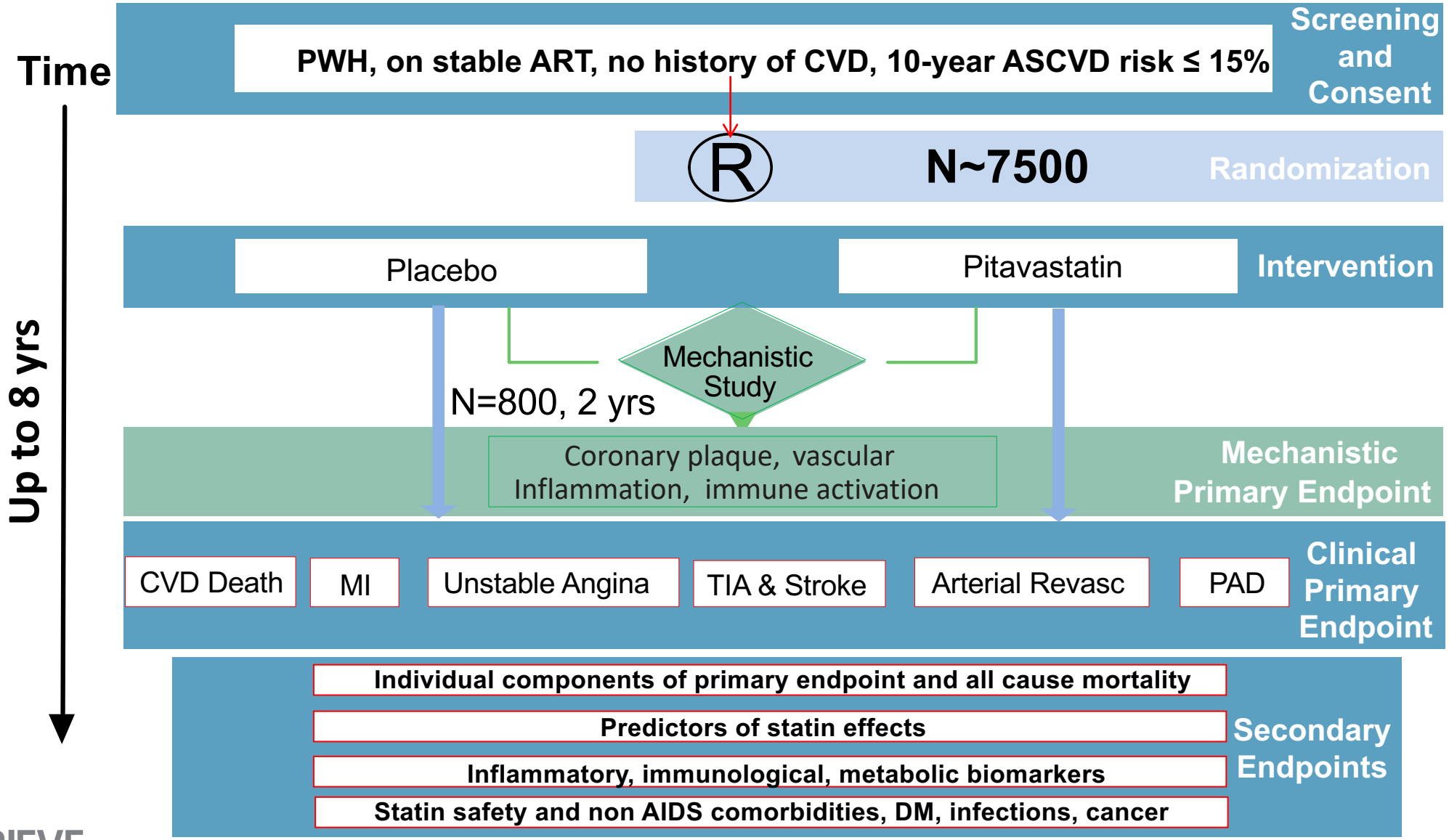
- Decreased non-calcified plaque in proximal left anterior descending (LAD) coronary artery in patient on atorvastatin for 12 months.

Lo, J. et al. Lancet HIV. 2015

Need for a Large RCT to Inform Clinical Practice

- PWH are at increased risk for CVD which is not explained by traditional CV risk factors alone
- It is unknown if statins will prevent *CVD events*
- Statins are largely well tolerated in small studies, there are no data from large RCTs in HIV investigating efficacy and tolerability
- There are currently no guidelines for the prevention and treatment of CVD for PWH

REPRIEVE Trial Schema



REPRIEVE

For more details see: Grinspoon, SK et al. AHJ. 2019; Hoffmann, U et al. AHJ, 2019

REPRIEVE Clinical Sites

Over 100 clinical sites in 12 countries globally

Importance

- Participant retention is imperative for accurate quantification of primary outcomes in this longitudinal study.
- Due to a large variety of social and health-related factors experienced by people living with HIV, study retention poses challenges.
- While this initiative was to conducted as part of REPRIEVE, much of what we learned applies to clinical trials in general.

Objective

- The REPRIEVE Clinical Coordinating Center (CCC) team, located at Massachusetts General Hospital, needed to better understand:
  1. site-specific participant retention strategies
  2. barriers and facilitators to participant retention
  3. ideas from sites on how the CCC could support sites' retention efforts
- In turn, share information and ideas learned from clinical sites to support retention efforts in order to *maintain* excellent retention rates.

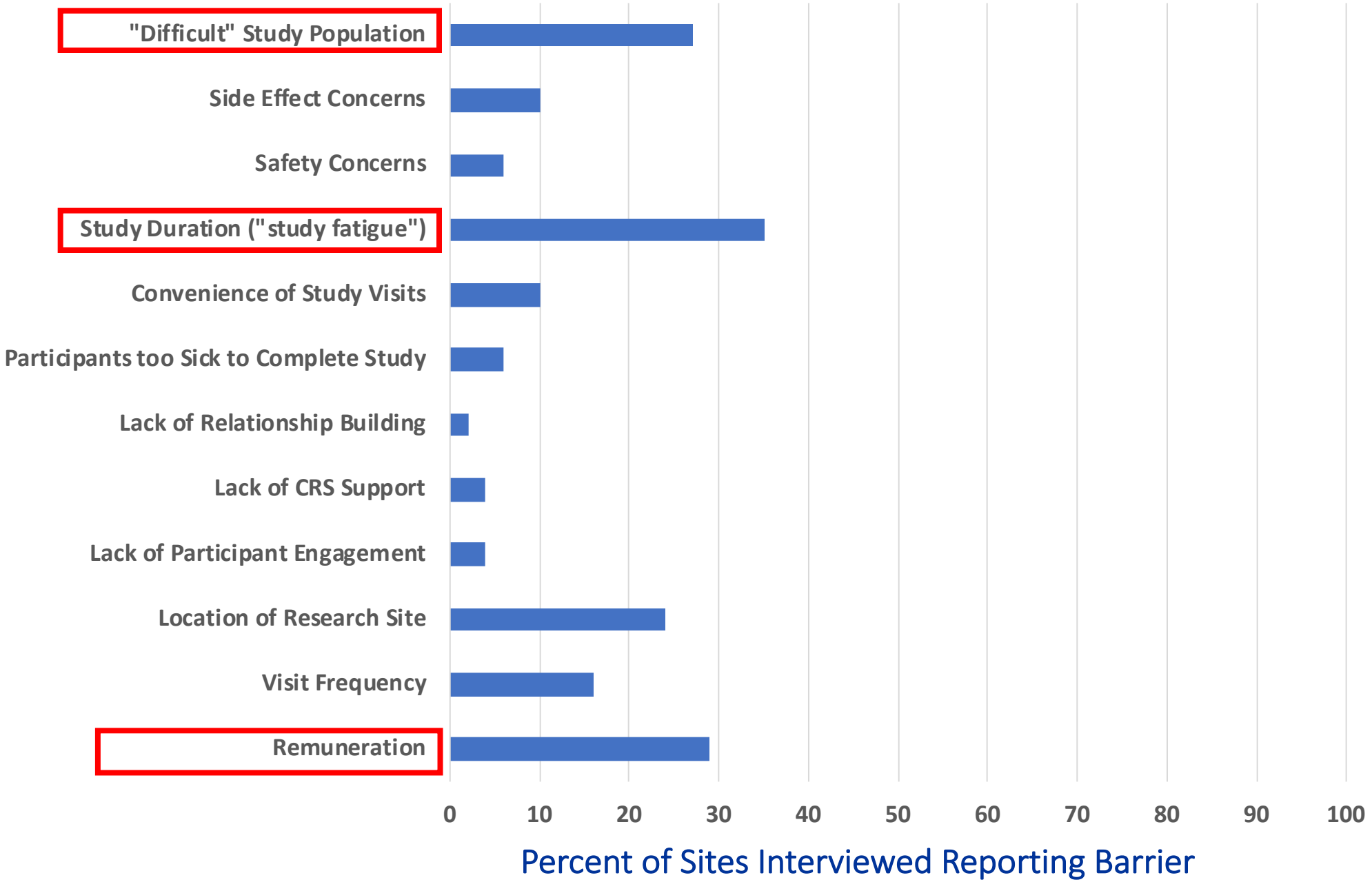
Implementation

- We developed a survey including multiple choice and open-ended questions to elicit current site retention practices and facilitators.
- Sample questions
  - What are barriers to retention at your site?
  - What **on-site** strategies does your site *carry out* to promote retention in the REPRIEVE trial?
  - What *materials* do you think would be helpful to your site team for retaining participants at your site?
  - What retention *efforts* do you think would be helpful for your site team to retain participants at your site?

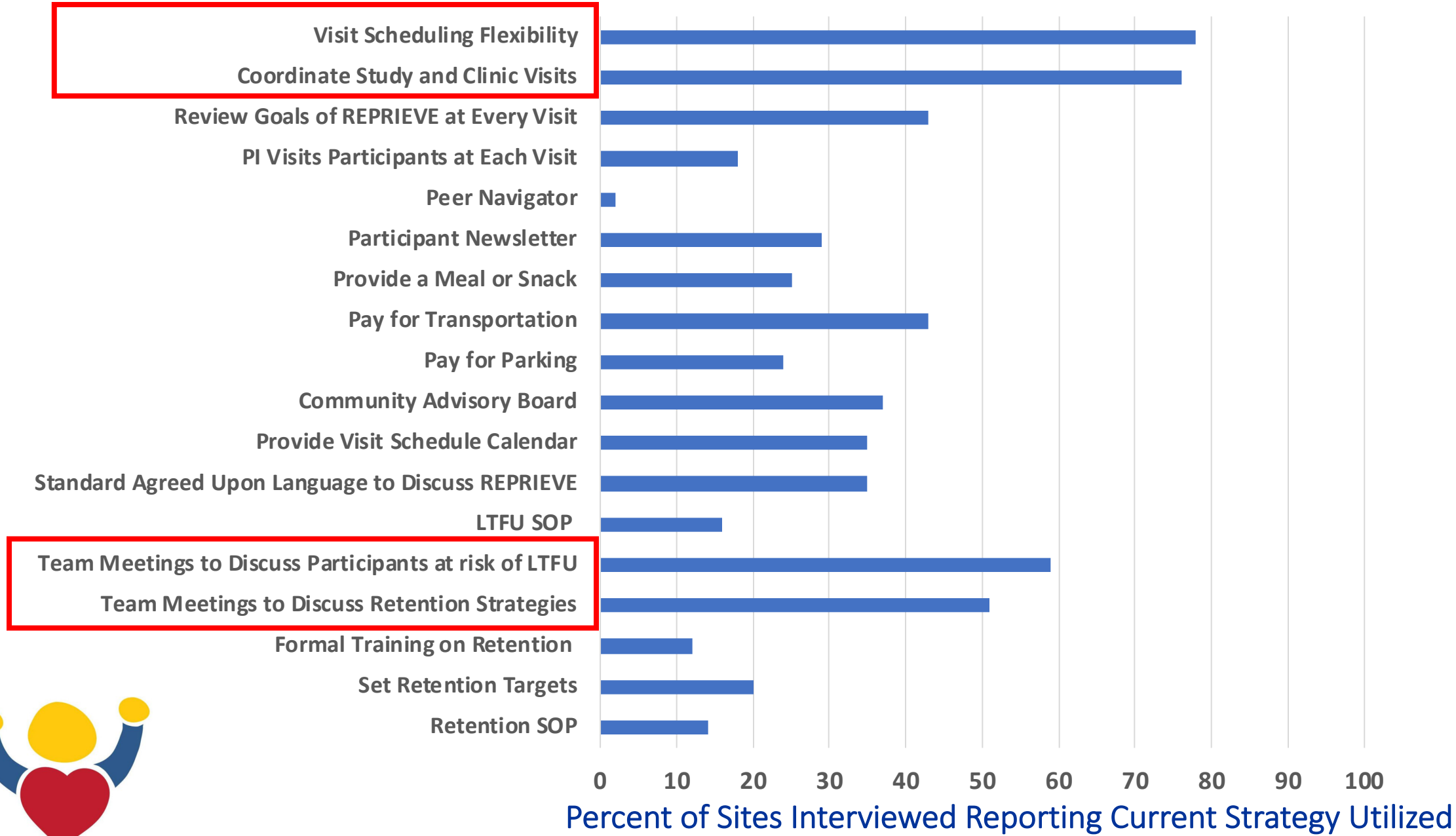
Implementation

- We reached out to all site PIs via email to ask them to identify a Retention Champion at their site, solicitations for Retention Champions were also included in site newsletters and during monthly site calls (51 surveys were completed with Retention Champions)
- The survey was administered with the site-identified “Retention Champion” by CCC Investigators via phone.
- Responses were keyed into REDCap
- Data were analyzed with descriptive statistics.

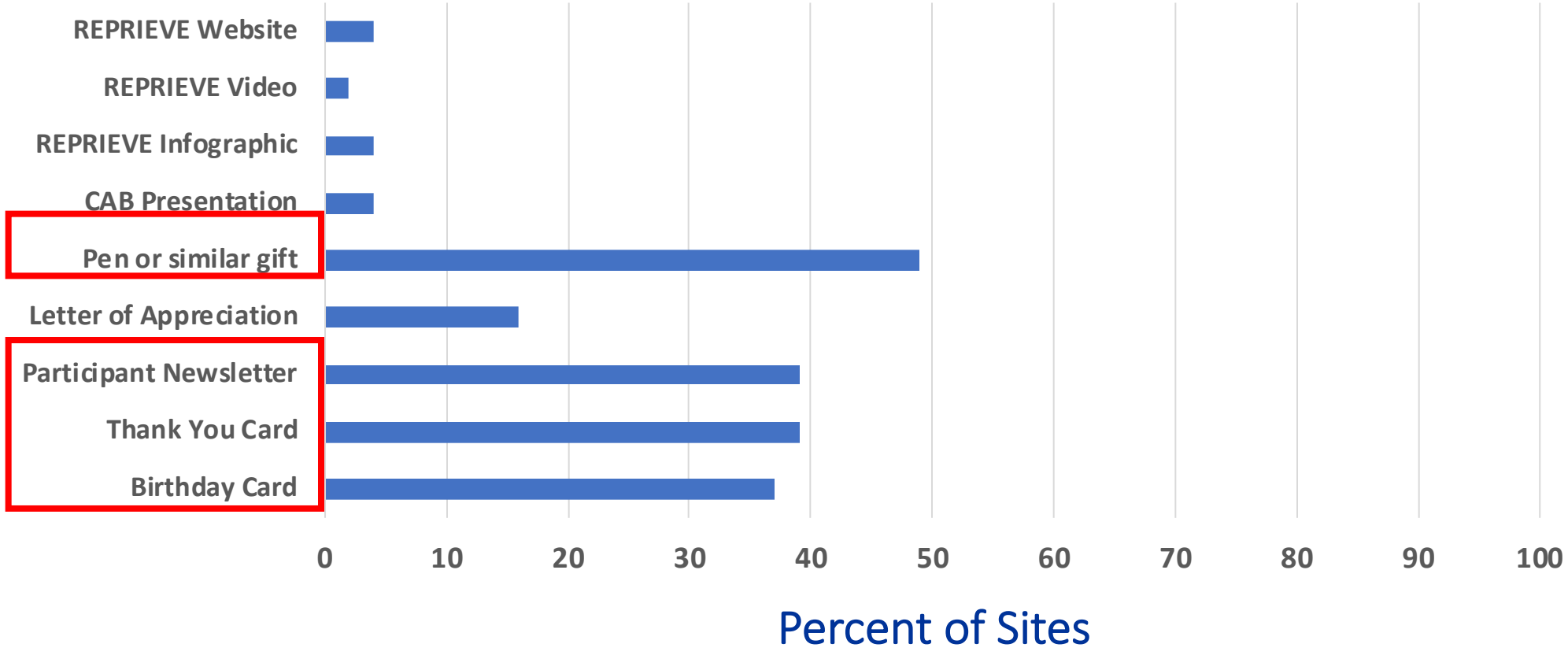
Common Barriers to Retention in REPRIEVE



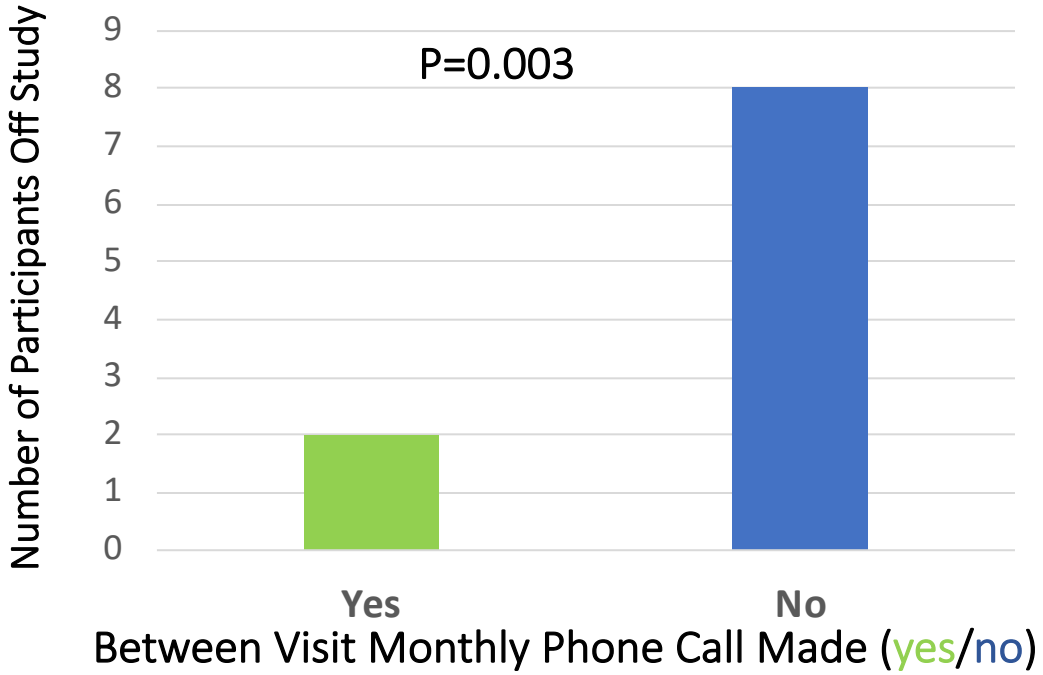
Current On-Site Strategies to Promote Retention in REPRIEVE



What Materials Do You Think Would be Helpful to Promote Retention in REPRIEVE?



Among sites with <5% participants off-study (vs. ≥5%)



- sites were significantly more likely to perform monthly check-in calls (P=0.003) **(Figure)**
- conduct team meetings to discuss at risk participants (P=0.01)
- pay for transportation (P=0.02)
- coordinate study and clinic visits (P=0.02)

How the CCC responded to findings…

SITE-IDENTIFIED BARRIERS to RETENTION	SITE-IDENTIFIED RESPONSES	CCC RESPONSES
Duration of trial	• Visit scheduling flexibility • Coordinate study visits with clinic visits • Monthly check in call	✓ **Visit schedule template and visit calendar are provided to sites** ✓ ***Increased visit windows for more flexibility***
Remuneration	• Pay for transportation • Pay for meals	✓ **Provision of additional funds for remuneration**

SITE-IDENTIFIED PROMOTION STRATEGIES	CCC RESPONSES
Provide participant Newsletters	✓ **CCC develops Participant Newsletter annually**
Provide thank you cards, birthday cards, pens, or other small tokens of appreciation	✓ **Tokens can be requested from CCC! pens, magnet calendars, and bracelets**

Giving Back: Sharing Findings with Site Teams

- Findings from the Retention Champion Initiative are shared with site teams in many ways:
  - Monthly site calls
  - Retention tip of the month (monthly site newsletters and site calls)
  - Investigator meetings
  - Retention Toolkit (hardcopies available and on REPRIEVE website)
    - REPRIEVE key messages
    - Listing of on-site strategies to promote retention
    - Instructions to order tokens of appreciation
    - Social media tools and tips
    - Instructions on getting involved in the community

Important Recurring Comment

- Anecdotally, a recurring common theme reported by Retention Champions included the importance of the participant-nurse and/or participant-provider relationship as pivotal to study retention.

Impact of COVID-19 on REPRIEVE

Some Activities on Hold or Cancelled…

REPRIEVE Ambassador Initiative

- 63 visits complete
- Visits consist of
  inf
  d pdates,
  retention, protocol amendment, and address any questions from the site

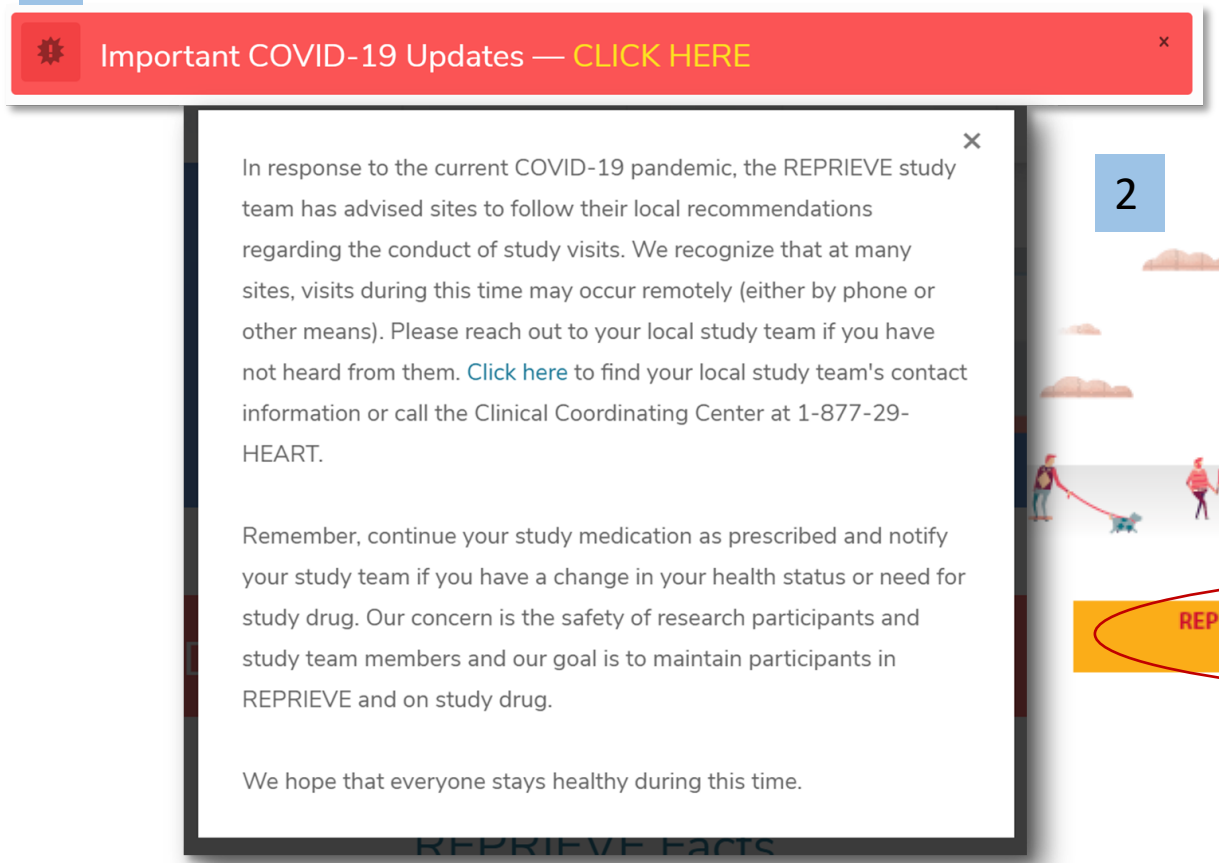
ON HOLD

→ **Will resume visits virtually summer 2020!**

→ **Going virtual, July 24th!!!**

Messaging to Participants

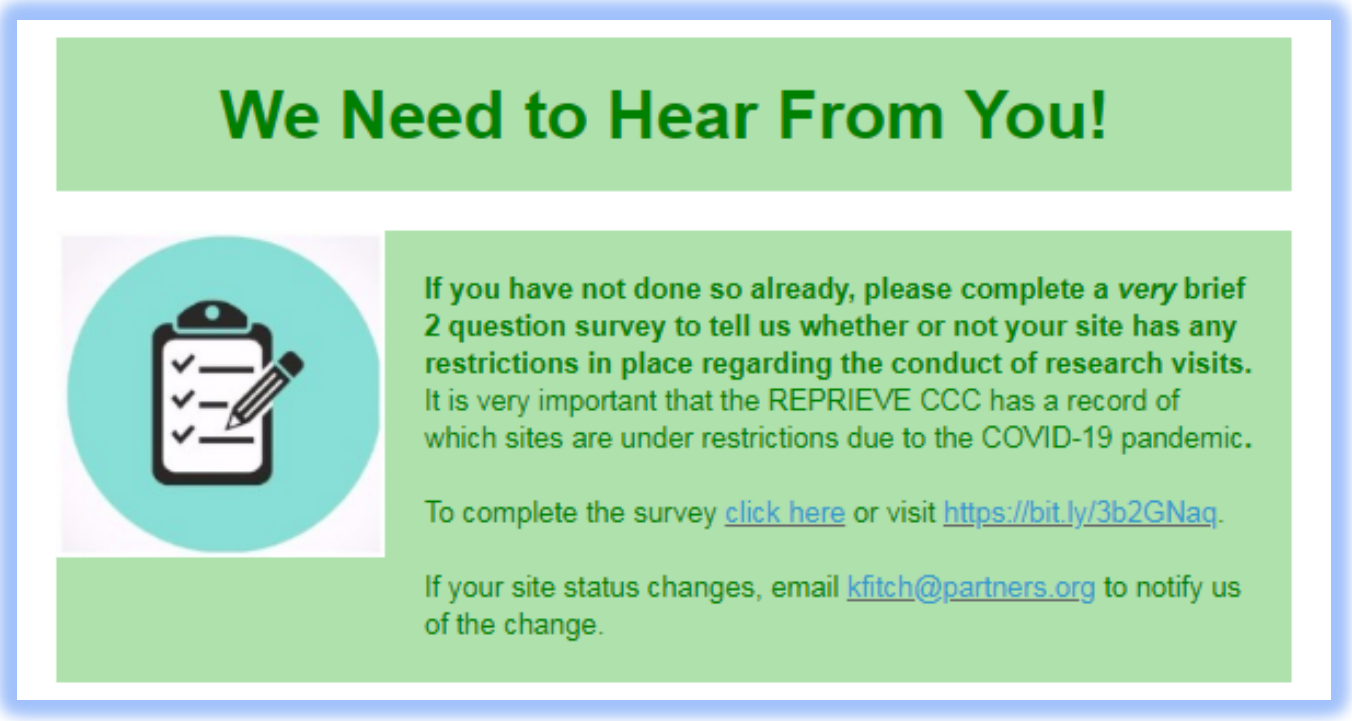
1 REPRIEVE Trial website



2

3 Social media messaging to ensure ongoing engagement of participants

Site status



Information collected via online survey or email inquiry

- 103 sites reported restrictions
- 21 sites reported no restrictions

Site Tools Developed

- The Study Team has developed 2 tools to use if a site's usual work practices have been affected by the COVID-19 pandemic

  1. Tracking Log

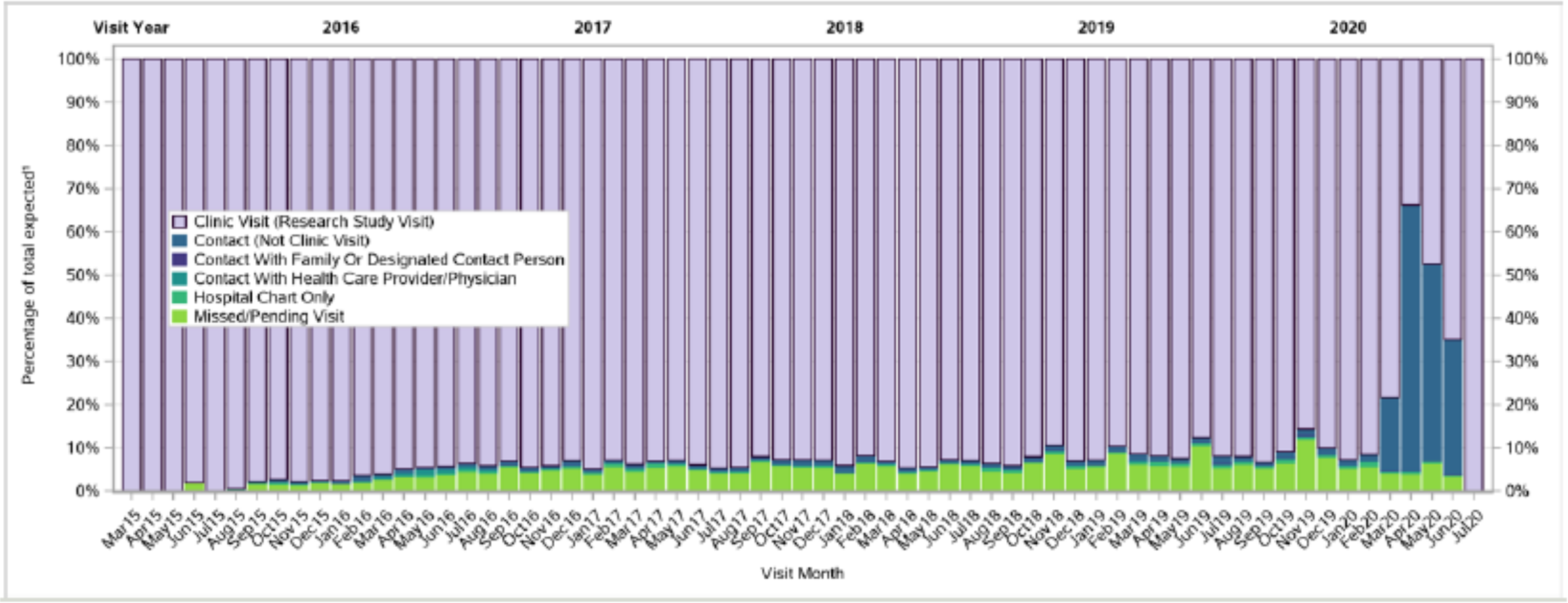
  - A tracking log was developed to document how a participant's participation in REPRIEVE may have been altered due to restrictions related to COVID-19.
  - The REPRIEVE CCC will collect the A5332 COVID-19 Tracking Log at the resolution of the Coronavirus Pandemic.
  - This log will not replace or substitute for any existing requirement for data entry.

  2. Sample Remote Visit Encounter Form

  - Data from a remote visit (i.e. phone visit or medical record review) can be documented for study records and referenced when keying data in OpenClinica at a later time.
  - Sites are advised to maintain with source documents

- Tools were developed to help ensure the integrity of the trial and proper reconciliation of data so that we have an accounting of study visits and changes in study drug dispensation that may lead to missing information (e.g., for protocol-specified procedures) during the COVID-19 pandemic.

What we know about number and mode of participant contact over time



What Can We Learn About COVID-19 in this Global Cohort of PWH?

- Is COVID-19 a risk factor for CVD events? i.e. ischemic events
- REPRIEVE presents a unique opportunity to obtain key details about how SARS-CoV-2 infection and COVID-19 illness may impact PWH.
- What we hope to learn:
  - Prevalence of COVID-19 in the REPRIEVE population through state of the art serology (Broad)
  - COVID-19 symptoms experiences
  - Hospitalizations and treatments
- *Effects of key Interventions:*
  - Pitavastatin effect on COVID in large RCT- unique opportunity
  - Effect of other medications→antiretroviral therapy (Tenofovir?), ACE-I/ARBs
- **COVID-19 Assessment CRF** was developed to collect this information
- **Additional blood is collected at annual visits** to evaluate COVID-19 biomarkers including serology

Summary

- Visit scheduling flexibility, coordinating study visits with clinic visits, team meetings and monthly check-in phone calls were strategies reported to be effective by clinical sites participating in REPRIEVE.
- Site shared that the CCC could provide materials to help with retention such as pens, thank you cards, birthday cards and participant newsletters to help with retention
- Important to thank participants for their time (on the phone, at visits)
- Retention reminders implemented in a variety of settings and situations
- Many findings may be applicable for retention in clinical trials in general
- Ensuring flexibility of trial to adapt to unanticipated events (i.e. COVID-19)

Acknowledgements

- Thank you to Dr. Inge Corless and the HOPE Nursing Conference for the opportunity to present today
- We would like to thank the REPRIEVE study participants for their contributions to this important trial
- Thank you to the REPRIEVE Study Sites and the REPRIEVE Retention Champions whose insight into the site-specific facilitators and barriers to retention provided invaluable knowledge and has helped to implement the REPRIEVE Retention Tool Kit
- Thank you to the REPRIEVE Clinical Coordinating Center Team for their help and guidance with this retention initiative:
  - Dr. Steven Grinspoon, PI
  - Dr. Markella Zanni
  - Dr. Sara Looby
  - Emma Kileel

Questions?

References

1. Updated systematic review identifies substantial number of retention strategies: using more strategies retains more study participants. Robinson KA, Dinglas VD, Sukrithan V, Yalamanchilli R, Mendez-Tellez PA, Dennison-Himmelfarb C, Needham DM. J Clin Epidemiol. 2015, 68(12):1481-7. doi: 10.1016/j.jclinepi.2015.04.013. Epub 2015 Jun 10. PMID: 26186981
2. Subject Recruitment and Retention: Barriers to Success. Applied Clinical Trials. Applied Clinical Trials Editors. April 1, 2004. Retrieved at: http://www.appliedclinicaltrialsonline.com/subject-recruitment-and-retention-barriers-success
3. Recruitment and retention strategies in clinical studies with low-income and minority populations: Progress from 2004-2014. Nicholson LM, Schwirian PM, Groner JA. Contemp Clin Trials. 2015 Nov;45(Pt A):34-40. doi: 10.1016/j.cct.2015.07.008. Epub 2015 Jul 16. PMID: 26188163
4. Recruitment and retention strategies in longitudinal clinical studies with low-income populations. Nicholson L.M., Schwirian P.M., Klein E.G., Skybo T., Murray-Johnson L., Eneli I., et al: Contemp Clin Trials. 2011 May;32(3):353-62. doi: 10.1016/j.cct.2011.01.007. Epub 2011 Jan 27. PMID: 21276876
5. Strategies to improve retention in randomised trials: a Cochrane systematic review and meta-analysis. Brueton VC, Tierney JF, Stenning S, Meredith S, Harding S, Nazareth I, Rait G. BMJ Open. 2014 Feb 4;4(2):e003821. doi: 10.1136/bmjopen-2013-003821. PMID: 24496696
6. Strategies for recruitment and retention of participants in clinical trials. Probstfield JL, Frye RL. JAMA. 2011 Oct 26;306(16):1798-9. doi: 10.1001/jama.2011.1544. PMID: 22028357
7. Best practice guidance for the use of strategies to improve retention in randomized trials developed from two consensus workshops. Brueton V, Stenning SP, Stevenson F, Tierney J, Rait G. J Clin Epidemiol. 2017 Aug;88:122-132. doi: 10.1016/j.jclinepi.2017.05.010. Epub 2017 May 22. PMID: 28546093
8. Identifying research priorities for effective retention strategies in clinical trials. Kearney A, Daykin A, Shaw ARG, Lane AJ, Blazeby JM, Clarke M, Williamson P, Gamble C. Trials. 2017 Aug 31;18(1):406. doi: 10.1186/s13063-017-2132-z. PMID: 28859674
9. Participant retention practices in longitudinal clinical research studies with high retention rates. Abshire M, Dinglas VD, Cajita MI, Eakin MN, Needham DM, Himmelfarb CD. BMC Med Res Methodol. 2017 Feb 20;17(1):30. doi: 10.1186/s12874-017-0310-z. PMID: 28219336
10. Strategies to enhance participant recruitment and retention in research involving a community-based population. McCullagh MC, Sanon MA, Cohen MA. Appl Nurs Res. 2014 Nov;27(4):249-53. doi: 10.1016/j.apnr.2014.02.007. Epub 2014 Feb 27. PMID: 24667018
11. Maximizing retention with high risk participants in a clinical trial. Kim R, Hickman N, Gali K, Orozco N, Prochaska JJ. Am J Health Promot. 2014 Mar-Apr;28(4):268-74. doi: 10.4278/ajhp.120720-QUAN-355. Epub 2013 Jul 22. PMID: 23875989
12. Challenges in recruitment and retention of clinical trial subjects. Kadam RA, Borde, SU, Madas, SA, Salvi SS, Limaye SS. Perspect Clin Res. 2016 Jul-Sep;7(3):137-43. doi: 10.4103/2229-3485.184820. PMID: 27453831

Data Collection Tool

SSW0040 - COVID-19 Assessment - v1.00 (03-31-20)

Instructions:
This assessment is intended to be completed via a participant interview and/or via review of the participant medical record. All questions are intended to be answered for the time-period since the participant's last study evaluation. Refer to the MOPs/SRM for further instructions regarding performance of the assessment

1.	**Date the COVID-19 Assessment was performed:**	__ __ - __ __ __ - __ __ __ __ (DD-MMM-YYYY)
2.	**Indicate how the assessment was performed:**	☐ Participant interview ☐ Medical record review
3.	**Has the participant been evaluated by a Health Care professional for COVID-19?**	○ Yes ○ No ○ Unknown
	If Yes: Complete Question 3a	
3a.	**Was testing recommended to the participant by a Health Care professional?**	○ Yes ○ No ○ Unknown
4.	**Was the participant tested for COVID-19 since the last study evaluation?**	○ Yes ○ No ○ Unknown
	If Yes: Complete Question 4a	
4a.	**Did the participant test positive for COVID-19?**	○ Yes ○ No ○ Unknown
	If Yes: Complete Question 4b and report the COVID-19 Diagnosis on the ADE0001 - Adverse Events Log	
4b.	**Was the participant prescribed medication for the treatment of COVID-19?**	○ Yes ○ No ○ Unknown
	If Yes: Key the clinician prescribed medications into the TXW0295 – Medications Log	
5.	**Was the participant hospitalized due to COVID-19?**	○ Yes ○ No ○ Unknown

	Has the participant experienced any of the following symptoms since the last study evaluation?	**Symptom Present?**
6.	**Fever >100.4F (38C)**	○ Yes ○ No ○ Unknown
7.	**Subjective fever (felt feverish)**	○ Yes ○ No ○ Unknown
8.	**Chills**	○ Yes ○ No ○ Unknown
9.	**Muscle aches (myalgia)**	○ Yes ○ No ○ Unknown
10.	**Runny nose (rhinorrhea)**	○ Yes ○ No ○ Unknown
11.	**Sore throat**	○ Yes ○ No ○ Unknown
12.	**Cough (new onset or worsening of chronic cough)**	○ Yes ○ No ○ Unknown
13.	**Chest tightness**	○ Yes ○ No ○ Unknown
14.	**Shortness of breath or difficulty breathing (dyspnea)**	○ Yes ○ No ○ Unknown
15.	**Nausea**	○ Yes ○ No ○ Unknown
16.	**Vomiting**	○ Yes ○ No ○ Unknown
17.	**Headache**	○ Yes ○ No ○ Unknown
18.	**Abdominal pain**	○ Yes ○ No ○ Unknown
19.	**Diarrhea (≥3 loose/looser than normal stools/24hr period)**	○ Yes ○ No ○ Unknown
20.	**Anosmia (loss of smell)**	○ Yes ○ No ○ Unknown
21.	**Ageusia (loss of taste)**	○ Yes ○ No ○ Unknown