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Meeting the challenges of retention and enrollment of study participants in clinical trials during the COVID-19 pandemic from the study leadership perspective: Experience from the Zoster Eye Disease Study (ZEDS)☆

MeeLee Tom [a,*], Elisabeth J. Cohen [b], Carlos LopezJimenez [a], Judith S. Hochman [c], Andrea B. Troxel [d], Bennie H. Jeng [e]

[a] Office of Science and Research, NYU Grossman School of Medicine, One Park Ave, 6th Floor, New York, NY, 10016, USA
[b] Department of Ophthalmology, NYU Grossman School of Medicine, One Park Ave, 6th Floor, New York, NY, 10016, USA
[c] NYU-HHC Clinical and Translational Science Institute, NYU Grossman School of Medicine, 530 First Ave, Skirball 9R, New York, NY, USA
[d] Department of Population Health, NYU Grossman School of Medicine, 180 Madison Ave, 5th floor, New York, NY, 10016, USA
[e] Department of Ophthalmology and Visual Sciences, University of Maryland School of Medicine, 419 W. Redwood Street, Suite 470, Baltimore, MD, 21201, USA

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ABSTRACT

Purpose: To describe steps taken that enabled a high rate of retention and early resumption of enrollment in the Zoster Eye Disease Study (ZEDS), a randomized controlled trial funded by the National Eye Institute, during the first 13 months (3/1/2020–3/31/2021) of the COVID–19 pandemic.

Methods: A number of responses were implemented in ZEDS when the focus shifted to retention of study participants at the beginning of the pandemic including frequent communication with the participating clinical centers (PCCs) about remote visits, local lab work, shipping study medication, and completion of revised case report forms. Additional payments were provided to the PCCs. Remote activation of PCCs continued. Screening and enrollment visits gradually resumed when allowed.

Results: Communication with PCCs increased, and average attendance at monthly coordinator teleconferences went up from 17 to 47. Remote visits peaked in April 2020, accounting for 75% (33/44) of study visits, then declined to less than 10% of study visits beginning August 2020. Overall, 97% (590/609) of study visits were completed. Only 5.5% (9/165) of study participants withdrew consent, and 2.4% (4/165) were lost to follow-up. Enrollment returned to pre-pandemic levels by September 2020.

Discussion: Strong communication and unwavering commitment, combined with the technological capability for remote work, visits, and shipment of study medication, were key to the successful retention of study participants and resumption of enrollment.

Conclusions: Rapid responses to challenges to trials caused by the COVID-19 pandemic can enable them to continue successfully and provide insights into the planning of future trials.

1. Introduction

The Zoster Eye Disease Study (ZEDS), funded by the National Eye Institute of the National Institutes of Health (NEI/NIH) is a multicenter, international, randomized, placebo-controlled clinical trial to determine whether prolonged suppressive antiviral treatment reduces complications of Herpes Zoster Ophthalmicus (HZO), including eye disease and/or postherpetic neuralgia. Study participants are randomized 1:1 to double-masked valacyclovir 1000 mg or placebo daily for one year with study visits every three months for 18 months [1]. Enrollment in ZEDS started in October 2017. At the time of this report, 254 study participants were enrolled, with an accrual goal of 780.

Similar to all clinical trials, the pandemic has affected the conduct of ZEDS [2–5]. On March 16, 2020, the NIH issued guidance to recipients conducting clinical trials affected by COVID-19 encouraging them to consult with their IRB and institutional policies about measures to protect the safety of study participants and research staff, including limiting study visits to co-occur with visits necessary for clinical care

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* Corresponding author. Office of Science and Research NYU Grossman School of Medicine One Park Avenue, New York, NY, 10016, USA.
E-mail address: MeeLee.Tom@nyulangone.org (M. Tom).

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[6]. Otherwise, virtual study visits were recommended.

The clinical operations team at the ZEDS Coordinating Center (CC) at NYU Grossman School of Medicine (NYUGSoM) immediately implemented COVID policies and procedures. The purpose of this report is to describe strategies put in place to enable strong retention and resumption of enrollment of study participants from March 2020 through March 2021.

2. Methods

This study adheres to the tenets of the Declaration of Helsinki. The IRB at Vanderbilt University, acting as the central IRB, institutional IRBs, and local research ethics boards provided approval at participating clinical centers (PCCs) in the U.S, Canada and New Zealand.

When the NIH guidance was issued, study leadership met to strategize on how to move forward with the study. The first priority was to communicate with all the investigators and study coordinators at over 80 PCCs. An email was sent immediately telling them to continue in-person study visits only if in compliance with their institutional policy regarding clinical research, and to perform virtual visits if in-person visits were not required for urgent care. The CC staff began working remotely. All study leadership and clinical operations meetings continued virtually.

The focus of the ZEDS CC immediately shifted from screening and enrollment to retention of study participants. Case report forms (CRFs) were revised to collect more data at phone visits, including data on COVID-19 infections and vaccinations.

2.1. Communication

Monthly calls with the study coordinators and newsletters to all study team members continued. Numerous emails were sent to the PCCs with additional information over time. Communication focused on new study procedures due to COVID-19, including data collection at phone visits, in-person visits for urgent care and possible endpoints, local blood work for eGFR testing when required, shipment of study medication to participants, and reporting of protocol deviations. Responses to relevant questions from the PCCs were shared in the monthly newsletter. When PCC staff had hours reduced, it was suggested other staff be trained so there was sufficient coverage to perform key study-related procedures.

2.2. Retention at follow-up visits

To promote compliance with study visits and retention of study participants, at the beginning of each month, CC staff sent each PCC a list of study participants who had visits due that month. Study coordinators were called to ensure the visits had been scheduled.

For the follow-up visits at 3, 6, and 9 months when study medication is dispensed, coordinators were trained on shipping study medication to participants. The CC provided thermometers for monitoring during shipment. For study participants who required follow-up blood work due to eGFR values of 45–59 at enrollment, coordinators were instructed to ship the lab kits so participants could obtain tests locally. Because of the extra effort required during the pandemic, the budget to the PCCs was increased. The CC worked with the PCCs to execute contract amendments quickly. This included weekly communications with the PCC PI and business office, and setting deadlines to return signed amendments. The NYUGSoM legal team was committed to the continuation of the study and was available to meet and facilitate necessary amendments.

2.3. Screening/consent and enrollment/randomization visits

PCCs were informed that it was possible to obtain informed consent at virtual screening visits using IRB-approved processes. Study teams were trained to obtain informed consent remotely at the monthly calls, and this was reinforced through our newsletters and one-on-one contact with the study teams. Because the enrollment visit requires an eye exam and cannot occur at a phone visit, the PCCs were informed enrollment should stop unless it was at the time of urgent care.

2.4. Activation of PCCs

The CC continued activating PCCs. PCC activation calls remained via WebEx. Due to the enrollment pause, the decision was made to open a PCC in New Zealand.

2.5. Role of the IRB

During discussions with the central IRB, it was decided since we did not want to have remote informed consent and shipping of the study medication to continue after the pandemic, these events would be reported to the IRB as protocol deviations at the time of continuing review. Virtual, or phone visits, were included in the protocol, however any missed assessments, such as eye exams, would also be reported as protocol deviations. This message was conveyed to those PCCs that were using their local IRBs.

3. Results

At the time the NIH guidance was issued, 63 PCCs had study participants. There were 243 study participants enrolled, including 150 who had not reached the 18-month visit. As of March 31, 2021, there were 81 PCCs with study participants, and 351 participants were enrolled, including 165 who had not reached the 18-month visit.

3.1. Communication

Study teams were receptive to enhanced communications, and emails and telephone calls increased. Attendance at monthly recorded coordinators calls increased substantially starting in May 2020 from a mean of 17 (range 14–20) in January–April 2020 to a mean of 47 (range 32–60) from May 2020–March 2021, out of over 80 coordinators working on the trial.

3.2. Retention

In March 2020, 36 PCCs had active participants who required follow-up visits. The number of active participants per PCC ranged from 1 to 9 (mean = 2.5). Following the federal and institutional guidances, remote visits started in March 2020 and peaked in April 2020, accounting for 75% (33/44) of all study visits (Table 1). Despite the ongoing pandemic, as practices instituted safety guidelines for in-person visits, phone visits began to decline in May 2020 and have accounted for 10% or less of all study visits from August 2020 through March 2021. There were a small number of missed expected study visits monthly (range 0–6/month) during the pandemic (Table 1). Overall, 97% (590/609) of expected study visits were completed. Of the study participants who had not reached the 18-month time point on March 31, 2021, 13 (13/165, 7.9%) either withdrew consent (9/165, 5.5%) or were lost to follow-up (4/165, 2.4%) during the pandemic. Of the nine who withdrew consent, four were due to COVID-19.

3.3. Screening and enrollment visits

Screening visits decreased after March 2020 and were low in April and May, but increased to pre-pandemic levels beginning in June 2020 (Table 2). Screening visits were in-person. Enrollment dropped precipitously in April, but did not stop at all PCCs, however it did remain low from May through August (range 1–8/month, average = 4.4). As institutions began easing clinical research policies, enrollment increased. Enrollment returned to pre-pandemic levels beginning in September

Table 1
Visits expected and completed during the pandemic.

	March 2020	April 2020	May 2020	June 2020	July 2020	August 2020	September 2020
Visits Expected	38	44	49	50	46	51	48
Visits Completed	36	43	46	50	42	48	48
Onsite	22 (58%)	10 (23%)	24 (49%)	40 (80%)	36 (78%)	43 (84%)	47 (98%)
Virtually	14 (37%)	33 (75%)	22 (45%)	10 (20%)	6 (13%)	5 (10%)	1 (2%)
Missed	2 (5%)	1 (2%)	3 (6%)	0 (0%)	4 (8%)	3 (5%)	0 (0%)

	October 2020	November 2020	December 2020	January 2021	February 2021	March 2021
Visits Expected	48	42	43	46	47	56
Visits Completed	48	41	43	45	47	53
Onsite	46 (96%)	40 (96%)	41 (95%)	45 (98%)	43 (92%)	53 (95%)
Virtually	2 (4%)	1 (2%)	2 (5%)	0 (0%)	4 (8%)	0 (0%)
Missed	0 (0%)	1 (2%)	0 (0%)	1 (2%)	0 (0%)	3 (5%)

Table 2
Screening and enrollment visits completed monthly since the pandemic shutdown.

	Screened	Enrolled
January 2020	11	10
February 2020	14	9
March 2020	9	14
April 2020	3	1
May 2020	3	5
June 2020	13	4
July 2020	13	8
August 2020	8	4
September 2020	19	13
October 2020	12	10
November 2020	14	16
December 2020	10	10
January 2021	14	7
February 2021	9	13
March 2021	15	11
TOTAL	**167**	**135**

2020.

3.4. PCC activation

In May 2020, permission was obtained from the NEI to activate a PCC in New Zealand. Eleven PCCs were activated from April through October 2020, including one in Canada and one in New Zealand. Of these, six PCCs screened and enrolled at least one participant during the period of this report, for a total of 20 participants enrolled at these PCCs from their time of activation through March 2021.

4. Discussion

Adapting to changing situations is key to achieving the goals of a clinical trial. As soon as the ZEDS CC was notified of the shutdown, study leadership implemented strategies to enable the successful continuation of the trial despite a pause in enrollment. A hallmark of our response has been very frequent communication via email, phone or WebEx between the CC and the PCCs, and among the leadership. There has been unwavering commitment on the part of the leadership, with support of the NEI and NYUGSoM, to do what was necessary to be successful. The PCCs all remained committed to the study and none withdrew their participation during the period of this report. Activities at academic and community-based PCCs were similar, and any differences seen were likely related to the regional level of COVID-19 infection. Our efforts to retain study participants in the trial yielded the desired results. The commitment and resilience of the staff at the CC and the PCCs have contributed to the high rate of expected follow-up visits completed. Of the study participants who had not reached the 18-month time point on March 31, 2021, the 7.9% who withdrew consent or were lost to follow-up is comparable to 2019 (7%, 10/142). In September 2020, the focus returned to enrollment, as had been the priority prior to the pandemic, and enrollment recovered to pre-pandemic levels.

This clinical trial has several design features that facilitated a positive response to the pandemic, including remote monitoring and training of PCCs, and oral study medication that is FDA approved. Use of a web-based electronic data capture system facilitated working remotely. Oral study medication was shipped from the PCC. Safety monitoring could be done by local blood tests in study participants with below normal eGFR's at enrollment. A limitation was that eye exams could not be done at the time of phone visits, and therefore endpoints could not be diagnosed and may be missed. The development of technology to do ophthalmic exams via telehealth in the future would advance remote study visits in eye trials.

Many non COVID-19 clinical trials face similar challenges during the pandemic, including paused recruitment and continued treatment of enrolled participants while ensuring their safety [2–5]. Technological solutions, including remote visits and monitoring, necessitated by the pandemic should be included in future trial designs [3,4]. Due to the key role of clinical trials in developing high-quality evidence-based best practices, it is very important to commit the necessary resources to continue ongoing trials and design future trials mindful of what we have learned.

5. Conclusions

The COVID-19 pandemic has created challenges for all clinical trials, including ZEDS, with regard to retention, enrollment and safety monitoring of study participants. Rapid responses enabled ZEDS to retain study participants, activate new PCCs, and resume enrollment when and where possible. Strong commitment to the study by all involved and use of technology are keys to the success of current and future trials.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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