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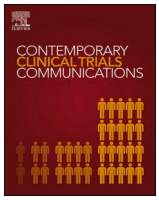

Operational changes to the lupus intervention fatigue trial as a result of COVID-19: An update to the study protocol

D. Kinnett-Hopkins [a,b,*], R. Ramsey-Goldman [b], H. Milaeger [b], J.S. Chmiel [b], A. Chung [b], D. Erickson [b], A. Kenney [b], L. Rosiles [b], L. Ehrlich-Jones [b,c]

[a] School of Kinesiology, University of Michigan, Ann Arbor, MI, USA
[b] Northwestern University, Chicago, IL, USA
[c] Shirley Ryan AbilityLab, Chicago, IL, USA

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ABSTRACT

Background: The coronavirus disease 2019 (COVID-19) global pandemic drastically impacted the health system and the research community. As a result, research institutions and funding agencies recommended a moratorium on conducting in-person research and study enrollment until protocol changes to protect participant safety were approved and implemented. We detail the operational modifications made to the Lupus Intervention Fatigue Trial (LIFT) protocol and summarize how we met the varied challenges created by COVID-19.
Methods: We evaluated study protocols and determined that scheduling, acquiring consent, in-person assessments and intervention baseline visits, patient reported outcomes, and data processing procedures needed modification.
Results: Operational modifications were made to ensure study progress while adhering to COVID-19 restrictions. Major changes included electronic consent, remote baseline visits for those in the intervention, self-report outcome measures at home via emailed weblinks, and telemedicine physician assessment visits. The collection of safety labs presented the largest challenge since this required an in-person visit to a laboratory. The study team elected to delay this up to one month after the physician assessment. All follow-up visits were completed, and no participants withdrew from the study.
Conclusion: LIFT was severely impacted by COVID-19. We provide insight into how our study protocol was modified without compromising the integrity of the primary and secondary outcomes of the study. The modifications utilized by the LIFT study resulted in efficiencies that will be included in a revised protocol and may serve as a useful example for other behavioral interventions to adapt their research studies.

1. Background

Systemic lupus erythematosus (SLE; lupus) is a chronic autoimmune disease with a prevalence of approximately 204,000 persons in the US [1]. Fatigue is the most prevalent SLE symptom and affects up to 80% of patients, with 58.6% considering fatigue the most disabling disease symptom [2]. The Lupus Intervention Fatigue Trial (LIFT) is described in detail in a previously published protocol paper [3]. Briefly, LIFT is modeled after successfully combined physical activity and diet health promotion programs, including the Diabetes Prevention Program [4]. LIFT is an ongoing 12-month phase II randomized, controlled parallel, single-blind two-group trial to compare the effectiveness of a motivational interviewing program intervention versus an educational program control group to reduce fatigue in persons with SLE [3]. Two hundred and thirty-six participants will be recruited with an estimated 15% dropout rate to reach a sample size of 200 participants completing the six-month assessment in the LIFT study. All randomized participants will receive the physical activity and diet focused motivational interviewing for the intervention or the lupus educational control program. Both groups consist of four individual sessions. For those randomized to the motivational interviewing intervention, there is one in-person baseline coaching session and three phone call sessions. The coaching sessions are grounded in motivational interviewing and target physical activity and nutritional behavior change. For those randomized to the educational control, there are four phone call sessions that include information on lupus disease management. The calls occur at baseline, 1.5 months, 3 months, and 6 months. The primary study outcome is six-month change in fatigue from baseline, as measured by the Fatigue

* Corresponding author. 830 N. University Ave. Ann Arbor, MI, 48109, USA.
E-mail address: dlkh@umich.edu (D. Kinnett-Hopkins).

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Severity Scale (FSS). The secondary study outcome is accelerometer-measured physical activity. The exploratory study outcome is adherence to the LIFT dietary intervention, as assessed by nutrient density (diet quality) and recommended food groups/eating patterns in persons with SLE. There is one planned interim analysis once half of the randomized participants (n = 100) complete the six-month assessment.

The coronavirus disease 2019 (COVID-19) pandemic drastically impacted the health system and the research community. Many research institutions and funding agencies recommended a moratorium on conducting in-person research and study enrollment until protocol changes to protect participant safety were implemented and approved. At the time of the moratorium, 25 individuals were enrolled in the LIFT study, and 23 were randomized. We turned the guidance provided by the Institutional Review Board (IRB) into actionable items without compromising the integrity of the primary and secondary outcomes of the study. This paper aims to detail the modifications made to the LIFT protocol and summarize how we met the varied challenges of the pandemic.

2. Methods and results

The research team evaluated study protocols and determined the study required changes in the following areas: scheduling, acquiring consent, in-person assessments, in-person baseline intervention visits, patient reported outcomes, and data processing procedures. All modifications to the study procedures are described in Table 1.

Prior to COVID-19 restrictions, initial consent was obtained in-person before the physical assessment. Participants were scheduled to engage in four 2-h-long physical assessments at the National Institute of Health/National Center for Advancing Translational Sciences Clinical (NIH/NCATS CTSA) and Translational Science Awards funded Clinical Research Unit (CRU). These visits included the completion of surveys on an iPad, a physical exam performed by a physician, blood draws, urinalysis, a review of medications and adverse events, and collecting availability for the nutritional data system for research (NDSR) assessment.

Beginning March 17, 2020, a moratorium on recruitment was placed by Northwestern University and Northwestern Medicine. The 25 enrolled participants transitioned to the remote study and continued the LIFT protocol. Due to the COVID-19 pandemic and new safety requirements, such as social distancing, our research team halted in-person interaction with participants. Below we list the changes that were made based on the guidelines provided by the Northwestern University IRB.

2.1. Consent, surveys, scheduling self-report dietary assessment, and coaching sessions

Rather than completing initial consent and surveys in the CRU, participants were emailed a Research Electronic Data Capture (REDCap) survey link to complete at home. Similarly, when completing the nutritional data system for research, participants provided their availability over the phone to the research coordinator who then alerted the nutritionist to schedule the six-month follow up. The nutritionist then coordinated with the participant separately by telephone. For individuals randomized to the motivational interviewing intervention, the baseline in-person assessment was modified to be conducted remotely via telephone.

2.2. Remote assessments during COVID-19

Assessment Procedures. To prioritize participant safety, physical exams were substituted with a telemedicine visit. A medical doctor performed all telehealth visits via Doximity, Incorporated. Participants were given the option to collect their own vital signs (weight, blood

Table 1
Major Changes made to Protocol Pre and Post COVID-19.

Procedure	Pre-COVID-19	Post-COVID-19
Scheduling	Find common date with participant and provider via phone and email. Then confirm availability with CRU	Find common date with participant to schedule coordinator call for initial consent or re-consent, explanation of PROs, and accelerometer instruction, and schedule MD visit based on MD availability
Consent	Coordinator reviews new consent form with participant in CRU at time of appointment; coordinator, CRU, and participant all receive a signed copy	Coordinator reviews consent over the phone and obtains verbal consent from participant. Coordinator sends REDCap link via email for participant to electronically sign ICD. Participant downloads a copy from REDCap and coordinator downloads and saves a copy for participant data folder. An excel document was created with a list of ICD consent status to track which participants needed to re-consent
Payment Request Form	Participant fills out and signs the payment request form in the CRU. Research coordinator emails the financial assistant the payment request form and the participant's check is sent	Coordinators pre-fill out the payment request documentation and emails it to participants for them to electronically sign or includes a paper copy in with the accelerometer packet. Coordinator then sends the Financial Assistant the signed payment request form so participants are mailed their checks
Labs-Blood Labs - Urine Analysis	Blood draw is completed by the nurse in the CRU and stored in designated LIFT freezers Urine sample is collected by the nurse in the CRU	Participants were given several options for blood draw and urine sample: 1) Participants could refuse to have blood drawn/urine sampled for this visit; 2) Participants went to institutional main or medical satellite clinic site and all charges were assigned to the LIFT study; or 3) Participants could provide medical record data from a SOC visit within one month of the scheduled assessment. Blood was no longer stored in LIFT freezers at Northwestern University
Vital Signs (including waist: hip, height, and weight)	Nurse collects vitals in CRU	Participants were given two options: 1) Through telemedicine visit, the MD could guide participants on how to collect their own vitals depending on capability and availability of instruments (e.g., blood pressure cuff, scale); 2) Participant provides medical record from a SOC physician follow up visit if within a one month time period of scheduled visit
Physician Exam, History (Sledai-2K & SLICC	MD performs physical exam and takes	Participants attend a telehealth medicine visit

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Table 1 (*continued*)

Procedure	Pre-COVID-19	Post-COVID-19
Damage Index) & Pregnancy Test	participant history in CRU.	with MD via Doximity, Inc, or telephone. Pregnancy was reported via self-report.
Medication Log	MD reviews medical log in the CRU with the participant	MD reviews the medical log with participant during telemedicine visit
AE/SAE Log	If needed, MD documents in CRU with participant	If needed, MD documents with participant during telemedicine visit
Accelerometer & Timesheet Given	Accelerometer is prepped by coordinator with timesheet, and mailing materials (shipping label and envelope) in the laboratory. Participant is given materials at the end of the CRU visit	ActiLife software was installed on coordinator's secured laptop. Accelerometers were prepped and shipped from the personal residence of the research coordinator. Materials shipped to participant include accelerometer, timesheet, shipping label, and pre-paid return envelope
Accelerometer Returned	Participants send accelerometer and timesheet log back to coordinators at institution using provided shipping materials	Participants ship all accelerometer items back to the research coordinator's home using provided shipping materials
Accelerometer Data Download to ActiLife	Coordinator downloads information via ActiLife and sends it to data analyst to confirm number of valid wear time days	No change
Patient-reported outcomes	Participants complete all surveys in CRU on an iPad with coordinator present to answer questions, if necessary	A REDCap survey link is emailed to participants to complete all surveys at home. Research coordinator reviews surveys for completeness and is available to be contacted by phone concerning questions participants may have while completing survey
Physical Activity Questionnaires	Date is set during scheduling appointment between participant and coordinator; coordinator calls participant to do questionnaires via phone at designated time	No change
NDSR (six-month only)	Participant provides availability in CRU during visit; coordinators alert nutritionist of 6 month follow up and nutritionist coordinates with participant separately	Participant gives availability over the phone to coordinator and coordinator enters data directly into REDCap; coordinators alert nutritionist of six-month follow up and the nutritionist coordinates with participant separately
CPMIE (six-month only)	Participants complete survey in CRU on an iPad with coordinator present to answer questions, if necessary	A REDCap survey link is emailed to participant to complete at home. Research coordinator reviews for completeness and is available to be contacted by phone for any questions participants have while completing survey
Data Entry - REDCap	Coordinator enters data (medications, SLEDAI, SLICC Damage, AE/SAE) directly from paper sources provided by MD in laboratory	Coordinator enters data (medications, SLEDAI, SLICC Damage, AE/SAE, lab results, vitals) directly from paper sources; MD provides coordinators paper sources to enter onto REDCap

Notes: CRU = Clinical Research Unit, PROs = Patient Reported Outcomes, MD = Medical Doctor, ICD = Informed Consent Document, LIFT = Lupus Intervention Fatigue Trial, SOC = Standard-of-Care, AE/SAE = Adverse Event/Serious Adverse Event, SLEDAI = Systemic Lupus Erythematosus Disease Activity Index, SLICC = Systemic Lupus International Collaborating Clinics, PROMIS = Patient Reported Outcomes Measurement Information System, NDSR = Nutrition Data System for Research, CPMIE = Client Perception of Motivational Interviewing Encounter, REDCap = Research Electronic Data Capture.

pressure, etc.) using equipment available to them at home, or participants could provide medical records from a standard-of-care visit within one month of the scheduled research assessment visit. Height reported from the prior visit was used. Participants that opted to complete their vital signs at home did so under the supervision of a physician during the telemedicine visit when possible or provided vital signs to the medical doctor after the telemedicine visit. Participants' medication logs were reviewed through Epic Systems, and any reports of adverse events were reviewed during the telemedicine exam. Disease activity measured by the Systemic Lupus Erythematosus Disease Activity Index-2K was determined based on reported symptoms and observations of the medical doctor. One participant had poor bandwidth, and the medical doctor could not access video during the telehealth visit. Pictures were sent to the medical doctor for evaluation via a secure medical record link, MyChart function in EPIC© to address this barrier. As heart and lung exams were not possible, the medical doctor utilized professional judgment to evaluate heart and lung function. Participants were given three options for completing the blood draw and urinalysis testing. Participants could:

(1) Refuse to have urine collected or blood drawn for this visit
(2) Go to institutional main or medical satellite clinic site, and all charges were assigned to the LIFT study
(3) Provide medical record data from a standard-of-care visit within one month of the scheduled assessment

The blood draw and urinalysis were completed at Northwestern University or an affiliate facility.

2.3. Data processing procedures

A restriction was placed by Northwestern University to prohibit any non-essential in-person research. To minimize contact and time spent in public places, accelerometers were prepared and shipped to participants directly from the research coordinator's personal residence. All original required materials were included in the shipment, including the accelerometer, timesheet, shipping label, and pre-paid return label. ActiLife was transferred from the laboratory to the research coordinator's secured laptop for remote analysis. Further, the participants shipped all accelerometer equipment back to the research coordinator's residence after completion.

Data entry was conducted by transferring paper sources into REDCap following CDC guidelines. The principal investigator had the sole responsibility for all data collected on paper. These documents were uploaded to a secured drive for the coordinator to enter data or were given directly to the coordinator to enter data while maintaining strict safety precautions to minimize contact.

The collection of safety labs presented the biggest challenge due to the possibility of a one-month delay in the timeframe of attending a standard-of-care visit. At the time of the moratorium, 25 participants

were enrolled. We completed 13 three-month visits and 21 six-month visits once protocol revisions were approved for remote assessment. Of the 34 visits completed, all primary, secondary, and exploratory outcomes were successfully completed with no participant attrition. For some assessments, specimen samples (7 labs (either blood, urine, or both) from 7 participants) and vitals (waist-to-hip ratio from 22 participants, and 10 vitals from 8 participants) were not collected.

On June 17th, 2020, Northwestern University designated our study eligible to resume recruitment. On July 8th, 2020 Northwestern University designated our study eligible to resume in person procedures as necessary for research. All procedures related to consent, surveys, scheduling self-report dietary assessment, and intervention and control group coaching phone calls adopted due to the COVID-19 restrictions have been maintained for all enrolled and new participants. For labs, vital signs, and the physical exam and history participants are offered the choice between the original in-person option and the remote option as adopted in response to COVID-19. Prior to the moratorium 12 three-month, 4 six-month, and 0 twelve-month assessments were completed with the original protocol. Of the 25 participants enrolled at the time of the moratorium, 13 completed their 3-month assessment remotely, 21 completed their 6-month assessment remotely, and 11 completed their 12-month assessment remotely. Between June 17th, 2020, and September 19th, 2023, 108 participants were enrolled. The LIFT study is still actively recruiting participants.

2.4. Data analysis considerations

The LIFT protocol was designed to conduct an intention-to-treat (ITT) analysis for the primary and secondary objectives and endpoints at the completion of the study. Persons with missing data will be included in all analyses to the extent that the data permit; multiple imputation will be used to impute missing covariable data where feasible for the primary study analyses.

As previously described, the protocol had one planned interim analysis based on the primary objective and endpoint (change in FSS score at 6-months vs. baseline for eligible, randomized participants). No changes in the planned statistical analyses were considered when the operational changes were implemented due to pandemic restrictions. As our design used a stratified randomization with random block sizes, the two study treatment arms should still be statistically balanced, and statistical comparisons should not be biased due to the pandemic-related protocol modifications. If we encounter ambiguity when interpreting results of the interim analysis, limited subgroup analyses may be conducted separately for each randomization arm to describe and compare changes in FSS at 6-month follow-up for the subgroup of participants who provided data for the interim analysis but were not directly impacted by the remote protocol changes. If those subgroup results are consistent with the full ITT analysis results, we would have some assurance that our COVID-related protocol changes did not influence the main results of our study. An additional subgroup analysis to examine baseline characteristics of the randomized participants for enrollees during the pre-COVID period versus those enrolled subsequent to the COVID remote study period might be conducted, overall, and by ITT study group assignment, but statistical power would be limited for any comparisons.

3. Discussion

The transition from an in-person to remote protocol due to the COVID-19 pandemic successfully captured essential components of an in-person experimental design while presenting some challenges through the data collection experience. The flexibility afforded to participants during the remote procedures allowed for follow-up visits to be completed with full retention, and all primary, secondary, and exploratory outcomes were collected. The transition to remote procedures offered challenges to recruitment and enrollment. While telemedicine presents many benefits during a pandemic and otherwise, obstacles persist, related to collecting biospecimens for safety and for research. The delays in appointment scheduling due to attaining approval of the revised protocol made it less likely for participants to obtain laboratory-based appointments within the one-month time window resulting in missing data. Conducting and collecting participant's vital signs through the direction of a physician over telemedicine may lead to discrepancies in measurement or not receiving data for participants who did not have the necessary equipment (e.g., scale, measuring tape). Disease activity measured by the Systemic Lupus Erythematosus Disease Activity Index-2K is not validated for telehealth visits but was utilized during remote assessments. There may be variation in results due to differences in assessment procedures.

4. Future directions

Although the impact of the COVID-19 pandemic on the future of clinical research remains uncertain, we expect more studies to adopt remote modifications to experimental procedures. This adaption to clinical research may enhance participant involvement in research as it eases scheduling, and participants may feel more comfortable with remote procedures. Additionally, the improved efficiency with a hybrid model may reduce study costs as the telehealth visits require less time. Remote procedures may promote retention rates by emphasizing flexibility and accessibility to participation in research studies.

5. Conclusion

The onset of the COVID-19 pandemic caused substantial modification of the LIFT study, resulting in a hybrid of in-person and remote components, many of which have remained in the current protocol. The lessons learned and modifications implemented by LIFT resulted in efficiencies to be added to a revised protocol. The revisions will encourage novel ideas to overcome challenges regarding alternative/missing data collection. Modifications of the LIFT protocol may serve as an example for future behavioral interventions to revise their research studies given COVID-19 restrictions, or to aid in the delivery of remote interventions.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: DKH, RRG, JSC, AY, LB, AC, DE, HM, AK, and LR have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. LEJ would like to disclose consulting work with Zimmer Biomet for training of Community Health Workers in motivational interviewing for a project to increase physical activity in disadvantaged populations of women with osteoarthritis.

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